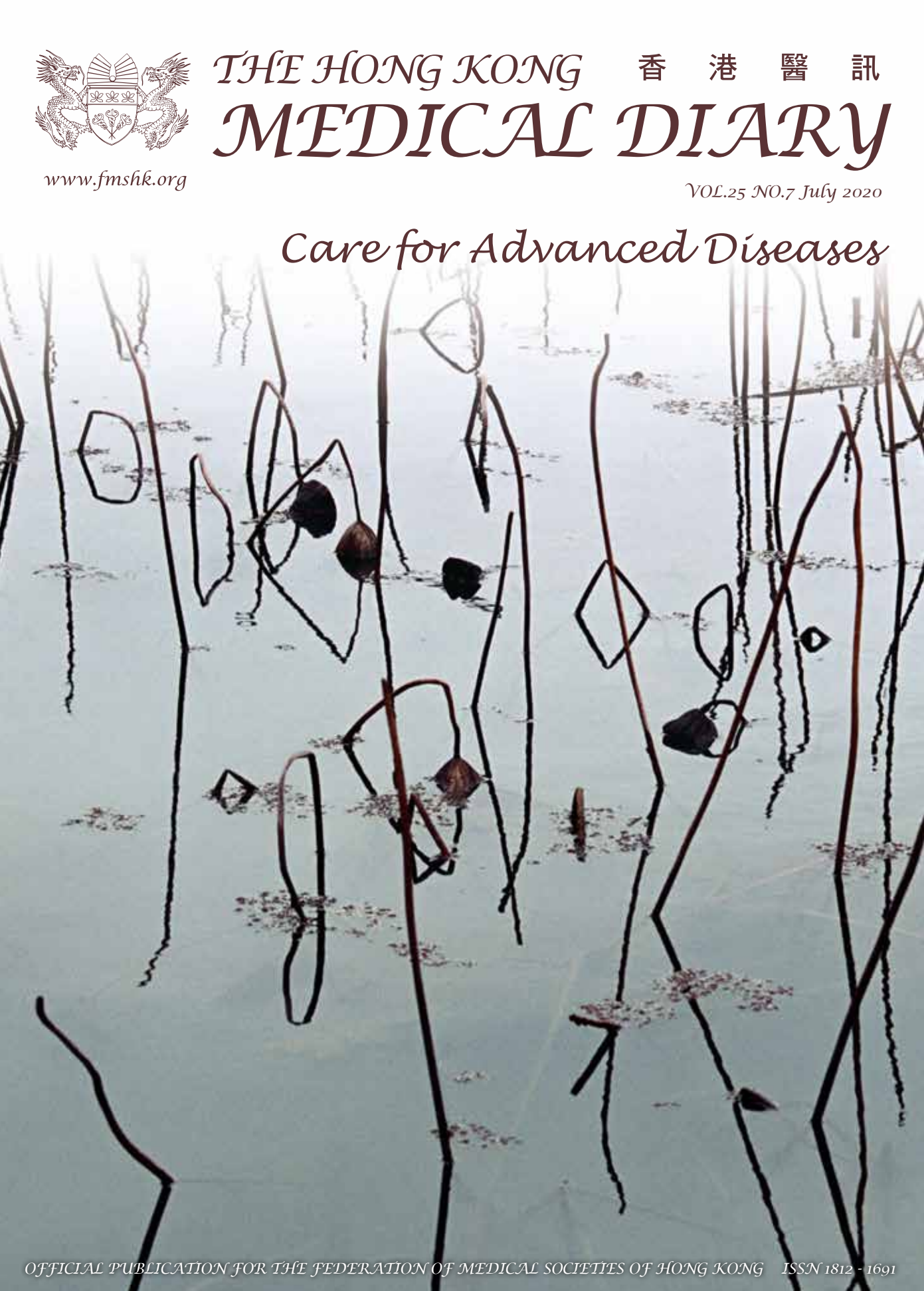
www.fmshk.org

THE HONG KONG MEDICAL DIARY

香 港 醫 訊

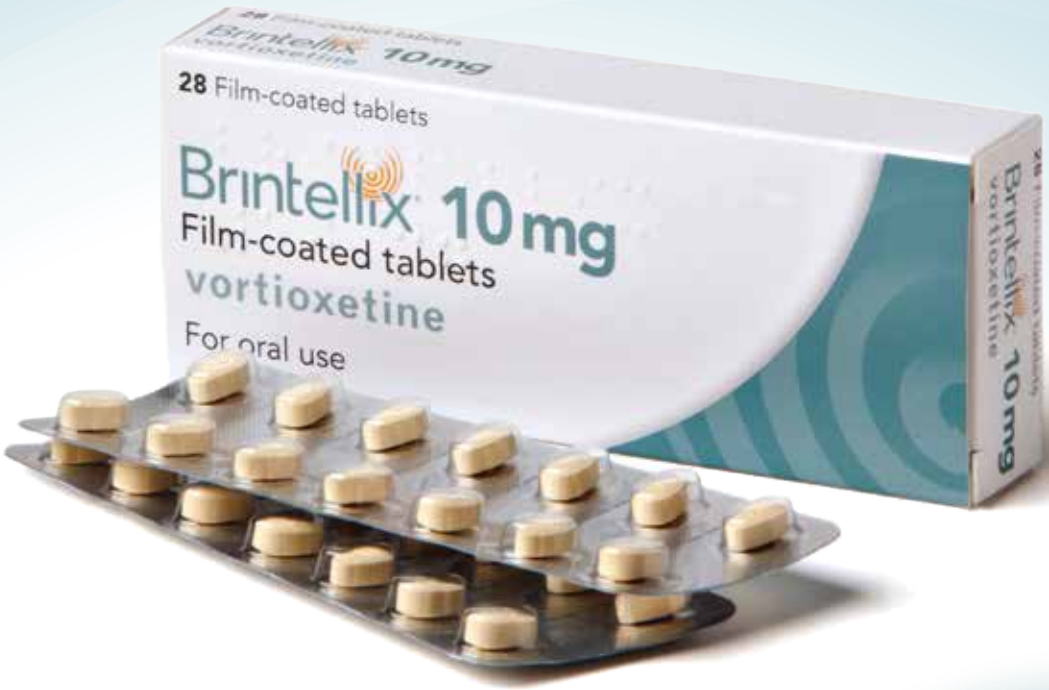
VOL.25 NO.7 July 2020

Care for Advanced Diseases



OFFICIAL PUBLICATION FOR THE FEDERATION OF MEDICAL SOCIETIES OF HONG KONG ISSN 1812 - 1691

Feel Better... Think Better! Do Better!



Lundbeck HK Limited
Suite 4303, Central Plaza,
18 Harbour Road, Wanchai, Hong Kong
Tel: 2244 8888 Fax: 2827 2228
www.lundbeck.com

Brintellix® vortioxetine

For the treatment of major depressive episodes in adults

BRINTELLIX® (VORTIOXETINE) – ABBREVIATED PRESCRIBING INFORMATION
Presentation: Film-coated tablets 5mg, 10mg and 20mg. **Indication:** Treatment of major depressive episodes in adults. **Dosage:** Adults: starting and recommended dose is 10mg, once-daily, taken with or without food. Elderly ≥65 years: Starting dose 5mg. Children and adolescents (<18 years): should not be used. **Discontinuation:** Patients can abruptly stop taking the medicinal product without the need for a gradual reduction in dose. **Contraindications:** Hypersensitivity to vortioxetine or to any of the excipients. Combination with MAO-inhibitors. Should not be used during pregnancy or lactation unless clearly needed and after careful consideration of the risk/benefit. **Special warnings and precautions:** Depression is associated with an increased risk of suicidal thoughts, self-harm and suicide. It is a general clinical experience that the risk of suicide may increase in the early stages of recovery. Close supervision of high-risk patients should accompany drug therapy. Patients (and caregivers) should be alerted about the need to monitor for any clinical worsening, suicidal behaviour or thoughts and unusual changes in behaviour and to seek medical advice immediately if these symptoms present. Should be introduced cautiously in patients who have a history of seizure or in patients with unstable epilepsy. Patients should be monitored for the emergence of signs and symptoms of Serotonin Syndrome or Neuroleptic Malignant Syndrome. Should be used with caution in patients with a history of mania/hypomania and should be discontinued in any patient entering a manic phase. There have been reports of cutaneous bleeding abnormalities with the use of SSRIs/SNRIs. Hyponatraemia has been reported rarely with the use of SSRIs/SNRIs Caution should be exercised for patients with renal or hepatic impairment. **Interactions:** Caution is advised when taken in combination with MAO-inhibitors, serotonergic medicinal products, products lowering the seizure threshold, lithium, tryptophan, St. John's Wort, oral anticoagulants or antiplatelet agents, and products predominantly metabolised by the enzymes CYP2D6, CYP3A4, CYP2C9 and Cytochrome P450. **Undesirable effects:** Adverse reactions are most frequent during the first or second week of treatment and usually decrease in intensity and frequency with continued treatment. Very common: Nausea. Common: abnormal dreams, dizziness, diarrhoea, constipation, vomiting, pruritus, including pruritus generalised. Uncommon: flushing, night sweats. Unknown: Serotonin Syndrome. **Overdose:** Symptomatic treatment. Marketing authorisation holder: Lundbeck HK Limited. Revision Date: May 2017. Full prescribing information is available upon request.

HK-BRIN-2019.08-AD05-MPL

Contents

Disclaimer

The Cover Shot

Withering lotus in the winter. The picture was taken in Wuxi in February where the withering stem from the lotus makes an unusual simple impressionist's subject for photography.

Prof Richard Yue-hong YU

MD, PhD, FRCP, FHKCP
Senior Advisor,
Hong Kong College of Physicians

Published by
The Federation of Medical Societies of Hong Kong

Design and Production
A-PRO MULTIMEDIA LTD www.apro.com.hk

Care for Advanced Diseases: Integral Health Care Component in the 21st Century and Beyond

Dr Raymond SK LO
MBBS (Lond), MD (CUHK), MHA (UNSW), Dip Geri Med (RCPS Glas), FRCP (Lond, Edin, Glas), FHKAM
Convenor, Care for Advanced Diseass Consortium
Immediate Past President,
The Federation of Medical Societies of Hong Kong
Editor


Dr Raymond SK LO

The advent of medical sciences and technology will continue to improve our health and life expectancy, though the inevitability of death and dying cannot be denied. Modern medicine will need to broaden its therapeutic vision to ensure holistic care, especially at advanced stages of diseases. Cure and care go hand in hand, with shifting focus for palliation towards the end of the trajectory of life.

Hospice and palliative care principles will need to be better integrated into the main streams of clinical practice, to meet the mounting needs from an increasing prevalence of advanced diseases. Cancer has been a mainstay of focus in palliative care, and much advance has been seen in palliative treatment options. When hope for curative treatment of a cancer diminishes, supportive and palliative care is not to be forsaken and should be proffered early. Patients' rights to receive palliative care are not to be neglected. Non-cancer advanced diseases also fittingly deserve palliative care, given its high symptom burden and complications. Organ failure may pose clinical challenges with often a longer and fluctuating course, yet earlier integration of palliative approach is even more indicated. Prognostic indicators and patient preferences will help as clinical triggers for palliative input. Advanced geriatric conditions with heavy burden like frailty, dementia, osteoporosis all require palliative approach, while innovative pharmacological and non-pharmacological preventive or ameliorative measures are being established. Curative care and palliative care are not mutually exclusive. Evidence is accumulating that early incorporation of palliative care can improve both quality and quantity of life, as seen in cancer patients. Indeed, quality of life would be more important than quantity of life at the end of life.

Patient-centred care for advanced diseases would benefit from a skilful application of science, art and communication. Communication in serious illness scenarios ranges from breaking bad news, prognostication, identifying priorities, discussing goal-concordant care, to support with comfort in the terminal stage. Similar to treatment and interventions in medicine, timing, setting, dosage and intensity of communication also require precision for an individualistic approach. It has been said that the success of most, if not all, health care delivery and outcomes depend on communication. A good and effective communication is most rewarding for patients, families and doctors. Conversation guide can aid towards a structured approach, yet the spirit of communication rests more in the art of delivery. The positive development of care for advanced diseases will rely on the humanity, ethics, and compassion of our medical and health professions, which the Federation together with leaders of our professional communities are endeavouring to uphold. A platform for continuing education is of course essential.

It is with this in mind that the Federation has dedicated and synergised efforts to promote the care for advanced diseases since 2016. Roundtable discussions, annual scientific meetings, public survey and promotion, responses to government consultations have been facilitated. It is timely that an issue of Medical Diary is now also devoted to this important notion. Palliative care also plays a significant role too in a global pandemic situation, though it is beyond the remit of this issue and deserves a separate focus. We are indebted to our expert authors in contributing articles in this issue, sharing their knowledge and experience in different spectrum of advanced illnesses. Many grateful thanks are to be given to Dr Leong Che-hung, for sharing with us his treasured insights and vision towards active ageing and good end-of-life.

Acknowledgement is also due to Professor Richard Yu, for contributing a spiritual and aesthetic cover picture for this issue.

We hope our discerning readers will find this Care for Advanced Diseases issue an enjoyable read, and as Hippocrates once said, wherever the art of Medicine is loved, there is also a love of Humanity.

BMA
British Medical Association
(Hong Kong Branch)

Advance in Therapeutics Course 2020

Online/Onsite*

Date : 6th July - 27th July 2020 (Every Monday Evening)
Time : Registration 6:45pm; Lecture: 7:15pm - 9:15pm
Option 1 : Online Lectures - Zoom
Option 2 : *Onsite Lectures (pending COVID situation & limited seats available)
Venue: Asia Medical Specialists, 8/F China Building, 30th Queen's Road Central, Hong Kong

6 July - Vaccination & Infectious Diseases

- **HPV and Cancer: Update on Screening and Prevention**
  Dr. Andrew Tin Yau WONG
  Specialist in Infectious Diseases
  Chairman - Prof Brian TOMLINSON, Council member, BMA (HK)
- **Prevention and Management of Herpes Zoster Infection: Update from a Neurological Perspective**
  Dr. Sonny Fong Kwong HON
  Specialist in Neurology

13 July - Cancer & Immunotherapy

- **Update on Kidney and Bladder Surgery**
  Dr. Edmond WONG
  Specialist in Urology
  Chairman - Dr Raymond SK LO, President, BMA (HK)
- **Immunotherapy in Urological Cancers**
  Dr. Siu Kie AU
  Specialist in Clinical Oncology

20 July - Pneumonia & Respiratory Diseases

- **Update on Airway Disease Management in the era of COVID 19 Pandemic**
  Dr. Chun Kong NG
  Specialist in Respiratory Medicine
  Chairman - Dr. Adrian WU, Vice President, BMA (HK)
- **Pneumococcal Pneumonia: Update on Prevention and Management**
  Dr. Kai Ming CHAN
  Specialist in Infectious Diseases

27 July - Orthopaedics & Musculoskeletal Pain

- **Current Concept Review of Lower Back Pain: Cause and Management**
  Dr. Hung Tsan CHOW
  Specialist in Orthopaedic and Traumatology
  Chairman - Dr. Jason BROCKWELL, Hon Treasurer of BMA (HK)
- **Diagnosis and Management of Myofascial Pain with Patient Case Sharing**
  Dr. Anne M.H. CHAN
  Specialist in Anaesthesiology

Places limited. Register early

Free for BMA paid-up members Join BMA as Ordinary or Associate member at annually fee $350 and course fee waived

For non-members $200 onsite / online for 1 evening; $400 onsite / online for all 4 evenings

Enquiries and Registration:
The Federation of Medical Societies of Hong Kong,
Tel. : 2527 8898 Fax : 2865 0345 Email : winnie.ng@fmshk.org

Zoom link and password to be sent after registration
Programme and arrangement may be subject to change with any unforeseen circumstances

Sponsored by :

MSD Pfizer Upjohn

asia medical specialists 亞洲專科醫生

Organized by :

BMA
British Medical Association (HK Branch)

Co-organized by :

The Federation of Medical Societies of Hong Kong

CME/CNE accreditations are in application

Advanced Heart Failure: Updates on the Latest Treatment Options

Dr Erik FUNG

Dr Erik FUNG

MB ChB, PhD, DABIM, DABIM(Cv), FACC

Specialist in Cardiology.
Division of Cardiology, Department of Medicine & Therapeutics, Faculty of Medicine, The Chinese University of Hong Kong

INTRODUCTION

After a decade of limited advances in the medical treatment for heart failure (HF), the past few years have seen a plethora of new and powerful therapeutic agents with a positive impact on hospitalisation, mortality and quality of life. In this article, we summarise the recent advances in medical therapy for heart failure with reduced ejection fraction (HFrEF), and provide an update on HF palliative care and management using inodilators to improve patients' quality of life with the potential to reduce hospital readmission.

ANGIOTENSIN RECEPTOR BLOCKER/NEPRILYSIN INHIBITOR (ARNI)

Studies from the late 1980–90s have taught us that angiotensin-converting-enzyme inhibitor (ACEI) or angiotensin II receptor blocker (ARB) provided survival benefits and reduced hospitalisation in patients with HFrEF. Benefits from ACEI or ARB are attributed to inhibition of the renin-angiotensin system that are maladapted in HF. Together with beta-blockers (e.g. carvedilol, metoprolol succinate, bisoprolol), ACEI or ARB, and mineralocorticoid receptor antagonist (e.g. spironolactone, eplerenone), this triple therapy (with ivabradine when heart rate is above 70 bpm despite maximised dosage of the aforementioned drugs) against neurohormonal activation has formed the backbone of HFrEF medical therapy for a long time before the therapeutic paradigm was taken to new heights by PARADIGM-HF[1].

PARADIGM-HF was a multicentre, international, randomised trial that compared standard-of-care enalapril with the combined drug of ARB (valsartan) and neprilysin inhibitor (sacubitril), or ARNI, in 8,399 patients with New York Heart Association (NYHA) functional class II–IV, left ventricular ejection fraction of ≤35–40%, elevated natriuretic peptide biomarkers, and optimised treatment including stable doses of ACEI and beta-blocker. Inhibition of neprilysin results in suppression of natriuretic peptide degradation, thereby increasing urinary water and sodium excretion (natriuresis). PARADIGM-HF showed that ARNI was associated with a significant 20% reduction in the primary efficacy outcome of cardiovascular mortality or hospitalisation due to HF (HHF). Secondary outcomes, including all-cause mortality, quality of life as measured by the Kansas City Cardiomyopathy Questionnaire, and the individual endpoints of cardiovascular mortality and HHF were also improved to a similar extent. Of note, patients in both treatment groups did not show any difference in the decline of renal function over time.

These practice-changing results led to recommendations by the European Society of Cardiology (2016) and American College of Cardiology/American Heart Association (2017) supporting ARNI in place of ACEI or ARB when the patient had already been on triple therapy, yet remained symptomatic (with or without low-dose digoxin) and required step-up therapy[2,3]. With the increasing use and clinical experience, ARNI is becoming a first-line agent (particularly, in North America and Europe) along with beta-blockers in HFrEF. For instance, patients hospitalised for new-onset acute HF may now receive ARNI once haemodynamically stabilised, with sufficient renal function as gauged by estimated glomerular filtration rate (eGFR) above 30 ml/min/1.73 m^2. When eGFR falls below 30 ml/min/1.73 m^2, a reduced renal dose (24 mg/26 mg (50 mg), oral, twice daily) rather than the standard dose (49 mg/51 mg (100 mg), oral, twice daily) of sacubitril/valsartan should be used. The upfront strategy of starting ARNI sooner is favoured by some physicians as it provides early risk reduction without requiring the patient to demonstrate recurrent decompensated HF or inadequacy of HF triple therapy. After titration over 2 - 4 weeks, the final maintenance dose should be 97 mg/103 mg (200 mg), oral, twice daily.

In 2019, the results of a much-awaited ARNI trial in HF with preserved ejection fraction (HFpEF), PARAGON-HF[4], was released to the disappointment of some in the clinical community. Detailed analysis of those trial data revealed a number of learning points, and emphasised the aetiological heterogeneity of HFpEF again. The study included individuals aged ≥50 years of age with NYHA II–IV symptoms, LVEF ≥45%, elevated natriuretic peptide levels, and presence of structural heart disease defined as left atrial enlargement or left ventricular hypertrophy. Under this broad umbrella is a range of cardiac pathologies including genetic, metabolic, infiltrative, immune-related and hypertrophic cardiomyopathies that can lead to HFpEF. Insights gleaned from PARAGRON-HF may improve future study designs and identification of HFpEF patient subgroups that may benefit from ARNI. Although ARNI narrowly missed statistical significance in reducing the primary composite outcome of cardiovascular mortality or HHF in HFpEF (P <0.06), it significantly improved the secondary outcomes of NYHA functional class and renal composite outcome, and reduced levels of NT-proBNP, a biomarker of ventricular stress, by 19%[4]. Improvement in echocardiographic features indicative of reverse remodelling were also observed. Interestingly, when stratified according to sex, the primary outcome was significant in women (hazard ratio (HR) 0.73, 95% confidence interval (CI) 0.59–0.90) but not in men (HR 1.03, 95% CI 0.84–1.25)[4]. This sex difference highlights the known differential response to treatment between male and female HFpEF patients. Further trials evaluating the efficacy of ARNI in specific cardiomyopathies are ongoing.

SODIUM GLUCOSE COTRANSPORTER 2 INHIBITOR (SGLT2i)

There is increasing recognition that HF is the most devastating and lifestyle-limiting chronic complication in patients with type 2 diabetes[5,6]. Empagliflozin, canagliflozin and dapagliflozin belong to a family of anti-diabetic drugs that inhibit the sodium-glucose cotransporter 2 (SGLT2) protein in renal early proximal tubules, resulting in glucosuria and other pleiotropic effects including natriuresis[7]. The EMPA-REG OUTCOME[8], CANVAS[9], and DECLARE-TIMI 58[10] trials have shown cardiorenal benefits of SGLT2 inhibitors.[11,12] EMPA-REG OUTCOME first reported that empagliflozin could reduce cardiovascular mortality by 38%.[8] Similar mortality benefits were seen in CANVAS[9] and DECLARE-TIMI 58[10] in spite of differences in background risks of the patient populations. Collectively, the data from multiple trials point to benefits driven by reductions in adverse HF and renal outcomes.

Of particular interest were findings from several recent trials investigating empagliflozin and dapagliflozin. While results from the phase 3 EMPERIAL-reduced and EMPERIAL-preserved designed to evaluate exercise capacity (e.g. 6-minute walk distance (6MWD)) and HF symptoms in HFrEF and HFpEF, respectively, were negative and disappointing, an interim analysis of the EMPRISE study including 190,000 diabetic patients with and without cardiovascular disease showed that empagliflozin was associated with 41% and 17% reduction in HHF compared with dipeptidyl peptidase-4 inhibitors and glucagon-like peptide-1 receptor agonists, respectively. Full publication of results from EMPRISE and EMPERIAL studies are awaited.

At the 2019 European Society of Cardiology Congress and World Congress of Cardiology in Paris, France, the results from the DAPA-HF study on dapagliflozin in HFrEF were well received. DAPA-HF was a phase 3, international, randomised placebo-controlled trial in 4,744 patients that evaluated dapagliflozin in reducing the primary composite outcome of worsening HF or death from a cardiovascular cause. Over a median of 18.2 months of follow-up, there was a 26% reduction in the primary endpoint in the dapagliflozin group compared with the placebo group (16.3% vs. 21.2%, P<0.001). The endpoints of worsening HF, and cardiovascular and all-cause mortality were reduced from 17% to 30%. Also, volume depletion and renal dysfunction were similar between the treatment groups. Surprisingly, in both diabetic and non-diabetic patients, the rates of the endpoints were similar, suggesting benefits irrespective of diabetes. DAPA-HF has affirmed the 'extra-glycaemic' benefits of dapagliflozin that are particularly pronounced in patients with HF and/or renal dysfunction. Although some patients were also on ARNI in DAPA-HF, the study did not appear to be powered to look at the effects of concurrent use of ARNI and dapagliflozin. As the exact extra-glycaemic mechanisms remain unclear, there are fertile grounds for further exploration in this research area.

PALLIATIVE INODILATORS AND CARE INTERVENTIONS

In advanced HFrEF, inotropic agents are used in acute cardiogenic shock to sustain cardiac output and blood pressure, or to palliate severe lifestyle-limiting symptoms including fatigue and shortness of breath at rest. In end-stage HF when continuous inotrope infusion is started, it is often continued through the end of life. A recent European multicentre double-blind, randomised, parallel-group, placebo-controlled trial, LION-HEART, showed that levosimendan could improve quality of life and reduce NT-proBNP levels and HHF in advanced HF outpatients when the drug was continuously infused for 6 hours, once every two weeks for 12 weeks[13]. That study was preceded by LevoRep which first demonstrated drug safety, but the primary endpoint including event-free survival was not met due to inadequate power[14]. LION-HEART has therefore achieved important milestones in the treatment of ambulatory advanced HF patients in regards to symptom palliation, quality of life improvement and reduction in HHF.

Levosimendan is a calcium-sensitising inotrope and potassium channel opener with vasodilatory properties (inodilator) that can reduce afterload and increase cardiac contractility, thereby providing a mechanical advantage for increasing cardiac output in a failing heart. In contrast to dobutamine that has a short half-life (2 minutes in plasma) and requires continuous infusion and discontinuation of beta-blocker (due to opposite effects at the beta-adrenergic receptor), infusion of levosimendan once every 2 weeks can be a useful option for end-stage HF patients in whom beta-blocker is continued for suppression of arrhythmias while remaining well enough to stay out of hospital or hospice. Another multicentre European study, LeoDor, is underway to address the utility of intermittent levosimendan in wider clinical settings following hospitalisation for acute HF, including as support therapy pre-transplantation or before ventricular support device implantation[15].

The use of inodilator therapy as a strategy to keep ambulatory advanced HF patients out of hospital has led clinicians and scientists to develop an extended-release formulation of oral milrinone[16]. In the 1-month open-label study, extended-release oral milrinone was demonstrated to be safe, and patients reportedly experienced an improvement in NYHA class, quality of life and 6MWD. A future placebo-controlled randomised trial is warranted. Either biweekly (once every two weeks) levosimendan administration or extended-release oral milrinone can be useful lifestyle-enhancing therapies for advanced HF patients who are stable enough for discharge to home but still require inotropic support for symptomatic relief and maintenance of daily function and activities.

PALLIATIVE CARE AS INTEGRAL PART OF ADVANCED HEART FAILURE CARE

Finally, the essential roles of palliative care as an integral part of advanced or end-stage HF care and management have been demonstrated in randomised clinical trials in the past 2–3 years. In particular, three landmark studies, PAL-HF, CASA and SWAP-HF, demonstrated that incorporation of palliative care in HF management led to a reduction in objective measures of depression, anxiety and suffering while improving quality of life, well-being and understanding of prognosis for patients that align with that of the physicians'[17–19].

Although the rates of hospitalisation and mortality were not significantly different between the standard care and intervention groups, it is again emphasised that alleviation of suffering and improvement in the quality

PecFent®

FENTANYL PECTIN NASAL SPRAY

Fast Relief[1-3], Effective Coverage[4]

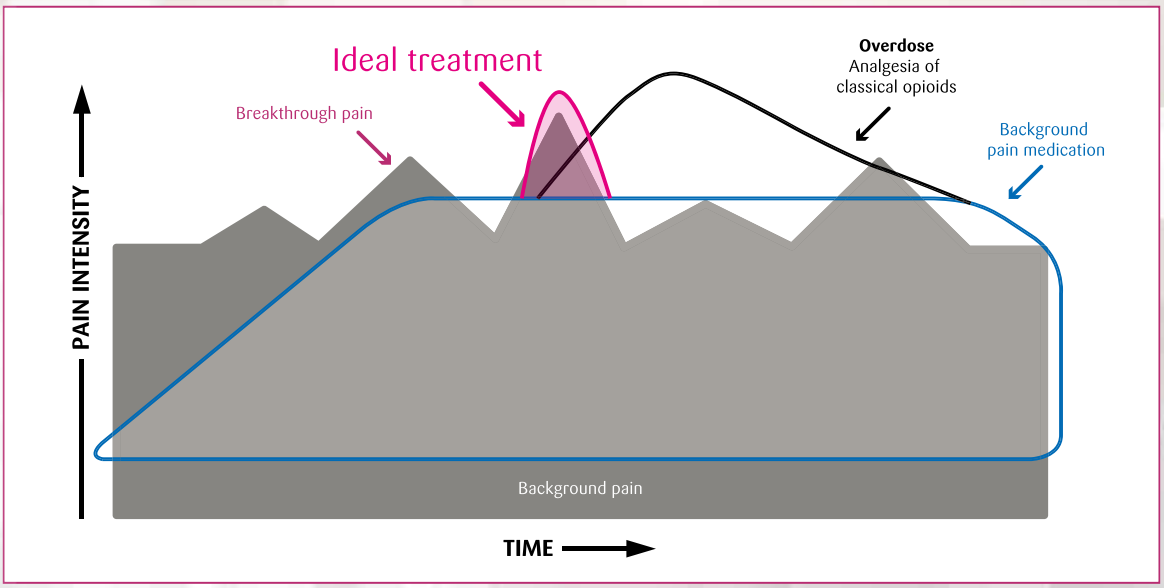
Breakthrough cancer pain relief in as little as

FA5T

5 minutes[1-3]

ADMINISTRATION

BTCP management: standard treatment (classical opioids) and ideal treatment[4]



PecFent is indicated for the management of breakthrough pain in adults who are already receiving maintenance opioid therapy for chronic cancer pain.

References:

1. Fallon M, et al. Efficacy and safety of fentanyl pectin nasal spray compared with immediate-release morphine sulfate tablets in the treatment of breakthrough cancer pain: a multicentre, randomized, controlled, double-blind, double-dummy multiple-crossover study; J Support Oncol 2011;9:224-231.
2. Portenoy RK, et al. A multicentre, placebo-controlled, double-blind, multiple-crossover study of Fentanyl Pectin Nasal Spray (FPNS) in the treatment of breakthrough cancer pain; Pain 2010;151:617-624.
3. PecFent Summary of Product Characteristics, November 2011.
4. Hansen MS, et al. Intranasal fentanyl in the treatment of acute pain - a systematic review; Acta Anaesthesiol Scand 2012;56:407-419.

如何輕鬆使用
PecFent噴鼻劑

Abbreviated Package Insert of PecFent

Composition: Fentanyl citrate; Indication: Management of breakthrough pain (BTP) in adults who are already receiving maintenance opioid therapy for chronic cancer pain; Dosage & Administration: Initially 100 mcg then titrated to an effective dose. Max: 4 doses/day, 800 mcg/dose. Wait for at least 4 hr after a dose before treating another episode; Contraindications: Hypersensitivity. Severe resp. depression or severe obstructive lung condition. Treatment of acute pain other than BTP. Patients w/o maintenance opioid therapy; Precautions: Resp. depression, increased intracranial pressure, bradycardia. COPD. Serotonin syndrome. Tolerance & physical &/or psychological dependence may develop. Positive doping test. Avoid IV or intra-arterial inj. Contains propyl parahydroxybenzoate. May impair mental &/or physical ability required for driving or operating machinery. Hepatic or renal impairment. Pregnancy & lactation; Children; Clinically significant adverse reactions: Disorientation; dysgeusia, dizziness, somnolence, headache; epistaxis, rhinorrhoea, nasal discomfort; vomiting, nausea, constipation; pruritus; resp. & circulatory depression, hypotension & shock; P/P: Nasal spray 100 mcg/spray x 1.55 mL x 1's. 400 mcg/spray x 1.55 mL x 1's.

Please refer to the full prescribing information before prescribing. Further information is available upon request

Kyowa KIRIN

Kyowa Kirin Hong Kong Co., Limited
Unit B, 13/F., 169 Electric Road,
North Point, Hong Kong
Tel.: (852) 2956-0828
http://www.kyowakirin/hk

KKHK-PEC-2-052020; Date of Production: 052020

of life should be primary goals in the management of end-stage HF. According to international guidelines,[2,3] early involvement of palliative care and development of an advance care plan are important components of HF care and management.

CONCLUSION

Major advancements have been made in recent few years in the medical management of patients with advanced or end-stage HFrEF. ARNI and SGLT2i are becoming a standard of care in addition to beta-blockers (with or without ivabradine) and aldosterone receptor antagonist for patients with HFrEF, and their use has been associated with improvements in clinical outcomes and objective measures of exercise capacity. Intermittent biweekly levosimendan infusion or extended-release oral milrinone are emerging treatment options for ambulatory advanced HF outpatients that can improve symptoms and quality of life. Palliative care has been demonstrated in randomised clinical trials to improve patients' symptoms and quality of life and should be introduced early in the course of advanced or end-stage HF.

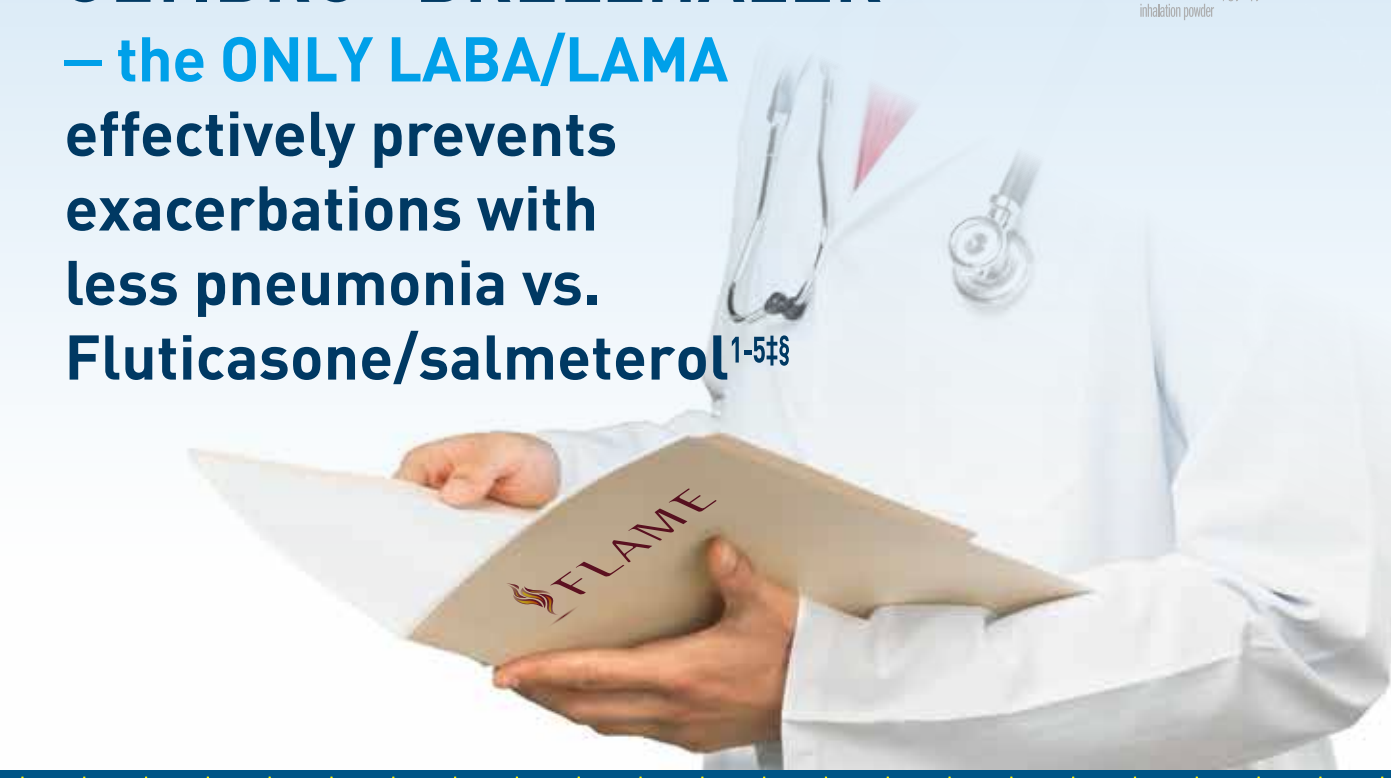
References

1. McMurray J.J.V., Packer M., Desai A.S., et al. Angiotensin-neprilysin inhibition versus enalapril in heart failure. N Engl J Med 2014; 371: 993-1004.
2. Ponikowski P., Voors A.A., Anker S.D., et al. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC). Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. Eur J Heart Fail 2016; 18: 891-975.
3. Yancy C.W., Jessup M., Bozkurt B., et al. 2017 ACC/AHA/HFSA Focused Update of the 2013 ACCF/AHA Guideline for the Management of Heart Failure: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Failure Society of America. J Am Coll Cardiol 2017; 70: 776-803.
4. Solomon S.D., McMurray J.J.V., Anand I.S., et al. Angiotensin-neprilysin inhibition in heart failure with preserved ejection fraction. N Engl J Med 2019; 381: 1609-1620.
5. Johansson I., Edner. M., Dahlström U., et al. Is the prognosis in patients with diabetes and heart failure a matter of unsatisfactory management? An observational study from the Swedish Heart Failure Registry. Eur J Heart Fail 2014; 16: 409-418.
6. Bank I.E.M., Gijsberts C.M., Teng T.H.K., et al. Prevalence and clinical significance of diabetes in Asian versus white patients with heart failure. JACC Heart Failure 2017; 5: 14-24.
7. Madaan T., Husain I., Akhtar M., et al. Exploring novel pharmacotherapeutic applications and repurposing potential of sodium glucose CoTransporter 2 inhibitors. Clin Exp Pharmacol Physiol 2018; 10.1111/1440-1681.12963.
8. Zinman B., Wanner C., Lachin J.M., et al. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. N Engl J Med 2015; 373: 2117-2128.
9. Neal B., Perkovic V., Mahaffey K.W., et al. Canagliflozin and cardiovascular and renal events in type 2 diabetes. N Engl J Med 2017; 377: 644-657.
10. Wiviott S.D., Raz I., Bonaca M., et al. Dapagliflozin and cardiovascular outcomes in type 2 diabetes. N Engl J Med 2019; 380: 347-357.
11. Kosiborod M., Lam C.S.P., Kohsaka S., et al. Cardiovascular events associated with SGLT-2 inhibitors versus other glucose-lowering drugs: The CVD-REAL 2 Study. J Am Coll Czrdiol 2018; 71: 2628-2639.
12. Perkovic V., Jardine M.J., Neal B., et al. Canagliflozin and renal outcomes in Type 2 diabetes and nephropathy. N Engl J Med 2019; 380: 2295-2306.
13. Comín-Colet J., Manito N., Segovia-Cubero J., et al. Efficacy and safety of intermittent intravenous outpatient administration of levosimendan in patients with advanced heart failure: the LION-HEART multicentre randomised trial. Eur J Heart Fail 2018; 20: 1128-1136.
14. Altenberger J., Parissis J.T., Costard-Jaeckle A., et al. Efficacy and safety of the pulsed infusions of levosimendan in outpatients with advanced heart failure (LevoRep) study: a multicentre randomized trial. Eur J Heart Fail 2014; 16: 898-906.
15. Pölzl G., Allipour Birgani S., Comín-Colet J., et al. Repetitive levosimendan infusions for patients with advanced chronic heart failure in the vulnerable post-discharge period. ESC Heart Fail 2019; 6: 174-181.
16. Nanayakkara S., Mak V., Crannitch K., et al. Extended release oral milrinone, CRD-102, for advanced heart failure. Am J Cardiol 2018; 122: 1017-1020.
17. Rogers J.G., Patel C.B., Mentz R.J., et al. Palliative care in heart failure: the PAL-HF randomized, controlled clinical trial. J Am Coll Cardiol 2017; 70: 331-341.
18. Bekelman D.B., Allen L.A., McBryde C.F., et al. Effect of a collaborative care intervention vs usual care on health status of patients with chronic heart failure: the CASA randomized clinical trial. JAMA Intern Med 2018; 178: 511-519.
19. O'Donnell A.E., Schaefer K.G., Stevenson L.W., et al. Social worker-aided palliative care intervention in high-risk patients with heart failure (SWAP-HF): a pilot randomized clinical trial. JAMA Cardiol 2018; 3: 516-519.

ONCE DAILY
ultibro® breezhaler®
indacaterol maleate/glycopyrronium bromide
inhalation powder

ULTIBRO® BREEZHALER®

– the ONLY LABA/LAMA effectively prevents exacerbations with less pneumonia vs. Fluticasone/salmeterol[1-5‡§]



17%

RISK REDUCTION IN MODERATE–SEVERE EXACERBATIONS‡

VS.

Fluticasone / salmeterol

(RR: 0.83, p<0.001)

22%

RISK REDUCTION IN TIME-TO-FIRST MODERATE–SEVERE EXACERBATION

VS.

Fluticasone / salmeterol

(HR: 0.78, p<0.001)

33%

LESS PNEUMONIA§

THAN

Fluticasone / salmeterol

(p=0.017)

*Patients had at least one moderate or severe exacerbation in the previous 12 months.

†Fluticasone/salmeterol 500/50 µg BID.

‡Annual rate reduction of all exacerbations (mild/moderate/severe): ULTIBRO ® BREEZHALER® vs. fluticasone salmeterol was 11% (RR: 0.89, p=0.003). Annual rate reduction of severe exacerbations: ULTIBRO® BREEZHALER® vs. fluticasone salmeterol was 13% (RR: 0.87, p=0.23).

§Incidence of radiographically confirmed pneumonia was 3.2% with ULTIBRO ® BREEZHALER® and 4.8% with fluticasone salmeterol (p=0.017).

***ULTIBRO™ BREEZHALER®* Important note:** Before prescribing, consult full prescribing information. **Presentation:** Inhalation powder hard capsules containing indacaterol maleate equivalent to 110 microgram (mcg) indacaterol and glycopyrronium bromide equivalent to 50 microgram glycopyrronium. **Indications:** Ultibro Breezhaler is indicated as a once-daily maintenance bronchodilator treatment to relieve symptoms in patients with chronic obstructive pulmonary disease (COPD), and for the reduction of exacerbations of COPD in patients with a history of exacerbations. **Dosage: Adults:** recommended dosage is the once-daily inhalation of the content of one 110/50 mcg capsule using the ULTIBRO BREEZHALER inhaler. **Children (<18 years):** should not be used in patients under 18 years of age. **Special patients population:** *Renal impairment:* can be used at recommended dose in patients with mild to moderate renal impairment. Should be used only if expected benefit outweighs the potential risk in patients with severe renal impairment or end-stage renal disease requiring dialysis. *Hepatic impairment:* Can be used at the recommended dose in patients with mild and moderate hepatic impairment. No data are available for subjects with severe hepatic impairment. *Geriatrics:* can be used at recommended dose in patients 75 years of age and older. **Method of administration:** ULTIBRO BREEZHALER capsules must be administered by the oral inhalation route and only using the ULTIBRO BREEZHALER inhaler. Capsules must not be swallowed. ULTIBRO BREEZHALER should be administered at the same time of the day each day. If a dose is missed, it should be taken as soon as possible. Patients should be instructed not to take more than one dose in a day. Capsules must always be stored in the blister to protect from moisture, and only removed immediately before use. Patients should be instructed on how to administer the product correctly. Patients who do not experience improvement in breathing should be asked if they are swallowing the medicine rather than inhaling it. **Contraindications:** ◆Known hypersensitivity to indacaterol, which is one of the components of ULTIBRO BREEZHALER, or to any of the excipients. Ultibro Breezhaler capsules contain lactose. Therefore, patients with rare hereditary problems of galactose intolerance, severe lactase deficiency or glucose-galactose malabsorption should not take this medicine. **Warnings/Precautions:** ◆**ULTIBRO BREEZHALER** should not be administered concomitantly with other long-acting beta-agonists or long-acting muscarinic-antagonists, ◆**asthma:** should not be used in asthma, long-acting beta2-adrenergic agonists may increase the risk of asthma-related serious adverse events, including asthma-related deaths, when used for treatment of asthma ◆**not for acute use:** should not be used as rescue therapy ◆**hypersensitivity related to indacaterol:** If hypersensitivity reaction occurs, ULTIBRO BREEZHALER should be discontinued immediately and alternative therapy instituted ◆**paradoxical bronchospasm:** as with other inhalation therapy, administration may result in paradoxical bronchospasm that may be life-threatening. If paradoxical bronchospasm occurs, ULTIBRO BREEZHALER should be discontinued immediately and alternative therapy instituted ◆anticholinergic effects related to glycopyrronium: use with caution in patients with narrow-angle glaucoma and urinary retention ◆**systemic effects of beta2-agonists:** as with other beta2-adrenergic agonists, should be used with caution in patients with cardiovascular disorders (coronary artery disease, acute myocardial infarction, cardiac arrhythmias, hypertension); in patients with convulsive disorders or thyrotoxicosis; in patients who are unusually responsive to beta2-adrenergic agonists ◆**patients with severe renal impairment:** to be used only if expected benefit outweighs potential risk in patients with severe renal impairment including end-stage renal disease requiring dialysis. ◆**cardiovascular effects of beta2-agonists:** like other beta2-adrenergic agonists, may produce a clinically significant cardiovascular effect in some patients as measured by increases in pulse rate, blood pressure, and/or symptoms, ECG changes ◆**hypokalemia with beta2-agonists:** beta2-adrenergic agonists may produce significant hypokalemia in some patients, which has the potential to produce adverse cardiovascular effects. In patients with severe COPD, hypokalemia may be potentiated by hypoxia and concomitant treatment which may increase the susceptibility to cardiac arrhythmias ◆**hyperglycemia with beta2-agonists:** clinically notable changes in blood glucose (4.9%) at the recommended dose than on placebo (2.7%). ULTIBRO BREEZHALER has not been investigated in patients for whom diabetes mellitus is not well controlled. **Pregnancy:** should only be used during pregnancy if the expected benefit to the patient justifies the potential risk to the fetus. **Breast-feeding:** should only be considered if the expected benefit to the woman is greater than any possible risk to the infant. **Fertility:** No studies on the effect on fertility have been conducted with the indacaterol/ glycopyrronium combination. **Labor and delivery:** Information related to indacaterol - ULTIBRO BREEZHALER may inhibit labor due to a relaxant effect on uterine smooth muscle. **Interactions:** ◆No specific drug-drug interaction studies were conducted with ULTIBRO BREEZHALER. Information on the potential for interactions is based on the potential for each of its two components. ◆should not be given together with beta-adrenergic blockers (including eye drops) unless there are compelling reasons for their use ◆should be administered with caution to patients being treated with monoamine oxidase inhibitors, tricyclic antidepressants, or drugs known to prolong the QT-interval. Drugs known to prolong the QT-interval may increase the risk of ventricular arrhythmia. ◆concomitant administration of other sympathomimetic agents may potentiate the undesirable effects ◆concomitant treatment with methylxanthine derivatives, steroids, or non-potassium sparing diuretics may potentiate the possible hypokalemic effect of beta2-adrenergic agonists. ◆inhibition of the key contributors of indacaterol clearance, CYP3A4 and P-gp, has no impact on safety of therapeutic doses. ◆co-administration with other inhaled anticholinergic-containing drugs has not been studied and is therefore not recommended. ◆no clinically relevant drug interaction is expected when glycopyrronium is co-administered with cimetidine or other inhibitors of the organic cation transport. **Adverse reactions:** *Adverse reactions from ULTIBRO BREEZHALER* ◆**Very common (≥10%):** Upper respiratory tract infection ◆**Common (≥1% to <10%):** Nasopharyngitis, urinary tract infection, sinusitis, rhinitis, hypersensitivity, diabetes mellitus and hyperglycemia, dizziness, headache, cough, oropharyngeal pain including throat irritation, dyspepsia, dental caries, bladder obstruction and urinary retention , pyrexia, chest pain ◆**Uncommon (≥0.1% to <1%):** Insomnia, glaucoma, ischemic heart disease, atrial fibrillation, tachycardia, palpitations, epistaxis, paradoxical bronchospasm, dry mouth, gastroenteritis, pruritus/rash, musculoskeletal pain, muscle spasm, pain in extremity, myalgia, peripheral edema, fatigue, ◆**Rare (≥0.01% to <0.1%):** Paraesthesia **Packs:** 30 Inhalation Powder Hard Capsules/Pack **Legal classification:** P1S1S3 Ref: TGA Feb 2018 (0809s)

References:

1. Ultibro Breezhaler Local Prescription Information 2018. 2. Wedzicha JA, et at. Lancet Respir Med 2013;1:199-209. 3. Wedzicha JA, et al. N Eng J Med 2016;374:2222-2234.
4. Umeclidinium and vilanterol Prescription Information. 5. Aclidinium and formoterol Prescription Information. 6. Tiotropium bromide and olodaterol Prescription Information

NOVARTIS

Novartis Pharmaceuticals (HK) Ltd

7/F, Citi Tower, One Bay East, 83 Hoi Bun Road, Kwun Tong, Kowloon, Hong Kong

Tel: 2882 5222 Fax: 2577 0274

ONCE DAILY
ultibro® breezhaler®
indacaterol maleate/glycopyrronium bromide
inhalation powder

HK1907702687

Management of Advanced Airway and Lung Diseases

Dr Hon-cheung FAN

MBBS, FRCP(Edin), FHKCP, FHKAM(Medicine)
Consultant, Department of Medicine & Geriatrics, Ruttonjee Hospital

Dr Hon-cheung FAN

This article has been selected by the Editorial Board of the Hong Kong Medical Diary for participants in the CME programme of the Medical Council of Hong Kong (MCHK) to complete the following self-assessment questions in order to be awarded 1 CME credit under the programme upon returning the completed answer sheet to the Federation Secretariat on or before 31 July 2020.

INTRODUCTION

Medical advances and sophisticated life-supporting interventions have prolonged life of many patients with advanced airway and lung diseases who would not have survived long in the past. However, a gradual deterioration in health is common in chronic progressive illnesses, often with prolonged periods of physical dependency. Advanced respiratory diseases include but not limited to chronic obstructive pulmonary disease (COPD) and interstitial lung diseases (ILD), particularly idiopathic pulmonary fibrosis (IPF). Both diseases are not curable, have progressive courses and are associated with high symptom burden, psycho-spiritual distress, impaired functional status, poor health-related quality of life (HRQOL), and significant morbidity and mortality[1-5]. In addition, both require high rates of healthcare utilisation, particularly near the end of life, including frequent emergency room visits, hospitalisations, intensive care unit (ICU) admission and/or prolonged mechanical ventilation[1]. At the terminal stage, the treatment aim will shift from life-prolonging therapy to relieving patients' sufferings and providing support to patients and their families.

Chronic obstructive pulmonary disease (COPD) is currently the fourth leading cause of death in the world[6]. Globally, the COPD burden is projected to increase in the coming decades because of continued exposure to COPD risk factors and population ageing[7]. For advanced COPD, it progresses with worsening of dyspnoea during disease progression, deterioration in function and QOL, which is similar or worse than that of advanced cancer[1-3].

Idiopathic pulmonary fibrosis (IPF) is a progressive, irreversible, and fatal fibrosing lung disease with a median survival of 2 to 5 years from the time of diagnosis[8,9]. The 5-year survival rate of 20 - 40% is worse than that of many cancers[10]. IPF is the most common idiopathic interstitial lung disease (ILD), affecting about 5 million persons worldwide[11]. Progression of IPF is characterised by a decline in lung function, worsening symptoms of dyspnoea and cough, and deterioration in QOL[12].

CLINICAL COURSE

The disease trajectory in COPD is usually marked by a gradual decline in health status and increasing symptoms, with intermittent acute exacerbations that are associated with an increased risk of death[2-3].

The clinical course of IPF is progressive, highly variable and unpredictable and is frequently associated with a significant symptom burden[10]. Some patients progress relatively slowly; however, disease progression can be accelerated by an acute exacerbation, usually resulting in hospitalisation and is associated with very high mortality[12].

SYMPTOM BURDEN

Dyspnoea is the most prevalent and distressing symptom reported by patients with COPD. In advanced stage of COPD, refractory dyspnoea causes significant impairment in daily activities and leads to negative effect on the quality of life. In a comparison of symptoms experienced by patients with COPD and lung cancer, dyspnoea was more frequently reported and also more severe in patients with COPD while cancer patients reported higher levels of pain[13,14]. Advanced COPD patients experience poor HRQOL comparable to or worse than that of advanced lung cancer patients[3,14].

For patients with ILD, they have a high burden of respiratory symptoms such as dyspnoea and cough, accompanied by fatigue, anxiety and depression in the advanced stages. In addition, they experience more upper gastro-intestinal symptoms (heartburn, regurgitation and belching).

Table 1. Prevalence of symptoms in advanced COPD and PIF-ILD (Excerpted from Janssen DJ et al[4] and Carvajalino S et al[5])

Symptoms	Advanced COPD	PIF-ILD
Dyspnoea	56-98%	58-98%
Cough	59-80%	59-94%
Tiredness	49-96%	8-29%
Anorexia	11-81%	48.2%
Insomnia	55-77%	6-47%
Pain	21-77%	9%
Dry Mouth	59-67%	-
Constipation	27-44%	-
Heartburn	-	29-48%
Depression	17-77%	10-49%
Anxiety	32-57%	22-58%

PIF-ILD, Progressive Idiopathic Fibrotic-Interstitial Lung Disease

PSYCHOLOGICAL & SPIRITUAL DISTRESS

A chronic progressive and life-threatening disease usually raises questions regarding existence, the meaning of life, regret, destiny and dignity. During the course of their respiratory disease, most patients suffer from psychological distress, and they are at a substantially higher risk for depression and anxiety than healthy persons[4,5]. The vicious cycle of physical, social, psychological symptoms and decreasing quality of life[16] in advanced COPD is illustrated in Fig. 1. Nonpharmacological interventions like psychological therapies (using a cognitive-behavioural therapy-based approach) may be effective for treating COPD-related depression[15]. Pharmacological treatment includes anti-depressive medications such as methylphenidate, serotonin selective reuptake inhibitors, tricyclic antidepressants, and anxiolytic medications such as benzodiazepines.

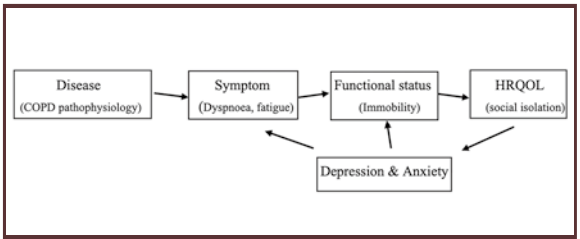


Fig. 1 Think conceptually about physical symptoms, QOL and health status. (Excerpted from Wilson IB et al[16]).

SYMPTOM MANAGEMENT OF DYSPNOEA

Appropriate Pharmacological Therapies for Underlying Diseases

Currently, long-acting β2 agonist and long-acting anticholinergic plus inhaled corticosteroid are the recommended treatment for advanced COPD patients. A combination of all three classes of drugs improve lung function and quality of life[17,18] and may further reduce exacerbations. A phosphodiesterase-4 inhibitor can be added in selected patients.

For the treatment of IPF with mild to moderate impairment in lung function [forced vital capacity (FVC) > 50% predicted], both nintedanib and pirfenidone reduce the rate of decline in FVC (i.e. slow progression) by approximately 50% over 1 year of treatment[19]. Moreover, nintedanib and pirfenidone may reduce the risk of severe acute deteriorations which are associated with high mortality[20,21].

Nonpharmacological Therapies

For COPD, pulmonary rehabilitation (PR) relieves dyspnoea and fatigue, improves emotional function and enhances the sense of control that individuals have over their condition[22]. For ILD, PR improves functional exercise capacity, dyspnoea and QOL, with benefits also evident in IPF[8,23].

Other nonpharmacological interventions include chest wall vibration; neuroelectrical muscle stimulation, walking aids and breathing training[24]. A randomised controlled trial (RCT) study showed that a handheld fan reduced breathlessness when directed to the face[25]. Moreover, multidisciplinary support services (MSS) may be more effective in delivering complex nonpharmacological interventions such as breathlessness intervention services (BIS)[26].

Pharmacological Treatment of Refractory Dyspnoea

Dyspnoea is the most common distressing symptom in most advanced lung diseases. For distressing dyspnoea refractory to specific therapies for their underlying diseases, systemic opioid is the first-line pharmacological drug of choice. A systematic review evaluated the use of opioids for dyspnoea in 18 double-blinded RCTs, in which 11 of 18 studies included only COPD patients[27]. The review confirmed overall beneficial effects of oral or parenteral opioids (but not nebulised opioids) on the sensation of breathlessness in COPD without any impact on exercise capacity[28]. Moreover, no serious adverse effects (hospitalisations, respiratory depression, or CO2 retention) were reported[28]. The possible mechanism seems to be mediated mainly by a reduction in central ventilatory demand and altered perception of breathlessness[28].

Common side effects are drowsiness, sedation, nausea and vomiting, which are transient and typically resolve in 3 to 5 days. Constipation typically worsens with dose escalation and requires regular laxatives[29]. Confusion and urinary retention are more frequent in the elderly with comorbidities and polypharmacy. There is no data to suggest that the use of opioids for the management of breathlessness is associated with a reduction in a patient's life expectancy[30].

In general, regular low-dose oral opioid (≤ 30 mg per day oral morphine equivalent) should be considered for refractory dyspnoea in advanced COPD despite best medical management[27]. The opioid dose should be titrated to the lowest effective dose that reduces the dyspnoea (rated using either the Borg scale or Visual Analogue Scale) and minimises the adverse effects of opioid with regular monitoring of symptom control and adverse effect.

Benzodiazepines may be considered as a second- or third-line treatment, when opioids and nonpharmacological measures have failed to control breathlessness[31]. Benzodiazepines caused less drowsiness compared to morphine[29]. There is evidence supporting the short term use of benzodiazepines for the treatment of anxiety and insomnia.

SUPPLEMENTAL OXYGEN

The usefulness of supplemental oxygen for hypoxaemic patients is well-documented[32]. Long term oxygen therapy has significant survival benefit when used for at least 15 hours per day in hypoxaemic COPD patients[33,34]. Supplemental oxygen is also recommended for patients with advanced IPF with significant resting hypoxaemia, commonly defined as a resting SpO2 of < 88%[8,35].

There is no evidence of the additional symptomatic benefit of oxygen over room air for relieving refractory dyspnoea related to life-limiting illness in non-hypoxaemic patients[36]. Routine application of supplemental oxygen to patients who are near death is not supported. Oxygen should be given only to hypoxaemic patients with moderate to severe levels of breathlessness[37]. And it should be withdrawn if the patient does not report relief of breathlessness within a few days[37].

NON-INVASIVE VENTILATION (NIV)

NIV as Life-sustaining Treatment

NIV is beneficial as a first-line intervention in conjunction with usual care for reducing the likelihood of mortality (46%) and endotracheal intubation (65%) in patients admitted for acute hypercapnic respiratory failure secondary to an acute exacerbation of COPD regardless of the severity of respiratory acidosis and the location of NIV application (i.e. ICU/ward setting)[38]. A recent RCT has found that 12 months of high-intensity home NIV prolonged the time to readmission or death (a survival benefit)[39].

For ILD, NIV responsiveness does not seem to impact on the poor prognosis related to the underlying disease with a 1 year mortality rate of ≥70%[40].

NIV as a Palliative (Comfort) Measure

For a do-not intubate (DNI) patient with advanced lung diseases, the intention of NIV is for palliation of dyspnoea, not as life-sustaining treatment. Several international guidelines support the use of NIV to dyspnoeic patients for palliation in the setting of terminal cancer or other terminal respiratory conditions with appropriate patient selection and staff training.

If NIV use is considered in end-of-life care, it is important to discuss the advance care planning with patient and family regarding the goals of treatment, patient preferences, benefits and burdens of treatment (i.e. symptom improvement versus ventilation discomfort and prolongation of dying process), issues of CPR and endotracheal intubation, and the option of terminating NIV if it is no longer effective at relieving the dyspnoea.

High Flow Nasal Cannula Oxygen Therapy (HFNC)

If a terminal patient declines or cannot tolerate NIV, HFNC may be an option for the palliation of terminal dyspnoea. HFNC, delivering up to 60 L/min of heated humidified high oxygen flow (up to100%) via nasal prongs, reduces the rate and work of breathing and improves oxygenation. When compared with NIV, HFNC causes less barrier to eating and talking, and less skin laceration and claustrophobia[41]. Moreover, it requires less staff training and can be applied in the general ward setting or even at home.

INTEGRATION OF PALLIATIVE CARE (PC) IN ADVANCED AIRWAY AND LUNG DISEASES

The goal of palliative care is to relieve patients' suffering and to optimise the quality of life of both patients and their families. Due to uncertainty in the prognosis of patients with advanced airway and lung diseases, difficulties are frequently encountered during the initiation of palliative care and the discussion of end-of-life issues. This is further aggravated by inadequate communication and counselling between patients, family members and healthcare professionals. For patients with advanced airway and lung diseases and limited life expectancy (i.e. six months or less), early pulmonary palliative care referral should be considered if patients fulfill the criteria in table 2.

Table 2. Referral criteria for pulmonary palliative care (essential criteria: 1 & 2; supportive criteria: 3, 4, 5) (Excerpted from US Medicare Referral for Hospice Care for Advanced Pulmonary Diseases[42].)*

1*	Severe pulmonary diseases as documented by both (a) and (b) a Disabling dyspnoea at rest, poorly or unresponsive to bronchodilators, resulting in decreased functional capacity (FEV1 post-bronchodilator <30% predicted is supportive evidence of disabling dyspnoea, but is not necessary to obtain) b Progression of advanced pulmonary disease, as evidenced by increasing hospitalisations for acute exacerbations and/or respiratory failure
2*	Hypoxaemia at rest on room air (pO2 <55 mmHg or oxygen saturation <88%) OR Hypercapnia (pCO2 >50 mmHg)
3	Cor pulmonale
4	Unintentional progressive weight loss >10% over the preceding six months
5	Resting tachycardia > 100/min

Early palliative care referral can alleviate symptom burden, address psychosocial and spiritual needs and enhance advance care planning (ACP) discussion. Advance care planning (ACP) is an overarching process of proactive communication regarding end-of-life care (EOL) at a point in time when the patient becomes mentally incompetent. Medical treatment decisions near EOL must be carefully made according to the goals of care and best interests of the patient (taking into account of the patient's wish, preferences and values), and weighing the benefits, risks and burdens of the treatment options. Patient's preferences on future life-sustaining treatments (e.g. CPR, intubation, NIV), relevance in care at EOL and the preferred site of care and death should be documented. A recent RCT showed that a nurse-led, facilitated ACP increased the uptake of ACP among patients with severe lung diseases[43].

The importance of collaboration model between palliative and respiratory medicine has been recognised in several international guidelines[44]. This model includes respiratory and palliative care physicians,

palliative care nurse, medical social workers, pastoral care officer & chaplain, clinical psychologist, physiotherapist and occupational therapist. Ideally, early palliative care referral should be initiated by the parent respiratory team in the outpatient clinic setting. It is important to identify patients with PC needs and offer coordinated and shared care in terms of joint/parallel clinic, case conference and inpatient PC consultative service.

CONCLUSION

Advanced airway and lung disease is associated with high symptom burden, but patients have limited access to palliative care service. Dyspnoea is an important, difficult-to-treat symptom with significant psychological consequences. Currently, systemic opioid is effective in alleviating refractory dyspnoea. As it is a chronic progressive and life-threatening disease with an intermittent exacerbation that may lead to death, early referral to palliative care is beneficial, and ACP should be initiated particularly on the EOL treatment discussion, i.e. CPR, NIV and intubation. A collaborative model between respiratory & palliative care physicians should be considered to provide a coordinated care service in order to address patients' need and improve the QOL of both patients and their families.

References

1. Au DH, Udris EM, Fihn SD, et al. Differences in health care utilization at the end of life among patients with chronic obstructive pulmonary disease and patients with lung cancer. Arch Intern Med 2006;166:326-31.
2. Suissa S, Dell'Aniello S, Ernst P. Long-term natural history of chronic obstructive pulmonary disease: Severe exacerbations and mortality. Thorax. 2012;67(11):957-63.
3. Weingaertner V, Scheve C, Gerdes V, et al. Breathlessness, functional status, distress, and palliative care needs over time in patients with advanced chronic obstructive pulmonary disease or lung cancer: A cohort study. J Pain Symptom Manage 2014;48:569-81.
4. Janssen DJ, Spruit MA, Uszko-Lencer NH, et al. Symptoms, comorbidities, and health care in advanced chronic obstructive pulmonary disease or chronic heart failure. J Palliat Med 2011;14:735-43.
5. Carvajalino S, Reigada C, Johnson MJ, et al. Symptom prevalence of patients with fibrotic interstitial lung disease: a systematic literature review. BMC Pulm Med. 2018 May 22;18(1):78.
6. Lozano R, Naghavi M, Foreman K, et al. Global and regional mortality from 235 causes of death for 20 age groups in 1990 and 2010: a systematic analysis for the Global Burden of Disease Study 2010. Lancet 2012;380(9859):2095-128.
7. Mathers CD, Loncar D. Projections of global mortality and burden of disease from 2002 to 2030. PLoS Med 2006;3(11):e442.
8. Raghu G, Collard HR, Egan JJ, et al. An official ATS/ERS/JRS/ALAT statement: idiopathic pulmonary fibrosis: evidence-based guidelines for diagnosis and management. Am J Respir Crit Care Med. 2011;183(6):788–824.
9. Nicholson AG, Colby TV, Du Bois RM, et al. The prognostic significance of the histologic pattern of interstitial pneumonia in patients presenting with the clinical entity of cryptogenic fibrosing alveolitis. Am J Respir Crit Care Med. 2000;162(6):2213–2217.
10. Ley B, Collard HR, King TE Jr. Clinical course and prediction of survival in idiopathic pulmonary fibrosis. Am J Respir Crit Care Med. 2011;183(4):431–440.
11. Meltzer EB, Noble PW. Idiopathic pulmonary fibrosis. Orphanet J Rare Dis. 2008 Mar 26;3:8. doi: 10.1186/1750-1172-3-8.
12. Collard HR, Ryerson CJ, Corte TJ, et al. Acute exacerbation of idiopathic pulmonary fibrosis. an international working group report. Am J Respir Crit Care Med. 2016;194(3):265–275.
13. Claessens MT, Lynn J, Zhong Z, et al. Dying with lung cancer or chronic obstructive pulmonary disease: insights from SUPPORT. Study to Understand Prognoses and Preferences for Outcomes and Risks of Treatments. J Am Geriatr Soc. 2000 May;48(S1):S146-53.
14. Habraken JM, ter Riet G, Gore JM, et al. Health-related quality of life in end-stage COPD and lung cancer patients. J Pain Symptom Manage 2009;37:973-81.
15. Pollok J, van Agteren JE, Esterman AJ, et al. Psychological therapies for the treatment of depression in chronic obstructive pulmonary disease. Cochrane Database Syst Rev. 2019 Mar 6;3:CD012347.
16. Wilson IB, Cleary PD. Linking clinical variables with health-related quality of life. A conceptual model of patient outcomes. JAMA. 1995 Jan 4;273(1):59-65.
17. Welte T, Miravitlles M, Hernandez P, et al. Efficacy and tolerability of budesonide/formoterol added to tiotropium in patients with chronic obstructive pulmonary disease. Am J Respir Crit Care Med 2009;180:741-50.
18. Aaron SD, Vandemheen KL, Fergusson D, et al. Tiotropium in combination with placebo, salmeterol, or fluticasone-salmeterol for treatment of chronic obstructive pulmonary disease: A randomized trial. Ann Intern Med 2007;146:545-55.
19. Raghu G, Rochwerg B, Zhang Y, et al. An official ATS/ERS/JRS/ALAT clinical practice guideline: treatment of idiopathic pulmonary fibrosis. an update of the 2011 clinical practice guideline. Am J Respir Crit Care Med. 2015;192(2):e3–e19.
20. Collard HR, Richeldi L, Kim DS, et al. Acute exacerbations in the INPULSIS trials of nintedanib in idiopathic pulmonary fibrosis. Eur Respir J. 2017;49(5):pii: 1601339.
21. Ley B, Swigris J, Day BM, et al. Pirfenidone reduces respiratory-related hospitalizations in idiopathic pulmonary fibrosis. Am J Respir Crit Care Med. 2017;196:756–61.
22. McCarthy B, Casey D, Devane D, et al. Pulmonary rehabilitation for chronic obstructive pulmonary disease. Cochrane Database Syst Rev. 2015 Feb 23;(2):CD003793.
23. Dowman L, Hill CJ, Holland AE. Pulmonary rehabilitation for interstitial lung disease. Cochrane Database Syst Rev. 2014 Oct 6;(10):CD006322.
24. Bausewein C, Booth S, Gysels M, et al. Non-pharmacological interventions for breathlessness in advanced stages of malignant and non-malignant diseases. Cochrane Database Syst Rev. 2008 Apr 16;(2):CD005623.
25. Galbraith S, Fagan P, Perkins P et al. Does the use of a handheld fan improve chronic dyspnea? A randomized, controlled, crossover trial. J Pain Symptom Manage. 2010 May;39(5):831-8.
26. Higginson IJ, Bausewein C, Reilly CC, et al. An integrated palliative and respiratory care service for patients with advanced disease and refractory breathlessness: a randomised controlled trial. Lancet Respir Med. 2014 Dec;2(12):979-87.
27. Ekström M, Nilsson F, Abernethy AA, et al. Effects of Opioids on Breathlessness and Exercise Capacity in Chronic Obstructive Pulmonary Disease. A Systematic Review. Ann Am Thorac Soc. 2015 Jul;12(7):1079-92.
28. Barnes H, McDonald J, Smallwood N, et al. Opioids for the palliation of refractory breathlessness in adults with advanced disease and terminal illness. Cochrane Database Syst Rev. 2016 Mar 31;3:CD011008.
29. Jennings AL, Davies AN, Higgins JP, et al. A systematic review of the use of opioids in the management of dyspnoea. Thorax 2002;57:939-44.
30. Ekström MP, Bornefalk-Hermansson A, Abernethy AP, et al. Safety of benzodiazepines and opioids in very severe respiratory disease: National prospective study. BMJ 2014;348:g445.
31. Simon ST, Higginson IJ, Booth S, et al. Benzodiazepines for the relief of breathlessness in advanced malignant and non-malignant diseases in adults. Cochrane Database Syst Rev. 2016 Oct 20;10:CD007354.
32. Albert RK, Au DH, Blackford AL, et al. Long-term oxygen treatment trial research group. A randomized trial of long-term oxygen for COPD with moderate desaturation. N Engl J Med. 2016;375(17):1617-27.
33. Continuous or nocturnal oxygen therapy in hypoxemic chronic obstructive lung disease: A clinical trial. Nocturnal Oxygen Therapy Trial Group. Ann Intern Med 1980;93:391-8.
34. Long term domiciliary oxygen therapy in chronic hypoxic cor pulmonale complicating chronic bronchitis and emphysema. Report of the Medical Research Council Working Party. Lancet 1981;1:681-6.
35. Visca D, Mori L, Tsipouri V, et al. Effect of ambulatory oxygen on quality of life for patients with fibrotic lung disease (AmbOx): a prospective, open-label, mixed-method, crossover randomized controlled trial. Lancet Respir Med. 2018;6(10):759–770.
36. Abernethy AP, McDonald CF, Frith PA et al. Effect of palliative oxygen versus room air in relief of breathlessness in patients with refractory dyspnoea: a double-blind, randomised controlled trial. Lancet. 2010 Sep 4;376(9743):784-93.
37. Ekström MP, Abernethy AP, Currow DC. The management of chronic breathlessness in patients with advanced and terminal illness. BMJ. 2015 Jan 2;350:g7617.
38. Osadnik CR, Tee VS, Carson-Chahhoud KV, et al. Non-invasive ventilation for the management of acute hypercapnic respiratory failure due to exacerbation of chronic obstructive pulmonary disease. Cochrane Database Syst Rev. 2017 Jul 13;7:CD004104.
39. Murphy PB, Rehal S, Arbane G, et al. Effect of Home Noninvasive Ventilation With Oxygen Therapy vs Oxygen Therapy Alone on Hospital Readmission or Death After an Acute COPD Exacerbation: A Randomized Clinical Trial. JAMA. 2017 Jun 6;317(21):2177-2186.
40. Faverio P, De Giacomi F, Sardella L et al. Management of acute respiratory failure in interstitial lung diseases: overview and clinical insights. BMC Pulm Med. 2018 May 15;18(1):70.
41. Koyauchi T, Hasegawa H, Kanata K, et al. Efficacy and Tolerability of High-Flow Nasal Cannula Oxygen Therapy for Hypoxemic Respiratory Failure in Patients with Interstitial Lung Disease with Do-Not-Intubate Orders: A Retrospective Single-Center Study. Respiration. 2018;96(4):323-329.
42. Medical guidelines for determining prognosis in selected non-cancer diseases. The National Hospice Organization. Hosp J. 1996;11(2):47-63.
43. Sinclair C, Auret KA, Evans SF et al. Advance care planning uptake among patients with severe lung disease: a randomised patient preference trial of a nurse-led, facilitated advance care planning intervention. BMJ Open. 2017 Feb 24;7(2):e013415.
44. Smallwood N, Moran T, Thompson M, et al. Integrated respiratory and palliative care leads to high levels of satisfaction: a survey of patients and carers. BMC Palliat Care. 2019 Jan 19;18(1):7.

MCHK CME Programme Self-assessment Questions

Please read the article entitled "Management of Advanced Airway and Lung Diseases" by Dr Hon-cheung FAN and complete the following self-assessment questions. Participants in the MCHK CME Programme will be awarded CME credit under the Programme for returning completed answer sheets via fax (2865 0345) or by mail to the Federation Secretariat on or before 31 July 2020 Answers to questions will be provided in the next issue of The Hong Kong Medical Diary.

Questions 1-10: Please answer T (true) or F (false)

1. **Advanced airway and lung diseases are not curable, have progressive courses and are associated with high symptom burden, psycho-spiritual distress and impaired functional status.**
2. **All patients facing life-limiting conditions should receive timely holistic palliative care to address their physical, psychosocial and spiritual needs.**
3. **The disease trajectory in COPD is usually marked by a slow decline in health status without acute exacerbation resulting in hospitalisation and associated with high mortality.**
4. **Advanced COPD patients have better function & QOL when compared with that of advanced lung cancer patients.**
5. **International guidelines do not support the use of NIV to dyspnoeic patients for palliation in the setting of a terminal illness.**
6. **The usefulness of supplemental oxygen for non-hypoxaemic patients is well documented.**
7. **Nebulised opioid is effective in relieving breathlessness in COPD.**
8. **The opioid dose should be titrated to the lowest effective dose that reduces the dyspnoea and minimises the adverse effects of opioid with regular monitoring.**
9. **Advance care planning is an important integral component of care for the patient with advanced COPD.**
10. **The importance of collaboration model between palliative and respiratory medicine has been recognised in international guidelines.**

ANSWER SHEET FOR JULY 2020

Please return the completed answer sheet to the Federation Secretariat on or before 31 July 2020 for documentation. 1 CME point will be awarded for answering the MCHK CME programme (for non-specialists) self-assessment questions.

Management of Advanced Airway and Lung Diseases

Dr Hon-cheung FAN

MBBS, FRCP(Edin), FHKCP, FHKAM(Medicine)
Consultant, Department of Medicine & Geriatrics, Ruttonjee Hospital

1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 ☐

Name (block letters):_____ HKMA No.: _____ CDSHK No.: _____

HKID No.: __ __ - __ __ __ __ X X (X) HKDU No.: _____ HKAM No.: _____

Contact Tel No.:_____ MCHK No. / DCHK No.: _____(must fill in)

Answers to June 2020 Issue

Pico-second Laser – Is it the Answer?

1. F 2. T 3. F 4. T 5. T 6. F 7. F 8. F 9. F 10. T

Dermatology Quiz

Dr Chi-keung KWAN
MBBS(HK), MRCP(UK), FRCP(Lond, Glasg), Dip Derm(Glasg), PDipID(HK), FHKCP, FHKAM(Medicine)
Specialist in Dermatology and Venereology

Dr Chi-keung KWAN

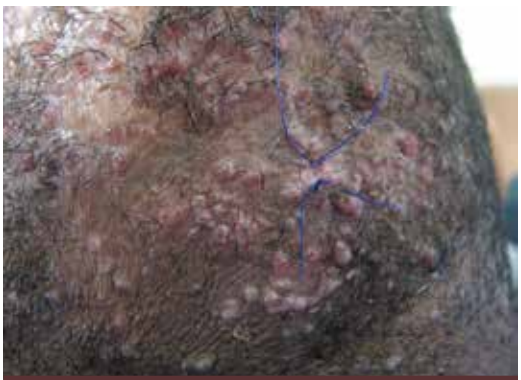


Fig.1: Multiple erythematous papules on scalp.

This 44-year-old man complained about hair loss and baldness, especially over the occipital region for 3-4 years. Although it was somewhat irritating with a tingling sensation, the lesions were not painful nor itchy. Physical examination revealed multiple erythematous papules, occasionally pustules with scarring alopecia on the occipital region of the scalp. (Fig. 1).

Questions

1. What is the diagnosis of the skin lesion?
2. What investigations will you order?
3. How do you manage this gentleman?

(See P.44 for answers)

Supportive Care and Palliation for Advanced Renal Failure

Dr Agnes Shin-man CHOY
MBChB (CUHK), MRCP (UK), FHKCP, FHKAM (Medicine)
Specialist in Nephrology
Associate Consultant, Department of Medicine and Therapeutics, Prince of Wales Hospital
Honorary Clinical Assistant Professor, The Chinese University of Hong Kong

Dr Alice Ka-wai MOK
MBChB (CUHK), MRCP (UK), FHKCP, FHKAM (Medicine)
Specialist in Palliative Medicine
Associate Consultant, Palliative Care Unit, Shatin Hospital
Honorary Clinical Associate Professor, Department of Medicine and Therapeutics, The Chinese University of Hong Kong


Dr Agnes Shin-man CHOY Dr Alice Ka-wai MOK

INTRODUCTION

Renal supportive care is a blooming subspecialty in the field of nephrology. It involves the application of palliative medicine principles and practices to patients with chronic kidney disease that can be applied to all patients with advanced kidney disease regardless of the underlying cause or dialysis modality. The main goal of renal supportive care is to alleviate patients' suffering throughout the trajectory of illness via the treatment of symptoms, empathic communication and support for psychosocial distress.

Patients who reach advanced stages of chronic kidney disease (CKD) often face decisions about whether or not to initiate treatment with maintenance dialysis, and if so, when. Although dialysis is commonly regarded as a life-prolonging therapy for patients with advanced CKD, the potential benefits of dialysis can be outweighed by the potential burdens and complications of treatment, especially at older ages. In the past two decades, there was growing evidence to suggest that patients with advanced age or comorbidities experience high mortality rates and high symptom burdens on dialysis. Patients who start dialysis at age 75 have on average 1-year and 3-year adjusted survival of 63% and 33% respectively. In addition, some observational studies showed that there is no survival benefit to start dialysis for patients older than 80 years of age as compared with active medical management[1-4].

Renal supportive care includes, but not limited to, end-of-life care. It involves numerous areas of focus that are applicable to patients across the illness spectrum of advanced CKD. Apart from managing patient's physical symptoms, physicians also need to explore patient's awareness on their disease prognosis. Physicians also need to pay extra attention to the non-physical demensions of patient's suffering and to elicit their preferences on managing advanced CKD without dialysis. Alternatively this can be called maximum conservative management or conservative care. Renal supportive care should include primary palliative care provided by nephrology team, as well as co-management with the palliative care team, especially for those patients with complex distress. Collaboration between nephrology team and the palliative care team can offer an additional layer of support to patients and families. The team may include physicians, nurses, social workers, chaplains and dietitians[5].

THE ROLE OF NEPHROLOGISTS

Patients with glomerular filtration rates (GFR) below 30 ml/min/1.73m^2 should be followed by nephrologist as the metabolic alterations secondary to CKD become noticeable at this level of renal function. The progression of CKD leads to the deterioration of metabolic parameters and consequently to the onset of symptoms. Interventions aimed at correcting the metabolic disturbance may reduce symptoms and improve the quality of life of patients who choose not to initiate dialysis[6].

Decision Making

Due to the ageing population worldwide, there are increasing numbers of elderly patients reaching end-stage renal disease. Age itself should not be a barrier to renal replacement therapy, however, increasing age commonly coincides with increasing frailty and comorbidities. As mentioned before, the survival advantage is lost for patients initiating dialysis at an older age[1-4].

Dialysis is usually considered as GFR falls to below 20ml/min/1.73m^2 as time needs to be spent discussing with patients and their carers about modalities of renal replacement therapy. With the peritoneal dialysis (PD) first policy set up in 1985 in Hong Kong, all patients requiring dialysis therapy are treated with PD first unless medical contraindications exist. Patients can choose to have hemodialysis (HD) first according to their personal preference, but they will have to bear the costs[7]. The decision about whether to start dialysis and which modality to choose should be a joint decision with the patients and their families or carers. The role of a nephrologist is to provide adequate information on disease prognosis, benefits and risks of treatment options available, and to facilitate the patient to express his/her values and preferences for treatment. Nephrology team should also encourage the family to listen to the patient's concerns and to elicit the views from family members so as to resolve the disagreement and to work towards a consensus for an agreed care plan.

If a patient with advanced CKD decided not for dialysis and opted for conservative management, the aims of care include managing fluid balance, anaemia, bone health and blood pressure as well as managing symptoms so as to maximise the quality of life of patients. Patients with high symptoms burden should involve joint management with the palliative care team[8].

MIRCERA®
methoxy polyethylene glycol-epoetin beta

Continuous activity. Targeted stability.

Truly once monthly[1]

Superior Hb stability[2]

Five dosages to suit every patient[3]

Improved patient care and quality of life[4,5]

References:

1. Roger SD, Locatelli F, Woitas RP, *et al.* C.E.R.A. once every 4 weeks corrects anaemia and maintains haemoglobin in patients with chronic kidney disease not on dialysis. *Nephrol Dial Transplant* 2011;26(12):3980-3986. **2.** Carrera F, Lok CE, de Francisco A, *et al.* Maintenance treatment of renal anaemia in haemodialysis patients with methoxy polyethylene glycol-epoetin beta versus darbepoetin alfa administered monthly: a randomized comparative trial. *Nephrol Dial Transplant.* 2010;25(12):4009-4017. **3.** MIRCERA® Hong Kong Prescribing Information. **4.** Klinger M, Alon M, Vargemezis V, *et al.* Efficacy of intravenous methoxy polyethylene glycol-epoetin beta administered every 2 weeks compared with epoetin administered 3 times weekly in patients treated by hemodialysis or peritoneal dialysis: a randomized trial. *Am J Kidney Dis.* 2007;50(6):989-1000. **5.** Saueressig U, Kwan JT, De Cock E, *et al.* Healthcare resource utilization for anemia management: current practice with erythropoiesis-stimulating agents and the impact of converting to once-monthly C.E.R.A. *Blood Purif.* 2008;26(6):537-546.

Abbreviated Prescribing Information - Mircera (methoxy polyethylene glycol-epoetin beta)

Indications: Treatment of anaemia associated with chronic kidney disease (CKD).

Dosage & administration: Can be administered subcutaneously or intravenously in order to increase haemoglobin(Hb) to not greater than 12g/dl (7.45mmol/l). Subcutaneous use is preferable in patients who are not receiving haemodialysis to avoid puncture of peripheral veins. Hb variability should be addressed through dose management, with consideration for the Hb target range of 10g/dl (6.12mmol/l) to 12g/dl (7.45mmol/l). A rise in Hb of greater than 2g/dl (1.24mmol/l) over a four week period should be avoided. Recommend to monitor Hb level every 2 weeks until stabilized and periodically thereafter. Patients not currently treated with an ESA: 1.2 mcg/kg every month or 0.6 mcg/kg every 2 weeks in order to increase the Hb level to > 10 g/dl (6.21 mmol/l). May increase dose by approximately 25% of previous dose if Hb rise < 1.0 g/dl (0.621 mmol/l) over 1 month. Further increases of approximately 25% may be made at monthly intervals until the individual target Hb level is obtained. Patients treated once every two weeks whose Hb level is above 10 g/dl (6.21 mmol/l) may receive Mircera administered once monthly using the dose equal to twice the previous once every 2 weeks dose. Patients currently treated with an ESA: Patients currently treated with and ESA can be switched to Mircera administered once a month. Starting dose of Mircera is based on previous weekly dose of darbepoetin alfa or epoetin at the time of substitution. Start the first injection at the next scheduled dose of previously administered darbepoetin alfa or epoetin. Monthly Mircera dose is 120 mcg if the previous weekly dose of darbepoetin alfa or epoetin is < 40 mcg/wk or <2000 IU/wk respectively. Monthly Mircera dose is 200 mcg if the previous weekly dose of darbepoetin alfa or epoetin is 40-80 mcg/wk or 2000-16000 IU/wk respectively. Monthly Mircera dose is 360 mcg if the previous weekly dose of darbepoetin alfa or epoetin is > 80 mcg/wk or > 16000 IU/wk respectively. If dose adjustment is required to maintain the target Hb concentration above 10 g/dl (6.21 mmol/l), increase the monthly dose by approximately 25%. For both situations: If rate of rise in Hb is greater than 2 g/dl (1.24 mmol/l) in 1 month or if the Hb level is increasing and approaching 12 g/dl (7.45 mmol/l), reduce dose by approximately 25%. If Hb level continues to rise, interrupt therapy until Hb level begins to decrease, at which point therapy should be restarted at a dose approximately 25% below the previously administered does. Dose adjustments should not be made more frequently than once a month.

Contraindications: Patients with uncontrolled hypertension or known hypersensitivity to the active substance or to any of the excipients.

Warnings & Precautions: Evaluate iron status for all patients prior to and during treatment and administer supplementary iron therapy if necessary to ensure effective erythropoiesis. Consider diagnosis of Pure Red Cell Aplasia (PRCA) if all the possible causative factors excluded. Discontinue Mircera and do not switch to another ESA in case PRCA is diagnosed. PRCA caused by anti-erythropoietin antibodies has been reported in association with ESAs and these antibodies have been shown to cross-react with all ESAs. Epoetins are not approved in the management of anaemia associated with hepatitis C. Adequately control blood pressure in all patients before, at initiation of, and during treatment with Mircera. Consider dose reduction or withheld treatment if high blood pressure is difficult to control by drug treatment or dietary measures. Withdraw Mircera immediately and an alternative treatment considered if signs and symptoms of skin reactions appear. Discontinue Mircera if SCARs has developed and ESA must not be restarted. In patients with chronic kidney disease, maintenance Hb concentration should not exceed the upper limit of the target haemoglobin concentration. As with all growth factors, there is a concern that ESAs could stimulate the growth of any type of malignancy. Caution in patients with haemoglobinopathies, seizures or with platelet levels > 500 x 109/l. Misuse of Mircera may lead to an excessive increase in Hb. This may be associated with life-threatening cardiovascular complications.

Drug Interactions: No interaction studies have been performed. There is no evidence that MIRCERA alters the metabolism of other medicinal products.

Use in Pregnancy & Lactation: There are no adequate data from the use of Mircera in pregnant women and caution should be exercised when prescribing to pregnant women. It is unknown whether Mircera is excreted in human breast milk. Risk-benefit ratio should be considered when use in nursing mothers.

Undesirable effects: Common: hypertension. Uncommon: vascular access thrombosis, headache.Rare: hypersensitivity, hypertensive encephalopathy, rash (macular, papular), hot flush.

Date of preparation: Dec 2017

Full prescribing information should be viewed prior to prescribing.

Roche Hong Kong Limited
22/F, FTLife Tower, 18 Sheung Yuet Road, Kowloon Bay, Hong Kong
Tel : +852 2723 2832

PM-HK-0733-03-2019
Valid until 23/3/2021 or until change is required in accordance with the regulatory requirements, whichever comes first.

THE ROLE OF PALLIATIVE CARE TEAM

Palliative care is the holistic care of the patient and family facing a life-limiting disease, encompassing the physical, psychological, spiritual, and social aspects of support through the illness journey. It is about the relief of sufferings, enhancing the quality of life, respecting patient's preferences, preparing for their end of life and supporting caregivers through to the bereavement. The palliative care team is the multi-disciplinary team dedicated to this field of care, comprising palliative care doctors and nurses, allied health professionals, social workers, clinical psychologists, and pastoral care workers. The team has the specialised skills in addressing these patients' sufferings, facilitating advance care planning, and providing counselling for their emotional stress and coping. Palliative care services are provided in various modalities, including in-patient care, out-patient clinics, homecare, daycare, and phone consultations.

With the current most-widely adopted model of palliative care, disease-modifying and palliative treatment are provided over the continuum of the disease trajectory, each assuming a proportion of care according to the needs of the patient. The proportion of palliative care usually increases with time until when the end of life approaches, it becomes the whole core of care for the patient and family, prioritising quality of life and allowing the loosening of futile restrictions such as tight diabetic control. While the rate of CKD progression can be highly variable depending on factors such as comorbidities, it is important that the integration of palliative care begin early and continue to be revisited throughout the course of the disease. With this in mind, renal supportive care is best provided in collaboration between the nephrology and palliative care teams. In Hong Kong, a territory-wide program of palliative care for end-stage renal failure patients was started in 2010. Under this program, patients suffering from advanced renal failure and who preferred not to receive renal replacement therapy are entitled to palliative care team referral.

SYMPTOMS MANAGEMENT

Patients with advanced CKD often experience a high frequency of physical and psychological symptoms, though the frequency and intensity of symptoms vary significantly from one individual to another. Symptoms of CKD may be directly related to uremia or complications of CKD, or they can be caused by underlying comorbidities. In general, the approach to symptoms management should involve the evaluation for causes, reversible factors and the level of distress or dysfunction caused by symptoms. Intervention can be either pharmacological or non-pharmacological, while the limitation of therapy should be acknowledged. Patients sometimes may underreport symptoms unless being asked explicitly, and there are robust data that regular assessments with validated tools can reduce symptom burden over time. Table 1 listed out the possible options for assessment tools[5].

Table 1: Symptom and Function assessment tools

Edmonton Symptom Assessment System Revised Renal (ESAS-r: Renal) (https://www.albertahealthservices.ca/frm-20351.pdf)
Integrated Palliative Care Outcome Scale Renal (IPOS-Renal) (https://pos-pal.org/maix/ipos-renal-in-english.php)
Karnofsky Performance Status (KPS) score (http://www.npcrc.org/files/news/karnofsky_performance_scale.pdf)
Eastern Cooperative Oncology Group (ECOG) (https://ecog-acrin.org/resources/ecog-performance-status)

Fatigue, skin pruritus, nausea and vomiting, oedema, dyspnoea, muscles cramping, sleep disturbance, pain and depression are among the frequently reported symptoms in advanced CKD[10, 18-19]. These symptoms can be prolonged and adversely affect patient's quality of life, and hence timely effective management of them is crucial.

Uremic Pruritus

Pruritus is one of the common distressing symptoms in CKD, and is associated with other symptoms such as poor sleep and depression[9]. A study of 179 advanced CKD patients in Hong Kong found that pruritus was among the top common symptoms, with a prevalence of 65.7% in the dialysis group and 57.8% in the non-dialysis group[10]. Presentation of pruritus can be variable. The itch is often generalised, affecting large and symmetrical areas of the body, with many describing its presence as being all-day long but worse during night time. Unfortunately, the pathophysiology of uremic pruritus is still poorly understood, and the symptom is difficult to be eliminated. Factors including hyperparathyroidism, xerosis, hyperphosphatemia, elevated magnesium, iron deficiency anaemia can be associated with the occurrence of uremic pruritus[11-13].

There is limited evidence to support any strong recommendations for the treatment of uremic pruritus. As a general measure, adequate skin hydration is the basis of management. Emollients should be applied generously. Hot baths and soaps are to be avoided especially for those prone to xerosis. Topical capsaicin cream has been used with effects in some patients[14] but mostly for localised areas of pruritus and with side effects of burning sensation upon application. Dietary phosphate restriction and medications, including phosphate binders and vitamin D may be indicated to decrease phosphate and parathyroid hormone levels.

Of all systemic therapies targeting uremic pruritus, gabapentin has been supported most for its effectiveness. In a group of 34 patients with advanced CKD being managed conservatively, Cheikh Hassan et al[15] showed that pruritus was reduced with a median daily dose of 100mg. Yet nearly half of the patients reported side effects such as drowsiness, leading to a 17% rate of discontinuation. On the other hand, despite being commonly prescribed for itchiness, antihistamines lack strong evidence on their efficacy for uremic pruritus, and any observed benefits may be achieved partially via their sedating effects. Other oral medications, including naltrexone, thalidomide, sertraline and montelukast have been used with variable success. For patients with uremic pruritus refractory to the above measures, UVB

NESP®
Darbepoetin alfa

Offers the Flexibility for your treatment

From Once Weekly to Truly Once per 4 Weeks[1-5]

Proven efficacy across the CKD spectrum[1-4]

References

1. Kubota M., Hiramatsu M., Yamakawa M., Fukuhara S., Morita S., Iwasaki M., Akizawa T., KRN321 SCA10 study group. Darbepoetin alfa (KRN321) is safe and effective when administered subcutaneously once every 2 or 4 weeks to patients on peritoneal dialysis in Japan. Clin Exp Nephrol. 2011; 15:884-892 **2.** Toto RD, Pichette V, Navarro J, et al. Darbepoetin alfa effectively treats anemia in patients with chronic kidney disease with de novo every-other-week administration. Am J Nephrol. 2004; 24:453-460 **3.** Agarwal AK, Silver MR, Reed JE, et al. An open-label study of darbepoetin alfa administered once monthly for the maintenance of haemoglobin concentrations in patients with chronic kidney disease not receiving dialysis. J Int. Med. 2006; 260:577-585 **4.** Carrera F, Oliveira L, Maia P, et al. The efficacy of intravenous darbepoetin alfa administered once every 2 weeks in chronic kidney disease patients on haemodialysis. Nephrol Dial Transplant. 2006; 21:2846-2850 **5.** NESP Product package insert

Please refer to the package insert when using a drug product.

Abbreviated Package Insert of NESP

Composition: Darbepoetin α; **Indication:** Renal anaemia; **Dosage and Administration:** Haemodialysis patients Initially 20 mcg single IV inj once wkly. When switching from erythropoietin prep or epoetin β, initially 15-60 mcg single IV inj once wkly. Maintenance dose: 15-60 mcg single IV inj once wkly. If alleviation of anaemia is maintained by once wkly inj. dose can be changed to 2-fold of the initial dose once every 2 wk. Max: 180 mcg single inj. Peritoneal dialysis patients & patients w/ chronic kidney disease not on dialysis Initially 30 mcg single SC or IV inj once every 2 wk. When switching from erythropoietin prep or epoetin β, initially 30-120 mcg single SC or IV inj once every 2 wk. Maintenance dose: 30-120 mcg single SC or IV inj once every 2 wk. If alleviation of anaemia is maintained by once every 2 wk inj. dose can be changed to 2-fold of the initial dose once every 4 wk. Max: 180 mcg single inj.; **Contraindication:** Hypersensitivity; **Precautions:** Patients w/ MI, pulmonary infarction, cerebral infarction or those w/ history of these conditions who may experience thromboembolism; HTN; history of hypersensitivity; allergic predisposition. Should not be used in patients w/ other types of anaemia. Assess patients for risk of reactions eg. shock. Monitor Hb conc or haematocrit level at regular intervals. Hypertensive encephalopathy; pure red cell aplasia; hyperkalaemia. Fe should be administered w/ Fe deficiency. Shunt occlusion or residual blood in hemodialyzers. Blistering & skin exfoliation reactions. Concomitant use w/ erythropoiesis stimulating agents. Pregnancy & lactation. Children. Elderly. Patients w/ chronic kidney disease not on dialysis: Closely monitor blood fluid & electrolyte balance, renal function & BP; serum creatinine conc & CrCl.; **Clinically significant adverse reactions:** Increased BP, shunt thrombosis/occlusion, headache, malaise; **P/P:** Inj (pre-filled syringe) 20 mcg/0.5 mL. 40 mcg/0.5 mL. 120 mcg/0.5 mL. 180 mcg/0.5 mL.

Please refer to the full prescribing information before prescribing. Further information is available upon request

KYOWA KIRIN

Kyowa Kirin Hong Kong Co., Limited
Unit B, 13/F., 169 Electric Road,
North Point, Hong Kong
Tel.: (852) 2956-0828
https://www.kyowakirin.com/hk/

KKHK-NESP-3-052020; Date of Production: 052020

irradiation therapy has demonstrated efficacy and can be considered[16].

Anorexia, Nausea and Vomiting

Anorexia, nausea and vomiting are uremia-induced symptoms that worsen with the progression of CKD. Uremic toxins exert their effects primarily on the chemoreceptor trigger zone causing nausea and vomiting. Therefore, the mainstay of treatment to reduce nausea and vomiting is the use of dopamine antagonists, such as haloperidol or chlorpromazine, which are known to act on this trigger zone. Metoclopramide, with its prokinetic effect, can benefit those with gastroparesis. Dosages must be adjusted for renal impairment, and side effects such as extrapyramidal reactions should be monitored closely.

Besides nausea and vomiting, anorexia may be further aggravated by oral conditions such as dry mouth, poor dental hygiene, candidiasis etc. These should be examined carefully and treated accordingly. Enhanced taste variety, food presentation, and eating environment are some of the non-pharmacological ways that family can help in coping with the condition.

Fatigue

Fatigue is consistently shown as the most common symptom in advanced CKD. It affected more than 70% of the patients, and the figure further increased to >80% during the last months of life among those without dialysis[10, 17-18]. Fatigue is a complex symptom often with multidimensional causes. Amongst them, anaemia, insomnia, malnutrition, depression and medication side-effects can all contribute to the development of it. Hence these should be assessed and managed appropriately when treating patients with the complaint of fatigue. Apart from medical therapy, patients should be encouraged to maintain daily activities and exercises if possible.

Anaemia in CKD

Patients with advanced CKD often experience fatigue from profound anaemia because erythropoietin is synthesised by the normal kidneys. Untreated anaemia is also associated with increased all-cause and cardiovascular mortalities[19]. Before the era of erythropoiesis-stimulating agents (ESA), anaemia in CKD was managed with regular blood transfusions and iron replacement, carrying the risks of fluid or iron overload and adding burden to the healthcare system because of hospitalisation needs. ESA is a recombinant human erythropoietin that acts to stimulate receptors on erythroid progenitor cells to trigger red cell maturation. Abundant studies on dialysis and pre-dialysis patients found that ESA was beneficial in terms of improving fatigue, well-being, appetite, sexual function, socialising, and sleep. ESA is now a recommended treatment for anaemia in CKD according to the Kidney Disease: Improving Global Outcomes (KDIGO) guideline[20]. For patients under palliative care, a local study demonstrated that ESA treatment was effective in raising the haemoglobin level at 3 and 6 months of injection, with corresponding significant reductions in fatigue score and hospitalisation rate[21]. A more recent study, in addition, suggested that ESA benefits patients under renal palliative care in lowering their needs for shospitalisation and blood transfusion by 2- and 3-fold reductions respectively[22]. ESA therapy is, therefore, a treatment option to be considered and individually tailored in the management of patients with CKD who opted not for dialysis.

CONCLUSIONS

Kidney supportive care is of growing importance worldwide. The main aim of it is to reduce patient's suffering through symptoms management, communication and support for psychosocial distress. It involves collaboration between nephrology team and the palliative care team via multi-disciplinary approach. End-of-life care and discussion of advanced care planning should be facilitated as an integral part of kidney supportive care.

References

1. Jassal SV, Chiu E, Hiadunewich M. Loss of independence in patients starting dialysis at 80 years of age or older. N Engl J Med. 2009; 361 (16): 1612-1613.
2. Montez-Rath ME, Zheng Y, Tamura MK et al. Hospitalizations and nursing facility stays during the transition from CKD to ESRD on dialysis: an observational study. J Gen Intern Med. 2017; 32(11): 1220-1227.
3. Murtagh FE, Marsh JE, Donohoe P et al. Dialysis or not? A comparative survival study of patients over 75 years with chronic kidney disease stage 5. Nephrol Dial Transplant. 2007; 22(7): 1955-1962.
4. Verbeme WR, Geers AB, Jellema WT et al. Comparative survival among older adults with advanced kidney disease managed conservatively versus with dialysis. Clin J Am Soc Nephrol. 2016; 11(4): 633-640.
5. Samantha LG, Jennifer SS, Holly MK. Kidney supportive care: core curriculum 2020. Am J Kidney Dis. Article in press. Doi: 10.1053/ j.ajkd.2019.10.016.
6. Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group. KDIGO 2012 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease. Kidney Int. Suppl 2013; 3:136-50.
7. Li PK, Chow KM. Peritoneal dialysis-first policy made successful: perspectives and actions. Am J Kidney Dis. 2013; 62:993-1005.
8. O'Connor NR, Kumar P. Conservative management of end-stage renal disease without dialysis: a systematic review. J Palliat Med. 2012 Feb; 15(2): 228-35.
9. Pisoni RL, Wikstrom B, Elder SJ, et al. Pruritus in haemodialysis patients: International results from the Dialysis Outcomes and Practice Patterns Study (DOPSS). Nephrol Dial Transplant. 2006; 21:3495-505.
10. Yong DS, Kwok AO, Wong DM, et al. Symptom burden and quality of life in end-stae renal disease: a study of 179 patients on dialysis and palliative care. Palliat Med. 2009; 23:111-9.
11. Chou FF, Ho JC, Huang SC, et al. A study on pruritus after parathyroidectomy for secondary hyperparathyroidism. J Am Coll Surg. 2000; 190:65-70.
12. Blachley JD, Blankenship DM, Menter A, et al. Uremic Pruritus: skin divalent ion content and response to ultraviolet phototherapy. Am J Kidney Dis. 1985; 5:237-41.
13. Narita I, Alchi B, Omori K, et al. Etiology and prognostic significance of severe uremic pruritus in chronic hemodialysis patients. Kidney Int. 2006; 69:1626-32.
14. Breneman DL, Cardone JS, Blumsack RF, et al. Topical capsaicin for treatment of hemodialysis-related pruritus. J Am Acad Dermatol. 1992; 26:91-4.
15. Cheikh Hassan HI, Brennan F, Collett G, et al. Efficacy and safety of gabapentin for uremic pruritus and restless legs syndrome in conservatively managed patients with chronic kidney disease. J Pain Symptom Manage. 2015; 49:782-9.
16. Sherjeena PB, Binitha MP, Rajan U, et al. A controlled trial of narrowband ultraviolet B phototherapy for the treatment of uremic pruritus. Indian J Dermatol Venereol Leprol. 2017; 83:247-49.
17. Murtagh FE, Addinton-Hall JM, Edmonds PM, et al. Symptoms in advanced renal disease: a cross-sectional survey of symptom prevalence in stage 5 chronic kidney disease managed without dialysis. J Palliat Med. 2007; 10:1266-76.
18. Murtagh FE, Addington-Hall J, Edmonds P, et al. Symptoms in the month before death for stage 5 chronic kidney disease patients managed without dialysis. J Pain Symptom Manage. 2010; 40:342-52.
19. Zoppini G, Targher G, Chonchol M, et al. Anaemia, independent of chronic kidney disease, predicts all-cause and cardiovascular mortality in type 2 diabetic patients. Atherosclerosis. 2010; 210(2):575-580.
20. KDIGO Anemia Work Group. KDIGO Clinical Practice Guideline for Anemia in Chronic Kidney Disease. Kidney int. suppl. 2012; 2:279-335.
21. Chan KY, Li CW, Wong H, et al. Effect of erythropoiesis-stimulating agents on hemoglobin level, fatigue and hospitalization rate in renal palliative care patients. Int Urol Nephrol. 2014; 46(3):653-57.
22. Chow KM, Szeto CC, Choy ASM, et al. Effect of Erythropoiesis-Stimulating Agent Therapy in Patients Receiving Palliative Care of Chronic Kidney Disease. Am J Hosp Palliat Care. 2019; 36(8):718-721.

Palliative Treatment for Metastatic Cancers: Recent Advances

Dr Inda S. SOONG

MB.Ch.B (CUHK), FRCR, FHKCR, FHKAM (Radiology), MSc in Palliative Medicine (Cardiff), MPH (HK)

Specialist in Clinical Oncology
Consultant Oncologist, Department of Clinical Oncology, Pamela Youde Nethersole Eastern Hospital
Honorary Clinical Associate Professor, Li Ka Shing Faculty of Medicine, The University of Hong Kong
Honorary Clinical Associate Professor, Faculty of Medicine, The Chinese University of Hong Kong

Dr Inda S. SOONG

THE CHANGING ONCOLOGICAL LANDSCAPE FOR CANCER

Cancer is a leading cause of death worldwide, accounting for an estimated 9.6 million deaths in 2018 and being the top killer in Hong Kong. In Hong Kong, the top 5 most common cancers have already accounted for over 50% of the cancer mortality (Table 1 and Table 2)[1,2]. Over the past 50 years, the advancement in cancer imaging, cancer biology, and cancer therapies have markedly altered the cancer illness trajectory with better survival than ever. The strategic integration of palliative medicine to oncology can improve patient outcomes along with this rapidly evolving landscape of oncology care.

Table 1: The Most Common Cancers (Summarised from WHO & HKCR[1,2])

Most Common Cancers Worldwide (2018)			Most Common Cancers in Hong Kong (2017)		
Rank	**Site**	**Number**	**Rank**	**Site**	**Number**
1	Lung	2.09 million	1	Colorectal	5,635
2	Breast	2.09 million	2	Lung	5,178
3	Colorectal	1.80 million	3	Breast	4,391
4	Prostate	1.28 million	4	Prostate	2,240
5	Skin cancer (non-melanoma)	1.04 million	5	Liver	1,834
			6	Stomach	1,314
			7	Non-melanoma skin	1,101
6	Stomach	1.03 million			

Table 2: The Most Common Cancer Cause of Deaths (Summarised from WHO & HKCR [1,2])

Most Common Cancer Cause of Deaths Worldwide (2018) (total cancer mortality: n= ~9.6 million)			Most Common Cancer Cause of Deaths in Hong Kong (2017) (total cancer mortality: n=14354)		
Rank	**Site**	**Number**	**Rank**	**Site**	**Number**
1	Lung	1.76 million	1	Lung	3,890
2	Colorectal	862,000	2	Colorectal	2,138
3	Stomach	783,000	3	Liver	1,552
4	Liver	782,000	4	Breast	724
5	Breast	627,000	5	Pancreas	690
			6	Stomach	682
			7	Prostate	443

PARADIGM SHIFTS TO PRECISION ONCOLOGY MEDICINE & CANCER IMMUNOTHERAPY

In 1949 after the World War II, nitrogen mustard was approved by the US Food and Drug Administration (FDA) for treating Hodgkin's lymphoma[3]. After this first FDA-approved chemotherapeutic agent, the blooming of chemotherapy continued until the late 1990s[4,5]. As we all know, cytotoxic chemotherapy cannot achieve cure in solid cancers, is limited by a narrow therapeutic index, non-selective toxicities to both the cancer and normal actively dividing cells due to its non-selective DNA damage, and acquired resistance.

In 1997, rituximab, a molecularly targeted cancer drug, was approved by the US FDA to treat patients with B-cell non-Hodgkin's lymphoma[6]. It marked the beginning of "Precision Medicine". Most biologic targeted therapy drugs are either small-molecule inhibitors (usually protein tyrosine kinases), which end with the stem "-ib", or monoclonal antibodies which can be recognised by the stem "-mab". Unlike the cytotoxic chemotherapy that kills both cancer and normal cells that divide rapidly, targeted therapies exert cancer-killing effect by acting against the altered key oncogene or tumor suppressor gene driven biochemical pathways or tumor-specific mutant proteins (Fig. 1) for tumorigenesis[7,8]. As such, the "actionable" mutational profile of the tumor can be a key guidepost for the therapy selection, hence allowing the patients to be offered a "Personalised" or "Tumour-specific" therapy. Because of the specific target-based mechanism of action, the toxicity profile of targeted therapies is distinctly different from those seen with conventional chemotherapy. There is an absence of the high risk of myelosuppression, diarrhoea, or alopecia, which are common in cytotoxic chemotherapy. The side effect profile varies among the targeted therapies along with their different action pathways. Common ones include skin rash, tiredness, headache, joint pain, nausea, diarrhoea, bleeding, bruising, and high blood pressure, which are usually well-tolerated and manageable.

Targeted therapy has successfully changed the illness trajectory of cancer, turning metastatic diseases from nearly invariable early fatality, to chronic diseases with prolonged progression-free survival (PFS) and overall survival (OS)[9]. As a result, it has been the standard therapy of choice for cancers that carry the specific genetic profile as the drug target (Table 3)[10,11].

In 2010, sipuleucel-T was approved by the US FDA for the treatment of metastatic castration-resistant prostate cancer. Sipuleucel-T was the first FDA-approved immunotherapy, that can induce an immune response targeting against PAP, an antigen expressed in most prostate cancers[12]. Since then, cancer immunotherapy has established itself to be another pillar of cancer

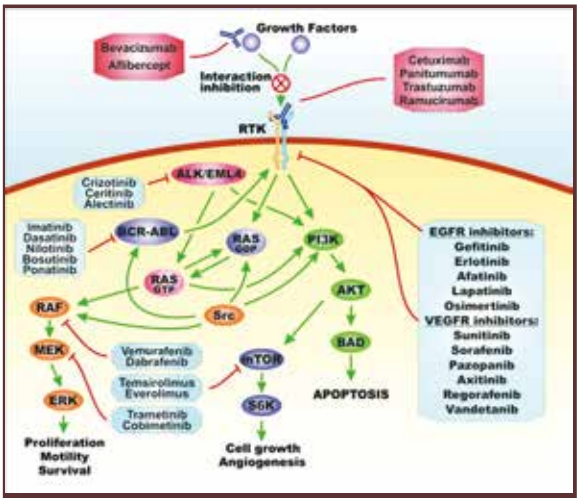


Fig. 1: Molecular Targets of Targeted Therapy
Protein kinase inhibitors are divided into EGFR inhibitors, VEGFR inhibitors, BCR/ABL inhibitors, ALK/EML4 inhibitors, RAF inhibitors, MEK inhibitors, and mTOR inhibitors. Monoclonal antibodies are directed toward extracellular growth factors or extracellular receptor tyrosine kinase.
Abbreviations: ABL, Abelson murine leukaemia viral oncogene homolog; AKT, protein kinase B; ALK, anaplastic lymphoma kinase; BAD, Bcl-2-associated death promoter; BCR, breakpoint cluster region; EGFR, epidermal growth factor receptor; EML4, echinoderm microtubule-associated protein-like 4; ERK, extracellular signal-regulated kinases; MEK, mitogen-activated protein kinase; mTOR, mammalian target of rapamycin; PI3K, phosphoinositide 3-kinase; RAF, rapidly accelerated fibrosarcoma kinase; RAS, RAS proto-oncogene GTPase; RTK, receptor tyrosine kinase; S6K, S6 kinase; src, proto-oncogene tyrosine-protein kinase Src; VEGFR, vascular endothelial growth factor receptor.
(Exerpted from Falzone L et al[8])

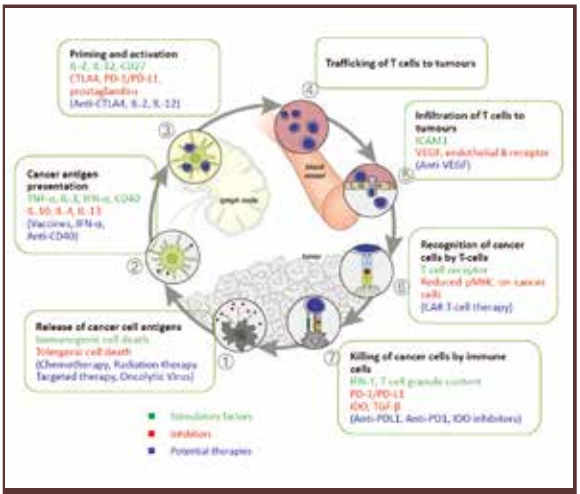


Fig. 2: Cancer-Immunity Cycle
Stimulatory factors (examples in green) promote immunity. Inhibitors (examples in red) negatively modulate the immune process to reduce immune activity and/or prevent autoimmunity. Potential cancer therapies(examples) are shown in blue. Abbreviations: CAR, chimeric antigen receptor; CTLA4, cytotoxic T-lymphocyte antigen-4; interleukin; ICAM1, intracellular adhesion molecule 1; IDO, indoleamine 2,3-dioxygenase, IFN, interferon; IL, PD-L1, programmed death-ligand 1; TGF, transforming growth factor, TNF, tumour necrosis factor; VEGF, vascular endothelial growth factor.
(Exerpted from Kunimasa, K & Chen DS et al[15,16]

care. Examples of cancer immunotherapy include preventive and therapeutic cancer vaccines, immune checkpoint inhibitors, bi-specific T-cell engager, and an oncolytic virus. Of these, the immune checkpoint inhibitors targeting the programmed death-1 (PD-1) checkpoint pathway have generated the most interest and accounted for the majority of the FDA approvals in the recent decade (Table 4). The approved clinical indications now cover multiple malignancies[13,14].

The immune system is our bodyguard orchestrating a group of immune cells such as cytotoxic T cells, to patrol our bodies for detecting and destroying any damaged cell or small tumour (Fig. 2)[15,16]. The "self" normal cells and "alien" cancer cells can be recognised by a group of molecules found on their cell surface. The immune response to cancer is a cyclic process that can be self-propagating, leading to an accumulation of immune-stimulatory factors that amplify and broaden the T cell responses. There is also an immune regulatory feedback mechanism via inhibitory factors such as PD-L1, that can halt or limit the immunity. This cycle can be divided into seven major steps (Fig. 2), starting with the release of antigens from the cancer cell and ending with the killing of cancer cells. Because of the rapid genetic changes, the cunning cancer cells can continue to grow and come up with ingenious ways of bypassing our immune cells and escaping their detection. The immune cells just cannot adapt fast enough to keep the cancer cells at bay.

One of the ways for the cancer cells to evade the immune system is to hijack the intrinsic immune checkpoint immunomodulatory mechanism by expressing the PD-L1, which is the ligand to a protein called PD-1 on the surface of T cells. When bound by its ligand, PD-L1, T cells become inactivated, and an "off" signal to the immune response is triggered. The cancer immunotherapy drug "immune checkpoint inhibitors" are able to block the PD-1 receptor present on the surface of the lymphocytes, or the PD-L1 ligands expressed by the cancer cells, thus preventing the binding of both and hence blocking the immunomodulatory signal. The halted antitumor immune response is then unleashed, and T cells are reactivated against the tumour. There are various types of cancer immunotherapy (Fig. 2), acting by harnessing the human immune response to break down the escaping mechanism of the cancer cells to achieve treatment effect[14,16].

Immunotherapy is a new pillar of cancer therapy. The awareness and skills in managing its side effects then become important. Taking the checkpoint inhibitors as an illustrating example, the sensitisation of the immune system is associated with a unique side effect profile (Fig. 3)[17]. Integrated cross-disciplinary care involving endocrinologists, rheumatologists, etc. has become more common on managing the toxicities.

賽馬會安寧頌

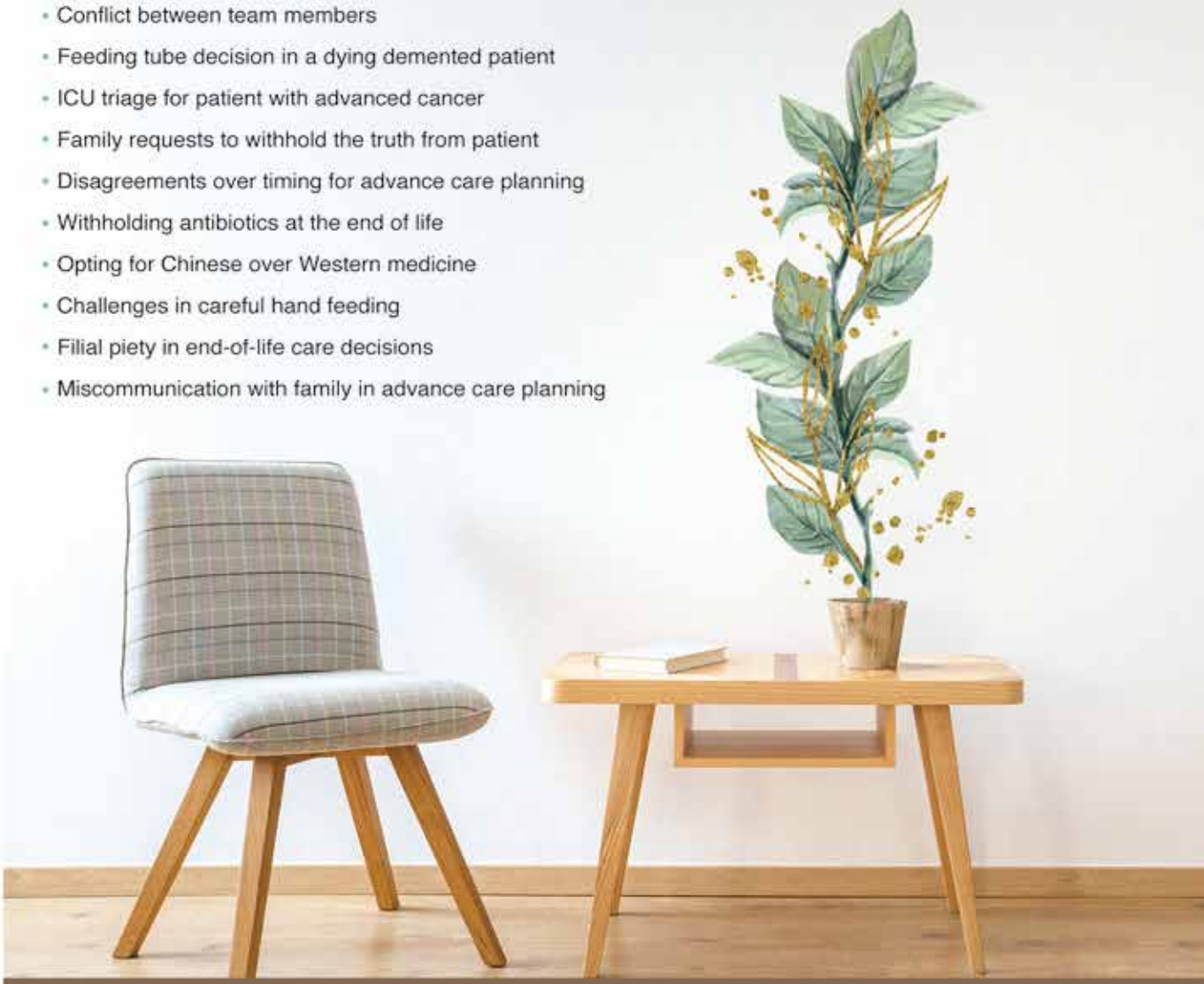
JCEcc

Jockey Club End-of-Life Community Care Project

This Casebook provides an open-access online resource for doctors, nurses, social workers and allied health professionals who face ethical issues when caring for older adults at the end of life.

The Casebook covers the following topics:

- Conflict between team members
- Feeding tube decision in a dying demented patient
- ICU triage for patient with advanced cancer
- Family requests to withhold the truth from patient
- Disagreements over timing for advance care planning
- Withholding antibiotics at the end of life
- Opting for Chinese over Western medicine
- Challenges in careful hand feeding
- Filial piety in end-of-life care decisions
- Miscommunication with family in advance care planning



An expert commentary for each case provides a perspective on the ethical challenges and a practical clinical approach. Background readings on key topics in end-of-life care of older adults and additional resources are also provided. The Casebook will continue to be updated with additional cases and background readings over time.

策劃及撥助 Initiated and Funded by

香港賽馬會慈善信託基金
The Hong Kong Jockey Club Charities Trust
同心同步同進 RIDING HIGH TOGETHER

合作院校 Partner Institution

香港中文大學
The Chinese University of Hong Kong

香港中文大學 賽馬會老年學研究所
CUHK Jockey Club Institute of Ageing

FEEDING TUBE DECISION IN A DYING DEMENTED PATIENT

Case Description:

Mr. Chan was an 84-year-old male, with a history of hypertension, diabetes and recurrent ischaemic stroke. His wife died a few years ago. He had two sons and one daughter living in Hong Kong. He was diagnosed to have vascular dementia five years ago and became chair-bound. For two years, he lived with his second son's family, cared for primarily by his daughter-in-law Mary. However, Mr. Chan had gotten progressively weaker in the last few months and Mary no longer could transfer him out of bed alone. Mr. Chan was then brought to live at a private old aged home.

In the last year, he became bed bound and double incontinent and required assisted feeding. He also had recurrent hospital admissions due to chest infections and the speech therapist recommended puree diet and thickener in fluid. After an episode of aspiration pneumonia, the speech therapist suggested non-oral feeding due severe oropharyngeal dysphagia.

The doctor asked to meet with the family and the second son and the daughter came. His son said, "Father would not want to have a feeding tube placed. He had seen many tube-fed elderly people at the old age home. They just lied in bed all day and it was not a life that he wanted. He told us that he would rather die than have one put into him."

The daughter had also heard her father express that and they both made the decision for careful hand feeding rather than tube feeding. They understood the risk of aspiration, pneumonia and death.

The patient tolerated careful hand feeding for several months. However, he then developed fever and became unarousable. He was transferred to the hospital and was found to have a severe pneumonia. He was kept nil by mouth and given parenteral antibiotics. His second son and daughter were informed of deteriorating clinical condition and imminent death. They understood and agreed to continue conservative management.

The next day, however, the oldest son turned up and insisted on starting tube feeding. He accepted that his father was dying and agreed to continue comfort care and continue DNACPR order. However, he said "It's important that my father would die with a full stomach. I do not want him to become a hungry ghost." The clinician was not sure whether he should simply reject the son's request or not.

Read the case and commentary :

Initiated and Edited by

香港中文大學 賽馬會老年學研究所
CUHK Jockey Club Institute of Ageing

Partner Institution

CUHK Centre for Bioethics
The Chinese University of Hong Kong
香港中文大學生命倫理學中心

Please visit http://www.ioa.cuhk.edu.hk/en-gb/casebook for more details on the Casebook

CUHK Jockey Club Institute of Ageing
Suite 908, 9/F, Yasumoto International Academic Park
The Chinese University of Hong Kong, Shatin, New Territories, Hong Kong
+852 3943 9450 ioa@cuhk.edu.hk

Table 3: Targeted Therapies Being the Standard Treatment of Choice (in bold) for Metastatic Malignancies (Summerised from U.S. Food and Drug Administration [6])

Disease		Biomarker (predicting response) & Drug Target	Targeted Drugs as the standard systemic treatment	Pivotal Trial Intervention	Efficacy with statistical significance
Lung Cancer (non-small cell) driver EGFR mutation positive non-small cell lung cancer	1st line	Biomarker: Driver EGFR mutation positivity e.g. Exon 19 deletions, Exon 21 L858R substitutions Target: EGFR & the mediated signaling pathway	EGFR TKIs 1st and 2nd generation e.g.: Gefitinib, Erlotinib, Afatinib 3rd generation: e.g. Osimertinib	**1st/2nd generation TKIs** vs platinum-based chemotherapy doublet **Osimertinib** vs 1st generation TKI (Gefitinib or Erlotinib)	mPFS (mo): (9-13) vs (5-7) mPFS(mo): 18.9 vs 10.2 mOS (mo): 38.6 Vs 31.8
Breast Cancer HER2 positive	1st line	Biomarker: HER2 positivity Target: HER2 & the mediated signaling pathway	Anti-HER2 Monoclonal Antibodies(MAbs) e.g. Pertuzumab, Trastuzumab	**Pertuzumab + Trastuzumab + Docetaxel** (chemo) vs Docetaxel (chemo)	mPFS (mo): 19 vs 12 mOS (mo): 56.5 vs 40.8
	2nd line	Biomarker: HER2 positivity Target: HER2 & the mediated signaling pathway	Anti-HER2 MAbs-chemo conjugate e.g. Ado-trastuzumab emtansine (T-DM1)	**TDM-1** vs Lapatinib + Capecitabine(chemo)	mPFS (mo): 10 vs 6 mOS (mo): 31 vs 25
	2nd line	Biomarker: HER2 positivity Target: HER2 & the mediated signaling pathway	HER2 Tyrosine Kinase Inhibitor (TKI) e.g Lapatinib	Lapatinib + Capecitabine (chemo) vs Capecitabine (chemo)	mPFS (mo): 6 vs 4 mOS: 75 vs 65 weeks
Breast Cancer ER/PR positive & HER2 negative	1st line	Biomarker: ER/PR positivity Target: CDK4 and CDK6 for cell division	CDK4/6 inhibitor (CDK4/6i) e.g. Palbociclib, Ribociclib, Abemaciclib	**CDK 4/6i + non-steroidal aromatase inhibitor(AI)** (hormone therapy) vs Non-steroidal AI (hormone therapy) alone	mPFS (mo): (25-28) vs (14-17)
Colorectal Cancer RAS wild type	1st line	Biomarker: RAS non-mutant Target: EGFR and the mediated signaling pathway	Anti-EGFR MAbs e.g. Cetuximab, Panitumumab	**Cetuximab + combination chemo** FOLFIRI vs FOLFIRI alone **Panitumumab + combination chemo** FOLFOX4 vs FOLFOX4 alone	mPFS (mo): 9.9 vs 8.7 mOS (mo): 24.9 vs 21 mPFS (mo): 9.6 vs 8.0 mOS (mo): 23.9 vs 19.4
Hepatocellular Carcinoma	1st line	Biomarker: nil Target: Several tyrosine kinases including vascular endothelial growth factor receptor (VEGFR-2/3), platelet-derived growth factor receptor (PDGF-R), Flt3 and c-Kit, and also targets Raf kinases involved in the MAPK/ERK pathway	Sorafenib – a multi-kinase inhibitor	**Sorafenib** vs Placebo	mPFS (mo): (2.8-5.5) vs (1.4 -2.8) mOS (mo): (6.5-10.7) vs (4.2-7.9)

Abbreviations: mPFS (mo): median professional free survival (months); mOS (mo): median overall survival (months)

Table 4: Cancer immunotherapies approved by the US FDA in the initial years since 2010. (Adapted from U.S. Food and Drug Administration & Emens LA, Ascierto PA, Darcy PK [6, 14])

Drugs (red) are the checkpoint inhibitors targeting the PD-1 / PD-L1 pathway.

2017	4 Mar 2017	Avelumab approved for merckel cell carcinoma
	10 Nov 2016	Nivolumab approved for metastatic head and neck squamous cell carcinoma
	24 Oct 2016	Pembrolizumab approved for 1st line PD-L1+ metastatic non-small cell lung carcinoma(NSCLC)
	18 Oct 2016	Atezolizumab approved for metastatic non-small cell lung carcinoma
2016	5 Aug 2016	Pembrolizumab approved for metastatic head and neck squamous cell carcinoma
	18 May 2016	Atezolizumab approved for urothelial bladder cancer
	17 May 2016	Nivolumab approved for Hodgkin's lymphoma
	18 Dec 2015:	Pembrolizumab approved for first line therapy of metastatic melanoma regardless of BRAF mutation status
	30 Nov 2015:	Elotuzumab approved for multiple myeloma
	21 Nov 2015:	Daratumumab approved for multiple myeloma
	24 Nov 2015:	Nivolumab approved for first line therapy of metastatic melanoma regardless of BRAF mutation status
	23 Nov 2015:	Nivolumab approved for metastatic renal cell carcinoma after progression on anti-angiogenic therapy
2015	28 Oct 2015:	Ipilimumab approved for adjuvant therapy of Stage 3 melanoma
	27 Oct 2015:	T-VEC approved for locally recurrent malignant melanoma
	9 Oct 2015:	Nivolumab approved for non-squamous NSCLC after progression on platinum chemotherapy
	2 Oct 2015:	Pembroliuzmab approved for PD-L1+NSCLC after platinum-based chemotherapy or therapy targeting EGFR or ALK mutations with companion diagnostic
	30 Sep 2015:	Ipilimumab+nivolumab approved for BRAF V600 wild-type unresectable or metastatic melanoma
	3 Apr 2015:	Nivolumab approved for squamous NSCLC after progression on platinum chemotherapy
2014	22 Dec 2014:	Nivolumab approved for unrespectable or metastatic melanoma after Ipilimumab or a BRAF inhibitor
	3 Dec 2014:	Blinatumomab approved for Ph-negative pre-B cell ALL
	9 Apr 2014:	Pembrolizumab approved for unresectable or metastatic melanoma after Ipilimumab or a BRAF inhibitor
2013	2013:	CAR T cell therapy achieves 89% response rate in ALL and complete responses in B-ALL
2012	2012:	Nivolumab [αPD1] showed a remarkable efficacy in phase 1 clinical trial in patients with advanced melanoma, non-small cell lung cancer, and renal carcinoma.
2011	2011	Ipilimumab for unresectable or metastatic melanoma
2010	2011:	Sipuleucel-T targeting a specific cancer antigen for advanced prostate cancer (The 1st FDA-approved specific immunotherapy)

KEYTRUDA®
(pembrolizumab)

Regardless of PD-L1 Expression Level[2]

THE ONLY ANTI-PD-1 FIRST-LINE COMBINATION TREATMENT FOR NONSQUAMOUS mNSCLC*

KEYTRUDA: **HELPING TO REDEFINE SURVIVAL EXPECTATIONS** FOR MORE PATIENTS WITH NONSQUAMOUS mNSCLC[1]

*** KEYTRUDA,** in combination with pemetrexed and platinum chemotherapy, is indicated for the first-line treatment of patients with metastatic nonsquamous non-small cell lung cancer (NSCLC), with no EGFR or ALK genomic tumor aberrations.[2]

22 MONTHS MEDIAN OS WITH KEYTRUDA + plat/pem[a] (95% CI, 19.5 - 25.2)

vs 10.7 months with plat/pem alone (95% CI, 8.7 - 13.6)

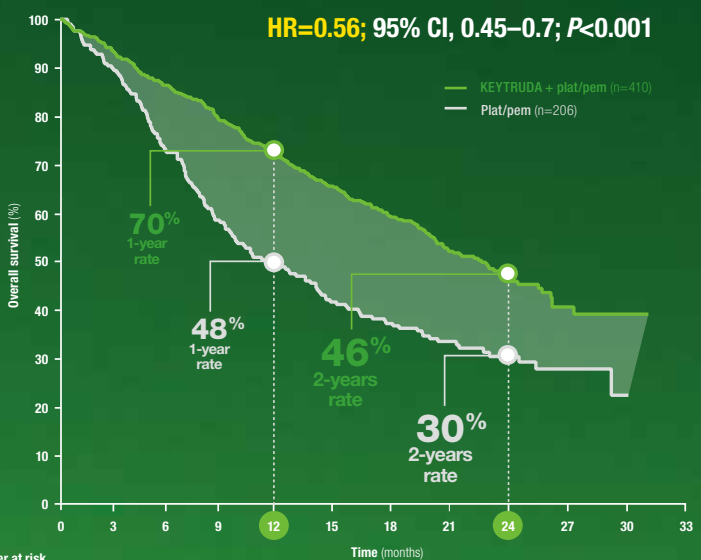
9 MONTHS MEDIAN PFS WITH KEYTRUDA + plat/pem[a] (95% CI, 8.1 - 9.9)

vs 4.9 months with plat/pem alone (95% CI, 4.7 - 5.5)

46% 2-YEAR OS RATE WITH KEYTRUDA + plat/pem[a]

vs 30% with plat/pem alone

Kaplan-Meier Estimates of OS in KEYNOTE-189 (ITT)[1,a,b]



Number at risk												
KEYTRUDA + plat/pem	410	377	346	316	283	256	234	144	79	28	2	0
Plat/pem	206	183	149	115	99	82	72	45	26	10	0	0

Adverse reaction profile for KEYTRUDA in combination with pemetrexed and platinum chemotherapy was consistent with that for each of the individual products.

[a] At data cutoff, median follow-up time was 23.1 months.[2] [b] HR based on the stratified Cox proportional hazard model; P value based on stratified log-rank test.[1]
mNSCLC = metastatic NSCLC; EGFR = epidermal growth factor receptor; ALK = anaplastic lymphoma kinase. Plat/pem = cisplatin or carboplatin + pemetrexed; OS = overall survival; HR = hazard ratio; CI = confidence interval.

Study Design: A Phase 3, randomized, multicenter, double-blind, placebo-controlled trial in treatment-naïve patients with nonsquamous mNSCLC, including patients with no PD-L1 expression. Patients with EGFR or ALK genomic tumor aberrations; autoimmune disease that required systemic therapy within 2 years of treatment; a medical condition that required immunosuppression; or patients who had received more than 30 Gy of thoracic radiation within the prior 26 weeks were ineligible. Randomization was stratified by smoking history, cisplatin vs carboplatin, objective response rate (ORR) and PD-L1 tumor expression (TPS <1% vs TPS ≥1%). Patients were randomized (2:1) to receive: KEYTRUDA 200 mg (n=410), cisplatin or carboplatin, and pemetrexed intravenously Q3W for 4 cycles followed by KEYTRUDA 200 mg and pemetrexed Q3W for up to 24 months; or placebo (n=206), cisplatin or carboplatin, and pemetrexed intravenously Q3W for 4 cycles followed by placebo and pemetrexed Q3W. Treatment continued until progression of disease or unacceptable toxicity. Primary efficacy outcome measures were OS and PFS as assessed by BICR per RECIST 1.1. Additional efficacy outcome measures were ORR and duration of response (DOR) as assessed by BICR per RECIST 1.1. Patients receiving placebo, platinum chemotherapy, and pemetrexed who experienced disease progression could cross over to receive KEYTRUDA as monotherapy.

Selected Safety Information for KEYTRUDA (pembrolizumab)
Indications: • Melanoma – KEYTRUDA (pembrolizumab) is indicated for the treatment of patients with unresectable or metastatic melanoma. • Non-Small Cell Lung Cancer – KEYTRUDA, in combination with pemetrexed and platinum chemotherapy, is indicated for the first-line treatment of patients with metastatic nonsquamous non-small cell lung cancer (NSCLC), with no EGFR or ALK genomic tumor aberrations. – KEYTRUDA, as a single agent, is indicated for the first-line treatment of patients with metastatic NSCLC whose tumors have high PD-L1 expression (Tumor Proportion Score (TPS) ≥50%) as determined by a validated test, with no EGFR or ALK genomic tumor aberrations. – KEYTRUDA, as a single agent, is indicated for the treatment of patients with metastatic NSCLC whose tumors express PD-L1 (TPS ≥1%) as determined by a validated test with disease progression on or after platinum-containing chemotherapy. Patients with EGFR or ALK genomic tumor aberrations should have disease progression on approved therapy for these aberrations prior to receiving KEYTRUDA. • Urothelial Carcinoma – KEYTRUDA is indicated for the treatment of patients with locally advanced or metastatic urothelial carcinoma who are not eligible for cisplatin-containing chemotherapy and whose tumors express PD-L1 [Combined Positive Score (CPS) ≥10] as determined by a validated test, or in patients who are not eligible for any platinum-containing chemotherapy regardless of PD-L1 status. – KEYTRUDA is indicated for the treatment of patients with locally advanced or metastatic urothelial carcinoma who have disease progression during or following platinum-containing chemotherapy or within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy. • Classical Hodgkin Lymphoma – KEYTRUDA as monotherapy is indicated for the treatment of adult patients with relapsed or refractory classical Hodgkin lymphoma (cHL) who have failed autologous stem cell transplant (ASCT) and brentuximab vedotin (BV), or who are transplant-ineligible and have failed BV. **Dosage and administration:** • Patient Selection: Select patients for treatment of metastatic NSCLC with KEYTRUDA as a single agent based on the presence of positive PD-L1 expression. • **Melanoma:** 2 mg/kg administered as an intravenous infusion over 30 minutes every 3 weeks until disease progression or unacceptable toxicity. • **NSCLC:** - In combination with pemetrexed and platinum chemotherapy or as a single agent for metastatic NSCLC patients that has not been previously treated with chemotherapy, 200mg. When administering KEYTRUDA in combination with chemotherapy, it should be administered prior to chemotherapy when given on the same day. - As a single agent for metastatic NSCLC patients that has been previously treated with chemotherapy, 2mg/kg. –KEYTRUDA should be administered as an intravenous infusion over 30 minutes every 3 weeks until disease progression, unacceptable toxicity, or up to 24 months in patients without disease progression. • **Urothelial Carcinoma:** 200 mg administered as an intravenous infusion over 30 minutes every 3 weeks until disease progression or unacceptable toxicity, or up to 24 months in patients without disease progression. • **Classical Hodgkin Lymphoma:** 200 mg administered as an intravenous infusion over 30 minutes every 3 weeks until disease progression or unacceptable toxicity, or up to 24 months in patients without disease progression. **Contraindications:** • None **Precautions:** • Immune-Mediated Pneumonitis • Immune-Mediated Colitis • Immune-Mediated Hepatitis • Immune-Mediated Endocrinopathies (hypophysitis; thyroid disorders - hyperthyroidism, hypothyroidism and thyroiditis; Type 1 diabetes) • Immune-Mediated Nephritis and Renal Dysfunction • Immune-Mediated Skin Adverse Reactions (SJS, TEN, exfoliative dermatitis or bullous pemphigoid) • Other Immune-Mediated Adverse Reactions • Infusion-Related Reactions (including hypersensitivity and anaphylaxis) • Complications of Allogeneic HSCT in Patients with Allogeneic HSCT prior to KEYTRUDA treatment • Increased Mortality in Patients with Multiple Myeloma • Embryofetal Toxicity • **For detailed precautions, please consult the full prescribing information. Adverse Events:** Most common adverse reactions (reported in ≥20% of patients) when Keytruda was used as a single agent were fatigue, musculoskeletal pain, decreased appetite, pruritus, diarrhea, nausea, rash, pyrexia, cough, dyspnea, constipation, pain, and abdominal pain; when Keytruda was used in combination with pemetrexed and platinum chemotherapy were fatigue/asthenia, nausea, constipation, diarrhea, decreased appetite, rash, vomiting, cough, dyspnea, and pyrexia. • Immune-mediated pneumonitis • Immune-mediated colitis • Immune-mediated hepatitis • Immune-mediated endocrinopathies • Immune-mediated nephritis and renal dysfunction • Immune-Mediated Skin Adverse Reactions (SJS, TEN, exfoliative dermatitis or bullous pemphigoid) Other immune-mediated adverse reactions • Infusion-related reactions • As with all therapeutic proteins, there is the potential for immunogenicity. • **For detailed adverse events, please consult the full prescribing information.**

Before prescribing KEYTRUDA®, please consult the full prescribing information.

Reference:
1. Gandhi L, Rodriguez-Abreu D, Gadgeel S, et al; for the KEYNOTE-189 investigators. Pembrolizumab plus chemotherapy in metastatic non–small-cell lung cancer. *N Engl J Med.* 2018; 378(22):2078–2092. **2.** Hong Kong Product Circular (KEYTRUDA, MSD) **3.** Gadgeel S, et al. KEYNOTE 189: Updated Overall Survival and Progression After the Next Line of Therapy With Pembrolizumab plus Chemotherapy With Pemetrexed and Platinum vs Placebo plus Chemotherapy for Metastatic Nonsquamous Non-Small-Cell Lung Cancer. Poster Presented at the 2019 American Society of Clinical Oncology Annual Meeting; May 31 to June 4, 2019; Chicago, IL, USA

MSD
Merck Sharp & Dohme (Asia) Ltd.
27/F., Lee Garden Two, 28 Yun Ping Road, Causeway Bay, Hong Kong. Tel: (852) 3971 2800 Fax: (852) 2834 0756 Website: www.msd.com.hk

HK-KEY-00040 07/19

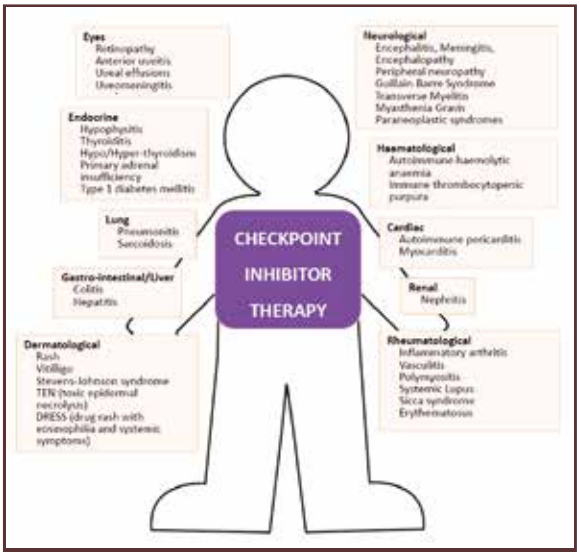


Fig. 3: Immune-Related Adverse Events by Checkpoint Inhibitor Therapy (Excerpted from Spiers L et al[17])

There are now more than 200 US FDA approvals of unique new oncology drugs over the past 70 years after the year 1949[18]. The novel therapies have brought to us many new challenges in cancer drug development and cancer care, including the quest for clinical trials to find robust predictive biomarkers for selecting the right patients, to identify the clinical endpoints that can reflect the clinical benefit, to understand the cancer biology of the emergence of drug resistance, the quest for skills to monitor and manage the unique toxicity profiles, and the quest for measures to deal with the financial burden to the society from these expensive agents.

PRECISION AND PERSONALISED PALLIATIVE RADIOTHREAPY

Principles of Palliative Radiotherapy

Radiotherapy has been used for treatment since the discovery of X-ray in 1896. However, it was not until the advent of megavoltage photon (high energy X-ray) radiation in the 1950s and 1960s that radiotherapy became extensively applied to treat tumours deep-seated inside the body.[18] Palliative radiotherapy is a safe and effective means to achieve the objectives of symptom control and improving the quality of life in patients suffering from advanced malignancies. Through a direct DNA damage, radiotherapy can rapidly relieve the sufferings from bleeding, pain, neurological, obstructive and pressure symptoms caused by tumours from all types of malignant cells, with their locations in all parts of the body from the head to toe. The delivery of palliative radiotherapy should mandate the lowest possible radiotherapy-associated side effects and the highest possible benefit and cost-efficiency. X-ray radiotherapy affects both the tumour and healthy normal tissue cells along the beam pathway to the target and beyond, hence the therapeutic window is limited by the normal tissue dose tolerance. Instead of a single big tumoricidal dose, the radical radiotherapy regimen has to breakdown the total dosage into multiple fractions e.g. for head and neck cancers, it consists of 1.8-2 Gray (Gy) daily fractional dose over a treatment period lasting for 6-7 weeks (30-35 fractions reaching total dose 60-70 Gy) in order to kill all the cancer cells while the normal tissue cells can recover and repopulate. For palliative radiotherapy achieving the objectives as above and "cure" is not the aim, radical tumoricidal doses need not be necessary. The usual regimen consists of a higher daily fractional dose e.g. 3-10 Gy i.e. hypofractionation (>2 Gy daily) over a much shorter period in 1-2 weeks, and this is also convenient to patients.

Precision in Radiation Oncology Widens the Therapeutic Window

A longstanding goal of radiotherapy is to conform the radiation dosage as closely as possible to the target volume while minimising the dose to surrounding normal tissues. Technical advances for target delineation, dosimetry planning, and treatment delivery in the past two decades have allowed us to get closer to the treatment goal mentioned above. It is no longer a two dimensional (2D) approach using plain X-ray for the designation of radiotherapy portal. Tumours can be visualised more precisely with computed tomography (CT), magnetic resonance imaging (MRI), positron emission tomography (PET) for the target delineation. Refinement in the radiation dosimetry and delivery techniques has enabled a superior than ever dose conformity and precise radiation delivery to the treatment targets. Examples of techniques nowadays include 3D conformal radiotherapy, intensity-modulated radiotherapy (IMRT), volumetric modulated arc therapy (VMAT), 4D (organ motion) radiotherapy planning and image-guided radiotherapy (IGRT) delivery for tracing the irradiated target during treatment. Development in physics and engineering sciences has realised radiation therapy by other modalities such as charged particles e.g. protons, that can deliver and stop the radiation dose to the targets and minimise damage to the surrounding healthy tissues and vital organs[19].

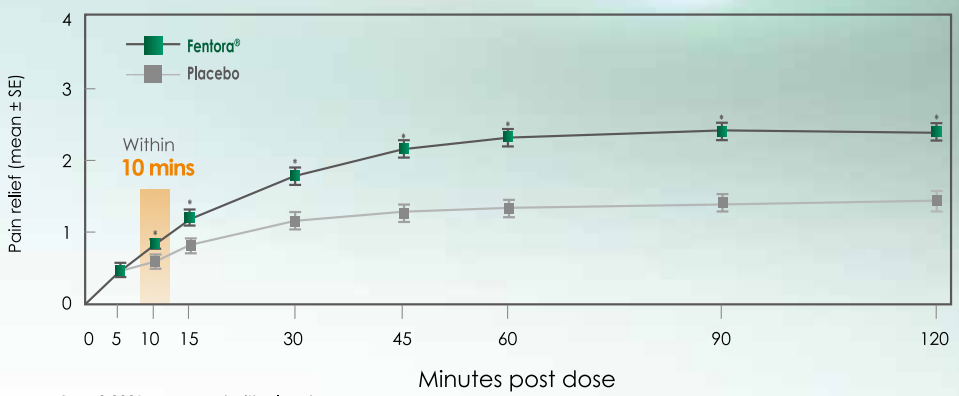
In the past ten years, there is numerous research on stereotactic radiotherapy (SRT). SRT can be delivered to the brain (stereotactic radiosurgery (SRS)), or to the body (stereotactic body radiotherapy (SBRT)). American Society for Therapeutic Radiology and Oncology (ASTRO) defined SBRT as "an external beam radiation therapy method used to very precisely deliver a high dose of radiation to an extracranial target within the body, using either a single dose or a small number of fractions" i.e. hypofractionation.[20] It is a "pinpoint" radiotherapy technique enabling focal high dose radiation with a rapid dose fall-off immediately adjacent. It widens the therapeutic window with a therapeutic gain in the local tumour control through a higher biological effective dose of irradiation. SRT is an aggressive approach that besides symptom control, it can prolong the survival for patients with oligometastatic disease i.e. less than five metastatic sites. In the landmark study on SBRT versus standard of care palliative treatment in patients with oligometastatic cancers by Palma DA, et al., the median overall survival was 28 months (95% CI 19-33) in the control group versus 41 months (26-not reached) in the SBRT group (hazard ratio 0·57, 95% CI 0·30-1·10; p=0·090)[21]

FENTORA®
(fentanyl buccal tablet)

When Breakthrough Cancer Pain Strikes, **ACT FAST with Fentora®**

For opioid-tolerant adult patients with BTcP

• Rapid Onset of Analgesia within 10 Minutes Which Closely Matches the Onset of BTcP[1,2]



* p < 0.0001 compared with placebo

• Improved Dissolution and Absorption by Oravescent® Technology[2-4]

Modifies pH levels to facilitate Fentora® delivery across the buccal mucosa†

- Transmucosal absorption = 48% ± 31.8%*
- Absolute bioavailability = 65% ± 20%*

• Simple Up-titration[4]

Initiates with 100 mcg‡ and individually titrates to achieve effective analgesia

* PK for Fentora® 400mcg
† This reaction is a dynamic process that results in repeated changes in pH over time.
‡ For opioid-tolerant adult patients new to Fentora® treatment.

Study design
A randomized, double-blind, placebo-controlled study was conducted in 78 aged 18 – 80 patients with a histologically documented diagnosis of a malignant solid tumor or hematologic malignancy causing cancer-related pain and a life expectancy of at least 2 months. First, an effective dose of Fentora® was identified during the dose-titration phase (100 mcg in 8%, 200 mcg in 12%, 400 mcg in 18%, 600 mcg in 28%, and 800 mcg in 34% of patients). Then, the patients were randomly assigned to 1 of 18 double-blind dose sequences (7 Fentora® tablets, 3 placebo) to treat 10 BTcP episodes. Pain intensity was measured on an 11-point scale (0 = no pain; 10 = worst pain). Pain relief was measured from 5 minutes through 2 hours.[1]

BTcP = breakthrough cancer pain. GI = gastrointestinal. SE = standard error.

Further information is available on request

References
1. Slatkin NE, Xie F, Messina J, and Segal TJ. Fentanyl buccal tablet for relief of breakthrough pain in opioid-tolerant patients with cancer-related chronic pain. J Support Oncol 2007;5:327-334. 2. Darwish M, Hamed E, and Messina J. Fentanyl buccal tablet for the treatment of breakthrough pain: pharmacokinetics of buccal mucosa delivery and clinical efficacy. Perspect Medicin Chem 2010;4:11-21. 3. Fentora (fentanyl buccal tablet). Visit Healthcare Professionals Site. Pharmacokinetics. Available at: http://www.fentora.com/hcp/bioavailability.aspx (on 21 Jan 2019). 4. Fentora® prescribing information.

FEN-HK-00039 March 2019

Further information is available on request

Teva Pharmaceutical Hong Kong Limited
Room 2303, 23/F., Mira Place Tower A, 132 Nathan Road,
Tsim Sha Tsui, Kowloon, Hong Kong.
Tel: +852 3188 4288 Fax: +852 3585 6220

teva

.For patients with multiple brain metastases, SRT is potentially superior to standard whole-brain irradiation for (1) one-day treatment (2) more than 80% of patients being able to achieve tumour control (3) lowering incidence and severity of neurocognitive function impairment. There has been mounting evidence that patients with up to 10 brain metastases might be potential candidates for SRT alone[22,23].

With the many innovations and advances in radiation oncology, treatment can be 'Personalised" in accordance with each individual's condition. Table 5 suggests some factors for deciding on the aggressiveness of palliative radiation therapy to obtain the optimal benefit[24].

Table 5: Factors for Deciding on the Aggressiveness of Palliative Radiation Therapy (Adapted from Jones J. [24])

Factors for Consideration	More Aggressive Approach e.g. stereotactic/ conformal, prolonged fractionation	Less Aggressive Approach e.g. less conformal, short fractionation	Best Supportive Care (Not for Radiotherapy)
Survival	>12 months to years	< 12 months	< 1 month
Karnofsky Performance Status (KPS)	KPS ≥70	KPS <70	Very poor KPS ≤30, or imminent death
Overall systemic disease control	Well-controlled	A large burden of systemic disease	Overwhelming burden of symptoms—radiotherapy affecting one symptom among many
Availability of effective systemic treatment	Multiple choices with good response rates	Few choices	NIL
Likelihood of significant late side effects	High	Low	
Morbidity of retreatment	High	Low	

Radionuclide therapy (RNT) is another rapidly growing field concerning precision radiotherapy for advanced malignancies.[25] RNT is a site- (tumour-) specific concentration of short-ranged biologically effective particulate radiation, allowing radiation to the targeted tumour while sparing the surrounding normal tissues. Examples of such include iodine-131 (^{131}I) for thyroid cancers, and strontium-90 (^{90}Sr) for bone metastases. Recent developments include Yttrium-90 (^{90}Y) microspheres for hepatocellular carcinoma (HCC), peptide receptor radionuclide therapy (PRRT) such as Lutetium-177 (^{177}lu)-DOTATATE for neuroendocrine tumours (NETs) expressing the specific peptide receptor, and radioimmunotherapy (RIT) which uses monoclonal antibodies labelled with a radionuclide directed against tumour-associated antigens such as ^{90} Y-ibritumomabtiuxetan for refractory non-Hodgkin's lymphoma[25].

INTEGRATING SUPPORTIVE AND PALLIATIVE CARE INTO ONCOLOGY

WHO defines palliative care as "an approach that improves the quality of life of patients and their families facing the problems associated with a life-threatening illness, through the prevention and relief of suffering by means of early identification and impeccable assessment and treatment of pain and other problems, physical, psychological and spiritual"[26]. A palliative and supportive care approach should not be utilised only at the end of life for cancer patients, who are facing much suffering and stress along the disease journey. As such, the American Society of Clinical Oncology (ASCO) and The European Society of Medical Oncology (ESMO) recommended palliative care be offered along with treatment for patients with metastatic cancer and those who have many or severe symptoms[27,28]. Hawley PH described the "Bow Tie Model of 21st Century Palliative Care" that acknowledges the duality of the disease management approach that prepares patients for the worst (death) and allows hope for the best (cure). This approach fits well along the cancer disease trajectory (Fig. 4)[29]. The integration of palliative care to oncology care was associated with better survival, quality of life, illness understanding, and patient satisfaction[30-33].

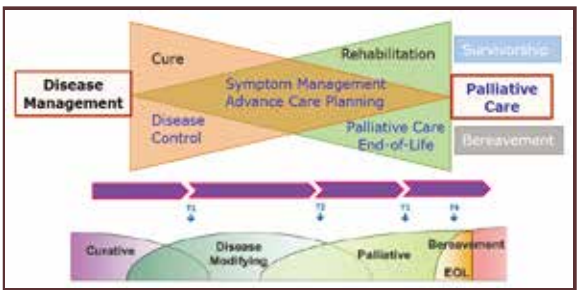


Fig. 4: Integration of Palliative Care along the Cancer Care Pathway (Adapted from Hawley PH et al. The Bow Tie Model of 21st Century Palliative Care) [29]

The rapidly evolving oncological advances hold promise with better treatment outcomes. Triggers for prognostic disclosure and goals of care discussion between oncologists and patients with advanced cancer are happening more than ever with the advent of novel treatment options. A candid prognostic disclosure and communication provide patients with a realistic framework of their life expectancy, upon which patients can tailor their treatment goals consistent with their personal preferences[34-35]. However, the preferences of healthcare professionals and patients cannot be the same. A British study of attitudes to chemotherapy reported a difference on the willingness to proceed with a toxic treatment regarding the chance of cure (patients: 1% vs doctors & nurses: 50%); chance of symptom relief (patients: 10% vs doctors & nurses: 75%); chance of prolonging life by (patients: 12 months vs doctors and nurses: 24-60 months)[36]. The more recent study similarly showed that patients were more likely to accept chemotherapy with only a modest survival compared to doctors[37-40], and they were prepared to attempt clinical trials using experimental therapies of mortality rates of 10% with uncertainty on the clinical benefit[40].

The goal of treatment for patients with advanced malignancy is to assist them to live longer and better. It is important to understand that the treatment recommendation in the best interest of patients cannot be based on the disease prognosis alone. Consideration of advance care planning, personal goals of care and

values, and an assessment of other palliative treatment options is paramount to a good shared decision-making between the patient and the oncologist and the multidisciplinary care team.

CONCLUSION

The rapidly evolving oncological treatment landscape and the continually changing cultural and social environment have created big challenges for us to keep apace. The aspirations of future palliative oncology care should be based on a model with early integration of palliative care along the cancer care pathway in a multidisciplinary approach. In addition, the best practice for the choice of cancer care should have a foundation with an effective and honest communication between the oncologists and patients regarding the disease prognosis, benefits and toxicities of the treatment options and what the patient values the most in the context.

References

1. World Health Organization. Available online & accessed April 2020 at: https://www.who.int/news-room/fact-sheets/detail/cancer
2. Hong Kong Cancer Registry. Available online & accessed April 2020 at: https://www3.ha.org.hk/cancereg/facts.html
3. Goodman L, Wintrobe M, Dameshek W, et al. Nitrogen mustard therapy. Use of methyl-bis(beta-chloroethyl)amine hydrochloride and tris(beta-chloroethyl)amine hydrochloride for Hodgkin's disease, lymphosarcoma, leukemia and certain allied and miscellaneous disorders. JAMA. 1946;251(17):2255-61.
4. Scott RB. Cancer Chemotherapy-The First Twenty-five Years. British Medical Journal, 1970, 4, 259-265
5. DeVita VT et al. A History of Cancer Chemotherapy. Cancer Res 2008; 68: (21): 8643 - 8653
6. U.S. Food and Drug Administration. Drugs. Available and accessed Apr 2020 at: https://www.fda.gov/drugs/
7. Imai K, Takaoka A. Comparing antibody and small-molecule therapies for cancer. Nat Rev Cancer. 2006; 6:714–727.
8. Falzone L, Salomone S, Libra M. Evolution of Cancer Pharmacological Treatments at the Turn of the Third Millennium. Front Pharmacol. 2018 Nov 13;9:1300. eCollection 2018. Available online & accessed April 2020 at: https://doi.org/10.3389/fphar.2018.01300
9. Wu J, Joseph SO, Muggia FM. Targeted therapy and its status and promise in selected solid tumours part I: areas of major impact. Oncology. 2012 Oct;26(10):935-43.
10. European Society of Medical Oncology Treatment Guidelines. Available online & accessed April 2020 at: https://oncologypro.esmo.org/guidelines
11. The NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®). Available online & accessed April 2020 at : https://www.nccn.org/professionals/physician_gls/default.aspx
12. US Food and Drug Administration. Sipuleucel T. Available online & accessed April 2020 at: https://www.fda.gov/vaccines-blood-biologics/cellular-gene-therapy-products/provenge-sipuleucel-t.
13. Lipson EJ, Forde PM, Hammers HJ, et al. Antagonists of PD-1 and PD-L1 in cancer treatment. Semin Oncol 2015;42:587e600.
14. Emens LA, Ascierto PA, Darcy PK, et al. Cancer immunotherapy: Opportunities and challenges in the rapidly evolving clinical landscape. Eur J Cancer. 2017 Aug;81:116-129.
15. Kunimasa, K.; Goto, T. Immunosurveillance and Immunoediting of Lung Cancer: Current Perspectives and Challenges. Int. J. Mol. Sci. 2020, 21, 597. Available online & accessed April 2020 at: https://www.mdpi.com/1422-0067/21/2/597#cite
16. Chen DS, Mellman I. Oncology meets immunology: the cancer-immunity cycle. Immunity. 2013 Jul 25;39(1):1-10.
17. Spiers L, Coupe N, Payne M. Toxicities associated with checkpoint inhibitors-an overview. Rheumatology (Oxford). 2019 Dec 1;58(Suppl 7):vii7-vii16.
18. Chao JH, Phillips R, Nickson JJ. Roentgen-ray therapy of cerebral metastases. Cancer 1954;7:682-9.
19. Baumann BC, Mitra N, Harton JG, et al. Comparative Effectiveness of Proton vs Photon Therapy as Part of Concurrent Chemoradiotherapy for Locally Advanced Cancer. JAMA Oncol. 2020;6(2):237–246.
20. Potters L, Kavanagh B, Galvin JM, et al. American Society for Therapeutic Radiology and Oncology (ASTRO) and American College of Radiology (ACR) practice guideline for the performance of stereotactic body radiation therapy. Int J Radiat Oncol Biol Phys. 2010;76(2):326-332.
21. Palma DA, Olson R, Harrow S, et al. Stereotactic ablative radiotherapy versus standard of care palliative treatment in patients with oligometastatic cancers (SABR-COMET): a randomised, phase 2, open-label trial. Lancet. 2019 May 18;393(10185):2051-2058.
22. Amendola BE, Wolf A, Coy S, Amendola MA. Radiosurgery as palliation for brain metastases: a retrospective review of 72 patients harboring multiple lesions at presentation. J Neurosurg 2002; 97: 511-514.
23. Yamamoto M, Serizawa T, Shuto T, et al. Stereotatic Radiosurgery for Patients with Multiple Brain Metastases (5LGK0901): A Multi Institutional Prospective Observational Study Lancet Oncol 2014;15:387-395.
24. Jones J. Too much, too little, or just the right amount: finding the balance in palliative radiotherapy. Curr Probl Cancer. 2011 Nov-Dec;35(6):325-36.
25. Dash A, Knapp FF, Pillai MR. Targeted radionuclide therapy--an overview. Curr Radiopharm. 2013 Sep;6(3):152-80. Review.
26. WHO Definition of Palliative Care, World Health Organization, 2002. Available online: http://www.who.int/cancer/palliative/definition/en/
27. Smith TJ, Temin S, Alesi ER, et al. American Society of Clinical Oncology provisional clinical opinion: the integration of palliative care into standard oncology care. J Clin Oncol. 2012 Mar 10;30(8):880-7.
28. Cherny NI, Catane R, Kosmidis P; ESMO Taskforce on Supportive and Palliative Care. ESMO takes a stand on supportive and palliative care. Ann Oncol. 2003 Sep;14(9):1335-7.
29. Hawley PH. The bow tie model of 21st century palliative care. J Pain Symptom Manage. 2014 Jan;47(1):e2-5.
30. Bakitas M, Lyons KD, Hegel MT, et al. The project ENABLE II randomized controlled trial to improve palliative care for rural patients with advanced cancer: baseline findings, methodological challenges, and solutions. Palliat Support Care 2009;7:75-86.
31. Temel JS, Greer JA, Muzikansky A, et al. Early palliative care for patients with metastatic non-small-cell lung cancer. N Engl J Med 2010;363:733-42.
32. Temel JS, Greer JA, Admane S, et al. Longitudinal perceptions of prognosis and goals of therapy in patients with metastatic non-small-cell lung cancer: results of a randomized study of early palliative care. J Clin Oncol 2011;29:2319-26.
33. Zimmermann C, Swami N, Krzyzanowska M, et al. Early palliative care for patients with advanced cancer: a cluster-randomised controlled trial. Lancet 2014;383:1721-30.
34. Enzinger AC, Zhang B, Schrag D, et al. Outcomes of Prognostic Disclosure: Associations With Prognostic Understanding, Distress, and Relationship With Physician Among Patients With Advanced Cancer. J Clin Oncol 2015;33:3809-16.
35. Jenkins V, Fallowfield L, Saul J. Information needs of patients with cancer: results from a large study in UK cancer centres. Br J Cancer 2001;84:48.
36. Slevin ML, Stubbs L, Plant HJ, et al. Attitudes to chemotherapy; comparing views of patients with cancer with those of doctors, nurses, and general public. BMJ 1990;300:1458–60.
37. Matsuyama R, Reddy S, Smith T. Why do patients choose chemotherapy near the end of life? A review of the perspective of those facing death from cancer. J Clin Oncol 2006;24:3490–6.
38. Silvestri G, Pritchard R, Welch HG. Preferences for chemotherapy in patients with advanced non-small cell lung cancer: descriptive study based on scripted interviews. Br J Med 1998;317:771–5.
39. Vaz-Luis I, O'Neill A, Sepucha K, et al. Survival benefit needed to undergo chemotherapy: patient and physician preferences. Cancer 2017;123:2821–8.
40. Agrawal M, Grady C, Fairclough D, et al. Patients' decision-making process regarding participation in phase I oncology research. J Clin Oncol 2006;24:4479–84

全新
醫務樓層
Brand New Medical Floor

始創中心
PIONEER CENTRE

乘勢而起
盡握先機

交通樞紐 • 中心地段 • 著名地標 • 極罕全層

- 毗鄰港鐵太子站、旺角東站、跨境巴士及直通車站，交通便捷
- 大量時租車位，正門設上落客區
- 升降機大堂設於地面，無障礙進出大樓
- 彈性可出租單位面積*，由452呎至全層22,137呎
- 設8層商場，匯聚逾200間商舖，食肆及銀行，配套完善

*所列之面積未經核實，以現場量度為準。

租務查詢
Leasing Enquiries
2399 6351 / 2399 6359
6223 4402
www.pioneer-centre.com.hk

旺角彌敦道750號
750 Nathan Road, Mongkok

九龍建業有限公司
KOWLOON DEVELOPMENT COMPANY LIMITED

IMPROVE-IT OUTCOMES RESULTS*

THINK BEYOND MONOTHERAPY

Atozet® (ezetimibe and atorvastatin) tablets

ACHIEVE TARGET LDL-C LEVELS WITH POWERFUL DUAL ACTION OF

ATOZET®

Abbreviation: LDL-C: low-density lipoprotein cholesterol.
Reference: 1. Hong Kong Product Circular (Atozet; MSD).

Selected Safety Information on ATOZET

Indications: *Prevention of Cardiovascular Events* ATOZET is indicated to reduce the risk of cardiovascular events in patients with coronary heart disease (CHD) and a history of acute coronary syndrome (ACS), either previously treated with a statin or not. *Hypercholesterolaemia* ATOZET is indicated as adjunctive therapy to diet for use in adults with primary (heterozygous familial and non-familial) hypercholesterolaemia or mixed hypercholesterolaemia where use of a combination product is appropriate •patients not adequately controlled with a statin alone •patients already treated with a statin and ezetimibe. Homozygous Familial Hypercholesterolaemia (HoFH) ATOZET is indicated as adjunctive therapy to diet for use in adults with HoFH. Patients may also receive adjunctive treatments (e.g., low-density lipoprotein [LDL] apheresis). Contraindications: • Hypersensitivity to the active substances or to any of the excipients. • Therapy with ATOZET is contraindicated during pregnancy and breast-feeding. Men in women of childbearing potential not using appropriate contraceptive measures. ATOZET is contraindicated in patients with active liver disease or unexplained persistent elevations in serum transaminases exceeding 3 times the upper limit of normal (ULN). Precautions: • Myopathy/Rhabdomyolysis ▶ In post-marketing experience with ezetimibe, cases of myopathy and rhabdomyolysis have been reported. Most patients who developed rhabdomyolysis were taking a statin concomitantly with ezetimibe. Rhabdomyolysis has been reported very rarely with ezetimibe monotherapy. ▶ Also, ATOZET contains atorvastatin, which is a HMG-CoA reductase inhibitor. Atorvastatin may in rare occasions affect the skeletal muscle and cause myalgia, myositis, and myopathy that may progress to rhabdomyolysis. ▶ A CPK level should be measured before starting treatment. If CPK levels are significantly elevated (>5 times ULN) at baseline, treatment should not be started. ▶ Patients must be asked to promptly report muscle pain, cramps, or weakness especially if accompanied by malaise or fever or if muscle signs and symptoms persist after discontinuing ATOZET. • Liver Enzymes ▶ Liver function tests should be performed before the initiation of treatment and periodically thereafter. Should an increase in transaminases of greater than 3 times the ULN persist, reduction of dose or withdrawal of ATOZET is recommended. • Hepatic Insufficiency ▶ Due to the unknown effects of the increased exposure to ezetimibe in patients with moderate or severe hepatic insufficiency, ATOZET is not recommended. • Interstitial lung disease ▶ If it is suspected that a patient has developed interstitial lung disease, statin therapy should be discontinued. • Diabetes mellitus ▶ Patients at risk (fasting glucose 5.6 to 6.9 mmol/L, BMI >30kg/m², raised triglycerides, hypertension) should be monitored both clinically and biochemically according to national guidelines. • Excipients ▶ ATOZET contains lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency, or glucose-galactose malabsorption should not take this medicine. Adverse events: • Common adverse reactions (≥1/100, <1/10) include diarrhoea and myalgia. • In controlled clinical trials, the incidence of clinically important elevations in serum transaminases (ALT and/or AST ≥3 X ULN, consecutive) was 0.6% for patients treated with ATOZET. These elevations were generally asymptomatic, not associated with cholestasis, and returned to baseline spontaneously or after discontinuation of therapy. Please consult the full prescribing information for detailed adverse events.

Before prescribing, please consult the full prescribing information.

MSD

Merck Sharp & Dohme (Asia) Ltd.

HK-ATO-00009-11/19

Communication in Care for Advanced Diseases

Dr Raymond SK LO

MBBS (Lond), MD (CUHK), MHA(UNSW), Dip Geri Med (RCPS Glas), FHKCP, FRCP (Lond, Edin , Glasg), FHKAM

Specialist in Geriatric Medicine
Clinical Professor (Honorary), Dept of Medicine and Therapeutics, Chinese University of Hong Kong

Dr Raymond SK LO

Care for serious and advanced illnesses necessitates good communication. Communication is, of course, a most essential component of all health services delivery, and an important contributor towards quality care. Good communication by itself is not only therapeutic for patients, and is also most rewarding for health professionals.

Communication encompasses different perspectives at different stages of serious illnesses, ranging from breaking bad news to supporting dying and bereavement. While there are useful guides and models regarding communication for different purposes, there are common underlying principles. Key communication skills need to be taught, yet therapeutic communication can only be achieved through a humanistic approach and compassion. As with any holistic and patient-centred care, the author finds a 5E approach should be helpful:

- Empathy
- Encourage
- Educate
- Empower
- Extend support

BREAKING BAD NEWS

Dr Robert Buckman has advocated six steps in breaking bad news since 1992[1]. The six steps comprise of 1. getting started with proper preparation; 2. establishing what the patient already knows; 3. ascertaining how much the patient wants to know; 4. following with sharing the information; 5. responding to family and patient's feelings; and 6. closure with planning and follow up. A SPIKES model utilising six similar steps emerges and forms a useful protocol in breaking bad news for patients with cancer[2].

S: Setting up the interview
P: Assessing the patient's perception
I: Obtaining the patient's invitation
K: Giving knowledge and information to the patient
E: Addressing the patient's emotions with empathic responses
S: Strategy and Summary

The principles outlined in the model can be adapted when disclosing unfavourable information in other health scenarios too. Prior to breaking any bad news, patients' background and previous understanding should first be ascertained. The level of patients' comprehension and cognition needs to be taken into account. Family presence is recommended. Amount and intensity of bad news to be covered would best be individualised and preferably delivered in steps, depending on the patients' preparedness. Time needs to be given to allow patients to digest and reflect. Appropriate silence is not necessarily awkward. Acknowledging patients' emotions is most supportive and will always be appreciated. Paraphrasing patients' words and comments are helpful in expressing our reassurance. Yet active listening may well speak better than words. Provided patients are ready, setting tentative goals naturally follows the discussion before closing the conversation. Documentation of the main points covered must not be forgotten for team members' record and reference, in preparation towards continuity of further discussion and planning.

PARTNERSHIP DECISION-MAKING

As the disease progresses, more discussion on treatment decisions would necessarily follow. Such decisions are likely to be difficult, and won't be easy for patients, families nor professionals. When diseases approach the advanced stages with no curative options, the aim of treatment assumes an increasing palliative focus. The emphasis will be not just on the quantity of life but also on the best interests and quality of life. Such decisions will, of course, need to be based on patients' own considerations. Approaches in communication will have to shift away from a traditional paternalistic style where the doctor knows best, and patients' views and preferences are not taken into any account. A laissez-faire style of discussion would not be appropriate either, when we are now at a medical era where treatments and interventions are complicated, for which patients and families are at a loss and may not always be able to decide. The best approach will be through partnership and shared decision-making, with reference to patient autonomy and balancing families' viewpoints. It is fully understood that no single mode of decision-making is best for all scenarios, with mix and match necessary with different settings. At times patients may delegate all decisions to professionals, or vice-versa decline seemingly the best recommended option. It is always important to clarify how involved a patient chooses to be during decision-making[3]. Efforts should be devoted to partnership with patients and families to reach the best cojnsensus. Guide for professionals in facilitating communication and decision-making can serve well towards this purpose.

SERIOUS ILLNESS COMMUNICATIONS

In view of the escalating need for better communication and decision-making in serious illnesses, a Serious Illness Conversation Guide was developed by professionals from Harvard University[4]. The Guide derived from five key questions, focusing on the following main aspects of patients' well-being:

- What is your understanding of where you are and of your illness
- Your fears or worries for the future
- Your goals and priorities
- What outcomes are unacceptable to you? What are you willing to sacrifice and not?
- What would a good day look like

A conversation flow can typically pursue the following steps:

Step 1: stepping up the conversation
Step 2: assessing illness understanding and information preferences
Step 3: sharing prognosis
Step 4: exploring key topics
Step 5: closing the conversation
Step 6: documenting the conversation.

In setting up the conversation, the purpose and benefits of the conversation are first introduced with the patient's permission to begin. Assessment of patients' understanding and information preferences then follows. Prognoses are then tailored and shared according to patients' readiness and preferences. Emotions are explored and heeded to with sensitivity and acknowledgement. The second main part of the conversation will then focus on the key issues: goals; fears and worries; sources of strength; critical abilities; trade-offs; and family perspectives. A discussion on trade-off will help the patient identify what interventions he or she is ready to endure, and what inherent abilities are not to be sacrificed. In closing, the main points discussed are summarised, with documentation of agreed goals and recommended actions. Throughout the conversation, commitment to the patient is affirmed with the realignment of hope. The Serious Illness Conversation Guide has been practiced in United States with good responses and outcomes[5,6]. A Hong Kong Chinese version is available after independent translation and back-translation with panel review, and the Institute of Ageing of the Chinese University of Hong Kong has produced for sharing an on-line video of its application using a real case scenario[7]. It should be noted that any communication guide is not meant to be a checklist, and flexible adaptation is advised.

ADVANCE CARE PLANNING

One of the goals of discussion in the care for advanced diseases is to prepare the patients and families well in advance, establishing a care plan and advance directives when facing an inevitable decline with incurable illnesses. The benefits are myriad. It is about:

- Understanding patients preferences
- Anticipating future plans
- Facilitating family discussions
- Respecting patients decisions and autonomy
- Maximising comfort and dignity at the end of life

There are common misconceptions to be clarified about advance care planning. It certainly is not about rationing treatment options, imposing one-off decisions, un-informed plan of treatment, painting a pessimistic future, or giving up. Clinical benefit from advance care planning is accumulating too even for old old patients. In a prospective randomised controlled trial in a university hospital in Australia of 309 elderly medical inpatients aged 80 and above who were followed up for six months or until death, significant improvement was seen from usual care plus facilitated advance care planning, versus usual care alone[8]. End-of-life wishes were more likely to be known and followed with advance care planning. Patients and families satisfaction with care were higher in the intervention group, and in particular, there were less stress, anxiety, and depression for family members. Older patients should not be denied of the benefit of well-conducted advance care planning. Patients should be given a right to understand that less is more, to reframe hope, and to be free from futile treatment and prolonged suffering.

More definitive evidence is emerging from further studies, systematic reviews and meta-analyses. An advance directive is the ultimate aim that is hoped to be achieved through advance care planning. However, it has to be borne in mind that the process of a fruitful discussion on advance care planning is a necessary pre-requisite, without which a proper advance directive cannot be sustained. Discussions and consultation on the need for legislation of advance directive continue. In the Federation survey on care for advanced diseases and palliative services, 775 public citizens and 779 doctors and dentists were surveyed by telephone. 80% of public and 88% of doctors/dentists would consider making an Advance Directive when facing serious illnesses. 63% and 67% respectively supported legislation of Advance Directive to safeguard the patients' decisions[9]. Plenty of many other barriers remain to be overcome, ranging from time, resources, professional engagement and public education.

LETTING GO

For patients and families with advanced diseases approaching the terminal stage, a peaceful death acceptance is an eventual goal that is hoped to be achieved. Likewise, for professionals providing end-of-life care, acceptance of dying is also a personal attribute that is desired for effective palliative practice[10] .Acceptance of death and dying may at times be difficult, often with fluctuations between preservation and letting go. The process is dynamic, though hopefully directed towards a general acceptance course if well supported. Quality communication is vital to support patients and families for this transition. Positive messages can still be delivered with the realignment of hope. Letting go is not the same as giving up, but rather a constructive approach in minimising painful futile treatment and prolonged suffering. Letting go is not the same as disconnection, but rather an affirmative coping in recognising the fate and the need to move forward with remembrance. Acceptance of dying can often be transformed into self-efficacy and productive strength of resilience. In the field of paediatrics palliative care where losing a child is especially painful and difficult, letting go could also be supported by a variety of factors: the certainty that child cannot be cured; postponed grief; perception of suffering; the ability to disentangle needs, and the ability to parent meaningfully[11]. Professionals can influence these factors to facilitate the transition through empathic communication.

The transition from fighting with preservation to acceptance with letting go is dynamic. Emotional reassurance that efforts have been given preceding

letting go, can help enable a peaceful acceptance yielding meaningful change in the sense of life. Hope is to be realigned always during the phases. A typical transition may go through four phases[12]:

- Reflection
- Understanding
- Presence
- Moving forward

Reflection is on perceiving the illness experience and the sufferings, with recognition of own preferences, expectations from both patient and family, and the view towards dying on spiritual, or faith aspects. Understanding is on embracing the certainty and uncertainty, exploring options and planning for goal-concordant care. Presence is regarding not abandoning the patient and family, allowing expression of feelings and emotions with time, pace and privacy. Bearing witness to patient's decline can help respect the patient wish to end suffering, and getting prepared for the final episode. Moving forward is vital in acceptance and letting go, with a shift of focus to dignity, quality of life, unfinished business, funeral affairs, legacy and ensuing goals for the bereaved[12].

COMMUNICATION IN CARE AND CARE IN COMMUNICATION

Many, if not all, aspects of health care and services delivery rely on good communication.

Quality communication is especially important in care for advanced diseases. The words of an older person in residential care home receiving our palliative home care are well worth reflecting:

"溝通固然重要，怎樣溝通、說甚麼話, 以甚麼態度說，有不同效果。所以是否說話的品質需要成為一種要求的品質？"

Quality of communication in medicine truly encompasses science, art and compassion.

References

1. Buckman R and Kason Y. How to break bad news: a guide for health care professionals. The Johns Hopkins University Press, Baltimore, 1992
2. Baile W F, Buckman R, Lenzi R et al. SPIKES—A six step protocol for delivering bad news: application to the patient with cancer. The Oncologist 2000; vol (5); issue 4:302-11
3. Politi MC, Dizon DS, Frosch DL, Kuzemchak MD, Stiggelbout A. Importance of clarifying patients' desired role in shared decision making to match their level of engagement with their preferences. BMJ 2013;347:f7066
4. Bernacki R, Hutchings M, Vick J. et al. Development of the Serious Illness Care Program: a randomised controlled trial of a palliative care communication intervention. BMJ Open 2015; 5(10):e009032.
5. Bernacki R, Paladino J, Neville BA et al. Effect of the Serious Illness Care Program in outpatient oncology: a cluster randomized clinical trial. JAMA Internal Medicine 2019; 179(6): 751-759.
6. Paladino J, Bernacki R, Neville BA et al. Evaluating an intervention to improve communication between oncology clinicians and patients with life-limiting cancer: a cluster randomized clinical trial of the Serious Illness Care Program. JAMA Oncology 2019: 5(6):801-809.
7. Lo R, Kong S, Natarajan D et al. Serious illness communication video. Institute of Ageing, Chinese University of Hong Kong. 2018. https://youtu.be/f55dlCKvH6w
8. Detering KM, Hancock AD, Reade MC, Silvester W. The impact of advance care planning on end of life care in elderly patients: randomised controlled trial. BMJ 2010; 340:c1345
9. The Federation of Medical Society of Hong Kong Foundation. Survey on care for advanced diseases and palliative services. The Hong Kong Medical Diary 2016; vol 21: issue 11; 35-36
10. Zimmermann C. Acceptance of dying. A discourse analysis of palliative care literature. Soc Sci Med 2012; 75(1):217-224
11. Kars MC, Grypdnock MHF, Beishuzen A, Meijen-van den Bergh EMM, van Delden JJM. Factors influencing parental readiness to let their child with cancer die. Pediatr Blood Cancer 2010; 54: 1000-1008
12. Lowry S. Letting go before a death: a concept analysis. J Adv Nurs 2008; 63(2):208-215

Prevenar 13®

Pneumococcal polysaccharide conjugate vaccine (13-valent, adsorbed)

Protect your patients and their families from Pneumococcal Diseases[1]

Elderly aged 65+ with chronic diseases are more likely to develop pneumococcal pneumonia:

DIABETES

2.8 folds[2*]

CHRONIC CVD[†]

3.8 folds[2*]

CHRONIC LUNG DISEASE

7.7 folds[2*]

YOUR ROLE IS KEY

PREVENAR 13® ABBREVIATED PACKAGE INSERT **1. TRADE NAME:** PREVENAR 13® **2. PRESENTATION:** A homogeneous white suspension for injection (0.5ml) supplied as a pre-filled syringe. **3. INDICATIONS:** Active immunisation for the prevention of pneumococcal disease caused by *Streptococcus pneumoniae* serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F and 23F in adults and children aged more than 6 weeks of age. The use of Prevenar 13 should be guided by official recommendations. **4. DOSE & ADMINISTRATION:** Intramuscular administration only. The immunisation schedules should be based on official recommendations. Infants aged 6 weeks - 6 months: The primary infant series consists of three doses, with the first dose usually given at 2 months of age and with an interval of at least 1 month between doses. The first dose may be given as early as six weeks of age. A fourth (booster) dose is recommended after 12 months of age, and at least 2 months after the third dose. Unvaccinated children aged 7–11 months: 3 doses. Unvaccinated children aged 12–23 months: 2 doses. Unvaccinated children aged 24 months to 17 years: One single dose. Adults: One single dose. For more dosage information, please refer to the full Prescribing Information. **5. CONTRAINDICATIONS:** Hypersensitivity to the active substances or to any of the excipients, or to diphtheria toxoid. Allergic reaction or anaphylactic reaction following prior administration of Prevenar (7-valent). **6. WARNINGS & PRECAUTIONS:** Not for intravenous or intravascular administration; as with other vaccines, the administration should be postponed in subjects suffering from acute moderate or severe febrile illness; should not be given to individuals with thrombocytopenia or any coagulation disorder that would contraindicate intramuscular injection unless the potential benefit clearly outweighs the risk of administration; will not protect against *Streptococcus pneumoniae* serotypes other than those included in the vaccine nor other microorganisms that cause invasive disease, pneumonia, or otitis media; may not protect all individuals receiving the vaccine from pneumococcal disease. Individuals with impaired immune responsiveness may have reduced antibody response to active immunisation. Safety and immunogenicity data for Prevenar 13 are available for certain high-risk groups such as children and adolescents with sickle cell disease and children and adults with HIV infection or with a haematopoietic stem cell transplant. Data are not currently available for individuals in other immunocompromised groups (e.g., malignancy, or nephrotic syndrome) and vaccination should be considered on an individual basis. Children below 2 years old should receive the appropriate-for-age Prevenar 13 vaccination series. The potential risk of apnoea and the need for respiratory monitoring for 48–72h should be considered when administering the primary immunisation series to very premature infants (born ≤ 30 weeks of gestation), and particularly for those with a previous history of respiratory immaturity. Antipyretic treatment should be initiated according to local treatment guidelines. Prophylactic antipyretic medication is recommended for children with seizure disorders or with a prior history of febrile seizures and for all children receiving Prevenar 13 simultaneously with vaccines containing whole cell pertussis. **7. INTERACTIONS:** Infants and children aged 6 weeks to 5 years: Can be given with any of the following vaccine antigens, either as monovalent or combination vaccines: diphtheria, tetanus, acellular or whole cell pertussis, *Haemophilus influenzae* type b, inactivated poliomyelitis, hepatitis B, meningococcal serogroup C, measles, mumps, rubella and varicella. Can also be given concomitantly between 12–23 months with the tetanus toxoid conjugated meningococcal polysaccharide serogroup A, C, W and Y vaccine. In clinical trials, where there was concomitant administration of Prevenar 13 and rotavirus vaccine, no change in the safety profiles of these vaccines was observed. When Prevenar 13 is administered concomitantly with Infanrix hexa (DTaP-HBV-IPV/Hib), the rates of febrile reactions are similar to those seen with concomitant administration of Prevenar (7-valent) and Infanrix hexa. Children 6 to 17 years of age and adults 18 to 49 years of age: No data are currently available regarding concomitant use with other vaccines. Adults aged 50 years and older: May be administered concomitantly with seasonal trivalent or quadrivalent inactivated influenza vaccine. Different injectable vaccines should always be given at different injection sites. **8. PREGNANCY AND LACTATION:** Prevenar 13 is not indicated or recommended for use in pregnant women and has not been evaluated for potential harmful effects during pregnancy in humans. Safety during lactation has not been established. **9. SIDE EFFECTS:** Children: Decreased appetite; fever; irritability; drowsiness/increased sleep; restless sleep/decreased sleep; any vaccination-site erythema, induration/swelling or pain/tenderness; vaccination-site pain/tenderness interfering with movement; diarrhoea, vomiting; rash. Children and adolescents aged 5 to 17 years of age: Decreased appetite; irritability; any vaccination-site erythema; induration/swelling or pain/tenderness; drowsiness/increased sleep; restless sleep/decreased sleep; vaccination-site tenderness (including impaired movement); fever; headache; rash; urticaria/urticaria-like rash; vomiting; diarrhoea. Adults: decreased appetite; headache; diarrhoea; vomiting; rash; chills; fatigue; vaccination-site erythema; vaccination-site induration/swelling; vaccination-site pain/tenderness; limitation of arm movement; joint pain; muscle pain; fever. **(Please refer to the full Prescribing Information for details)** **Reference:** HK LPD version July 2018. **Date of preparation:** APR 2019 **Identifier number:** PR13-0419 **FULL PRESCRIBING INFORMATION IS AVAILABLE UPON REQUEST.**

PP-PNA-HKG-0075 Feb2020

† Cardiovascular disease

* Relative to the healthy counterparts

References: 1. Pneumococcal polysaccharide conjugate vaccine, 13-valent adsorbed Prescribing Information. Pfizer Corporation Hong Kong Limited. (Version Jul 2018).
2. Shea KM, et al. Open Forum Infect Dis. 2014. doi:10.1093/ofid/ofu024.

Pfizer Corporation Hong Kong Limited

18/F., Kerry Centre, 683 King's Road, Quarry Bay, Hong Kong

Tel: (852) 2811 9711 Fax: (852) 2590 6364

Website: www.pfizer.com.hk

Positive Ageing and Good End of Life – Interview with Dr Edward Che-hung LEONG

Dr Edward Che-hung LEONG

Interviewee: Dr Edward Che-hung LEONG

GBM, GBS, OBE, JP, MBBS (HK), FRCS (ENG), FRCS (EDIN), FACS, FRACS, FCSHK, FHKAM (SURGERY)

Former Member, Legislative Council of Hong Kong;
Former Member, Executive Council of HKSAR;
Former Chairman, Elderly Commission;
Former Chairman, Hospital Authority;
Former Chairman, Council of University of Hong Kong

The issue of our ageing population in Hong Kong has been generating much concern and debate in the society. With a lower fertility rate and longer life expectancy, it is expected to result in a rise in the old-age dependency ratio and decline in the labour force in Hong Kong. Many people may have the misconception that the elderly are a burden to the society. In fact, with the improvement in healthcare services, the elderly are generally healthier and still able to contribute to the society.

For the lifestyle article in this issue, Dr Edward Che-hung Leong was interviewed by Dr Raymond SK Lo, our Immediate Past President and Issue Editor and Ms Nancy Chan, Executive Director of the Federation. During the interview, they shared and exchanged views on different issues related to positive ageing and a good end of life.

AGE IS ONLY A NUMBER

Q. : How can we attain a positive and happy life after retirement?

There are four key factors to a happy post-retirement life – active ageing, flexible retirement, self-esteem and tools to facilitate the daily life of the elderly.

The elderly can make contributions to the society by staying at the labour market, taking care of their family members or participating in social service as volunteers. "Age alone is not significant; it is only a number," said Dr Leong. Appointed to be the Chairman of Elderly Commission in 2005, Dr Leong visited parks and daycare centres to talk to the elderly. It was depressing to see them just watching old newspaper or sitting in the park to kill time. The elderly said they wished to learn new things, and this has led Dr Leong to the idea of establishing the Elder Academy. The Elderly Commission has been jointly organising with partners a school-based Elder Academy Scheme, offering various degree courses in some local universities as well as free courses in existing primary and secondary schools. With this arrangement, the elderly is able to go back to school to equip themselves with new knowledge and skills. Attending classes together will not only enhance the communication among the elderly, but will also encourage networking between the elderly and the younger generation. In the long run, this is an invaluable opportunity for the elderly to establish their self-esteem and no longer feel that they are a burden to their families and the society. The City University of Hong Kong is one of the successful examples. With the great success in developing the Elder Academy, Hong Kong was taken as a reference for other places, like Thailand, Malaysia, Taiwan and Singapore.

Since people are generally more health-conscious, and thus, much healthier nowadays, flexible retirement should be practised especially in public organisations. The retirement policy of the Hospital Authority is self-contradictory in the way that there are not enough medical professionals in the public health sector on one hand, but on the other hand, they are required to retire at age 60. The retired doctors are the most experienced and knowledgeable professionals in the medical field. It is commonly believed that the promotion of junior doctors will be obstructed if the retirement age is to be extended. To resolve this problem, retired doctors can withdraw from the management level and work as clinical doctors, consultants or mentors to the junior doctors. In addition, the Hospital Authority's part-time employment policy should also be reviewed by allowing the rehired employees to stay in the same hospital or clinic despite a change in the job nature. This may assist in encouraging more medical professionals to stay at work after their retirement.

It is a general belief that children products have a huge market, yet the purchasing power of the elderly is usually under-estimated. Enjoying life is not a privilege to only the young people. The elderly also need to dress up nicely, establish a positive public image as well as maintain a higher level of well-being. Currently, the silver hair market is always being associated with negative items, such as wheelchairs, crutches, adult diapers or shower commode chairs. Without tools to facilitate the elderly in daily life, they always need to seek help from others. If more tools could be developed, the elderly can take care of themselves better and have a lower reliance on others. As a result, this may boost their self-esteem and independence.

Furthermore, the elderly should adopt a positive mindset to all the signs and symptoms of ageing. Instead of complaining about these ageing signs, they can mentally prepare themselves for the changes ahead and try to embrace them with an open heart. They also need to change the way they communicate with their families. Paternalism is no longer applicable in today's world. In other words, the elderly may try to develop a habit of treating the younger family members as friends.

MEDICAL-SOCIAL COLLABORATION

Q. : What is your view towards the District Health Centre (DHC)?

The District Health Centre is a good concept for the elderly community. It helps to alleviate the burden of the Hospital Authority by providing primary healthcare services to the elderly in the community level. In order to enhance the quality of services at the DHC, improved communication between DHC and the elderly through social workers and better co-ordination between DHC and the private family physicians, pharmacies and the public health sector respectively are necessary.

NUTRICIA
Fortisip®
Compact Protein

FIGHT AGAINST WEIGHT LOSS TO IMPROVE CANCER TREATMENT OUTCOMES[1,2]

"Medical nutrition is an integral part of cancer treatment. It can have a positive effect on the outcomes of therapy and the quality of patient life." [1,3,4]

ESPEN recommendation

Increase protein intake to 1.5g/kg/day
to fulfill high protein need to support weight and muscle maintenance[1]

TASTE CAN CHANGE OUTCOMES SHOULDN'T

Introducing new sensational flavours

- Up to 70% of cancer patients experience taste changes during treatment which can have a negative impact on nutritional status and lead to greater weight loss.[5,6]
- Validated in partnership with patients - **New sensational flavours** have been developed to address the changing taste profiles of cancer patients undergoing treatment.

Hot Tropical Ginger flavour | Neutral flavour | Cool Red Fruits flavour

NEW
Cool Red Fruits flavour

Contains menthol derivatives which provide a cooling effect to activate the trigeminal nerve[7] and induce a pleasant cool sensation

84% of oncology patients like Cool Red Fruits flavour[8]

- **Highest Energy** — 306kcal / bottle*
- **Highest Protein Content** — 18g / bottle
- **Smallest Volume** — Only 125mL

References: 1. Arends J, Baracos V, Bertz H, et al. ESPEN expert group recommendations for action against cancer-related malnutrition. Clin Nutr. 2017;36(5):1187–96. 2. Kabata P, et al. Preoperative nutritional support in cancer patients with no clinical signs of malnutrition-prospective randomized control trial. Support Care Cancer. 2015. Feb; 23(2):365-370. 3. Baldwin C, et al. Oral nutritional interventions in malnourished patients with cancer: a systematic review and meta-analysis. Journal of the National Care Institute. 2012 Mar 7; 104(5):371-385. 4. Andreyev HJN, Norman AR, Oates J, Cunning D. Why do patients with weight loss have a worse outcome when undergoing chemotherapy for gastrointestinal malignancies? Eur J Cancer. 1998;34(4):503-509. 5. Spotten et al. Annals of Oncology. 2017; 28: 969–984. 6. Boltong A, et al. Support Care Cancer. 2012; 20(11): 2765–2774. 7. TRP Ion Channel Function in Sensory Transduction and Cellular Signaling Cascades Book. 8. Data on file: Sensory Study 2018. Nutricia.

Hotline: 3560 5498
www.nutricialclinical.com.hk
Nutricia Clinical (Hong Kong) Limited

AMN-FTS-2010

The government aimed to establish the District Health Centre in 18 districts within two years. Dr Leong suggested to slow down the process. The success of Kwai Tsing is largely due to the local District Council Member pioneers, who have been working on promoting district healthcare service for years, as well as the captive environment of Kwai Tsing where the residents preferred to stay in the community for medical services. Therefore, Kwai Tsing's success may not happen to other districts and careful consideration and planning are required to extend this to other districts.

ELDERLY HOUSING

Q. : What is your view towards elderly housing and what are the limitations?
There are four types of residential care services for the elderly – Elderly Home, Care and Attention Home, Nursing Home, as well as Infirmary. The elderly is distributed to different residential care services based on their health conditions and healthcare needs. They may need to transfer from one to another residential care service as they get older. However, the root of the problem is that the various residential care services are managed by different departments viz., the Social Welfare Department, the Department of Health and the Hospital Authority. Therefore, to ensure the quality of services, one-stop service should be introduced.

About 70% of Residential Care Homes are run by private organisations. Most of the elderly settle the payment by using the subsidy of Comprehensive Social Security Assistance Scheme. If their family members pay extra money for a better quality of services, the amount of subsidy will be deducted. As a result, the services received is restricted by the amount supported by the scheme. There is also much discussion on the shortage of Residential Care Homes/Contract Homes, and some elderly prefer to remain at their familiar homes. It results in the launch of the ageing-in-place scheme by the Elderly Commission as well as the home care voucher by the Social Welfare Department. Social service has to be enhanced to equip this group of elderly on the use of voucher and other services that are rendered to them.

A new model of loan arrangement - the Reverse Mortgage is designed for the elderly who own residential property. The elderly can use their residential property as security to borrow from a lender. They remain as the owner of the property and are able to stay in the property for the rest of their lives. However, the potential problem of this new model is that the descendants of these elderly may wish to inherit the residential property, leading to the difficulty to reach a consensus.

The Senior Citizen Residences Scheme is another option for the elderly. It provides other than the flat, recreation, medical and care services under one roof for the middle-income elderly. With the "long-lease" arrangement, it is not only that the elderly do not have to pay for the rental, they can also enjoy the various services by paying only a small amount of money. However, there is a restriction on the age. Only senior citizens aged 60 or above are eligible. There is a potential risk for couples with a huge age gap. If the deceased leaves a spouse aged below 60, he/she may be requested to move out even though they have already spent most of their saving for the scheme. Although there are options for elderly housing, there are also numerous potential problems yet to be resolved.

GOOD END OF LIFE

Q. : What do you envision is a good end of life?
For people who are suffering from terminal illnesses, resuscitation may only prolong one's pain unnecessarily. "It is a sin to kill, but it is also a sin to sustain an unnecessary life," said Dr Leong. Euthanasia has long been a controversial topic and contradicts the basic principle and value of the medical profession. There is however a need to legislate the wishes of patients if they have signed the "Do Not Resuscitate" Form. On occasions which the will of patients has been neglected, and the family members cannot come to a consensus, the elderly will have to undergo prolonged suffering unnecessarily.

The Chinese tradition of not discussing "death" during lifetime may lead to unfinished business and inadequate communication on after-death arrangement. It is always advisable for the elderly to keep an open communication with family members on all end-of-life issues.

A DAY IN LIFE OF DR LEONG

Q. : Can you share your daily life with us?
"I seldom have vacations. Work-life balance is important, yet my work is a part of my life," said Dr Leong. He wakes up at 6 am and goes to work at 7:15 am. He spends the morning in surgeries or on the news. After lunchtime, he spends his time in clinical practice or meetings. Dr Leong makes his rounds at the Hong Kong Sanatorium & Hospital in the evening. Under the COVID-19, since many meetings and events are cancelled, this allows him to spend more time with his family.

Q. : How to maintain a happy marriage?
"We both are working and involved in various roles in the community. The key to a happy marriage is mutual support, trust and appreciation towards each other's activities, "said Dr Leong.

Q. : Any advice for medical professionals regarding retirement?
Retirement should not be age-related. A doctor should retire from his practice if he knows that further practice may produce harm to his patients. There are, of course, other ways that he can continue to contribute to the society.

Dr CH Leong's distinguished family of NINE including four in the health care profession (The late Dr KL Leong, an Aberdeen HK family physician(4th from right); the late Mrs KL Leong(5th from left) a registered nurse; Prof John CY Leong(2nd from right) an orthopaedic surgeon; and Dr CH Leong(3rd from right))

Certificate Course for Doctors, Nurses, Paramedics and Allied Health Workers ■ Course No. C352 ■ CME/CNE Course

Certificate Course on

Complaint Management 2020

(Video Lectures)

Jointly organised by

The Federation of Medical Societies of Hong Kong

Hong Kong Society for Healthcare Mediation

Date	Topics	Speakers
17 Jul	Complaint system The rights-, interest-, and power-based complaint system Complaint system design - with resolution and preventive focus	Dr Nga-Lei HO 何雅莉醫生
24 Jul	Complaint – is somebody at fault? Complaint system of Medical Council and other regulatory bodies	Dr Robert LAW 羅致廉醫生
31 Jul	Media in complaint Handling media in adverse events	Dr Carl LEUNG 梁家駒醫生
7 Aug	Complaint – how-to Practical tips on handling complaints and how to survive a legal action	Ms Suk-chong LEUNG Ms Asha SHARMA Ms Janice DAO
14 Aug	Complaint – what's new Just culture, open disclosure and apology handling	Dr Kai-ming CHOW 周啟明醫生
21 Aug	Patients' complaint Patients' complaint avenue in HK What motivate patients to complain What they want and deserve	Dr Kim-lian ONG 王金蓮醫生

Date : 17, 24, 31 July & 7, 14, 21 August, 2020 (Every Friday)
Time : 7:00 p.m. – 8:30 p.m.
Course Feature : Video lectures (with Q&A platform)
Course Fee : HK$1,000 (6 sessions)
Enquiry : The Secretariat of The Federation of Medical Societies of Hong Kong
Tel.: 2527 8898 Fax: 2865 0345 Email: vienna.lam@fmshk.org
Application from can be downloaded from website : http://www.fmshk.org

Sunday	Monday	Tuesday	Wednesday	Thursday	Friday	Saturday
			1	* Certificate Course in Allergy 2020 (Video Lectures) 2	* Certificate Course on Ultrasound Diagnosis of Fetal Anomalies (Video Lectures) 3	4
5	6	* HKMA-HKS&H CME Programme 2019-2020 Topic: Management of Behavioural and Psychological Symptoms of Dementia 7	* The Hong Kong Neurosurgical Society Monthly Academic Meeting –To be confirmed * Certificate Course on Update in Clinical Sleep Medicine 2020 (Video Lectures) 8	* Certificate Course in Allergy 2020 (Video Lectures) 9	* Certificate Course on Ultrasound Diagnosis of Fetal Anomalies (Video Lectures) 10	* Refresher Course for Health Care Providers 2019/2020 - Common eye sympoms/signs/treatment from young to old for primary health care and new eye procedures 11
12	* Certificate Course in Clinical Cytogenetics and Genetics 2020 (Video Lectures) 13	* HKMA Annual General Meeting 14	* Certificate Course on Update in Clinical Sleep Medicine 2020 (Video Lectures) 15	* Certificate Course in Allergy 2020 (Video Lectures) 16	17	18
19	* Certificate Course in Clinical Cytogenetics and Genetics 2020 (Video Lectures) 20	* HKMA-GHK CME Programme 2020 Topic: Treatment on Breast Cancer 21	* Certificate Course on Update in Clinical Sleep Medicine 2020 (Video Lectures) 22	* Certificate Course in Allergy 2020 (Video Lectures) 23	24	25
26	* Certificate Course in Clinical Cytogenetics and Genetics 2020 (Video Lectures) 27	28	* Certificate Course on Update in Clinical Sleep Medicine 2020 (Video Lectures) 29	* Certificate Course in Allergy 2020 (Video Lectures) 30	31	

End-of-Life Care Workshops
Department of Medicine & Therapeutics
Faculty of Medicine
The Chinese University of Hong Kong

CU Medicine

Date:
24th September 2020 to 5th November 2020, every Thursday evening (7:00 p.m. – 9:00 p.m.)

Venue:
Lecture Theatre, 2/F Lui Che Woo Clinical Sciences Building, Prince of Wales Hospital, Shatin, N.T.

Target participants:
Doctors, nurses, allied health professionals, social workers and all health care professional interested in end-of-life care

Maximum number of Participants: 150

Course Fees: $1,800* (by crossed cheque)

Content:

Date	Topic	Speaker
24 Sept 20	01. Introduction: Principles and philosophy of palliative and end of life care	Dr Raymond Lo
	02. What is a good death? Patients' perspectives: dignity, autonomy, their expectations of health care professionals	Prof Jean Woo
8 Oct 20	03. Ethical issues: decision-making, advance directives, assisted death	Dr CY Tse
	04. Breaking bad news: a Chinese perspective	Dr CY Tse
15 Oct 20	05. Principles of pain control and use of opioids	Dr KY Chan
	06. Symptom control for advanced cancer and non-cancer patient	Dr Alice Mok
22 Oct 20	07. End-of-life care in non-cancer setting	Dr Raymond Lo
	08. Professionals' reflections in facing death and dying	Dr Vincent Tse
5 Nov 20	09. End-of-life for older patients	Prof T Kwok
	10. Grief and bereavement issues	Ms C Tsang

Registration/enquiries: ****Accreditation in progress**

Contact : Ms Yu/Ms Mow
Tel : 9168 7005
Email : b135095@cuhk.edu.hk
Address : End-of-Life Care Workshop, 9/F., c/o Dept. of Medicine & Therapeutics, Lui Che Woo Clinical Sciences Building, Prince of Wales Hospital, Shatin, NT

Website : http://www.med.cuhk.edu.hk/taughtpostgraduate.html (Deadline) : 24 Aug 2020

Updated on April 1, 2020 *Provisional

Date / Time	Function	Enquiry / Remarks
2 THU 7:00 PM	**Certificate Course in Allergy 2020 (Video Lectures)** Organiser: The Federation of Medical Societies of Hong Kong; Speaker: Dr Alson Wai-ming CHAN	Ms. Vienna LAM Tel: 2527 8898
3 FRI 7:00 PM	**Certificate Course on Ultrasound Diagnosis of Fetal Anomalies (Video Lectures)** Organiser: The Federation of Medical Societies of Hong Kong; Speaker: Dr Meliza Choi-wah KONG	Ms. Vienna LAM Tel: 2527 8898
7 TUE 1:00 PM	**HKMA-HKS&H CME Programme 2019-2020** **Topic: Management of Behavioural and Psychological Symptoms of Dementia** Organiser: Hong Kong Medical Association, Hong Kong Sanatorium & Hospital; Speaker: Dr PAN Pey-chyou; Venue: The HKMA Wanchai Premises, 5/F, Duke of Windsor Social Service Building, 15 Hennessy Road, Wanchai	HKMA CME Department 2527 8285 1 CME Point
8 WED 7:30 AM	**The Hong Kong Neurosurgical Society Monthly Academic Meeting –To be confirmed** Organiser: Hong Kong Neurosurgical Society; Speaker(s): Dr CHEUNG Wing-lok; Chairman: Dr PO Yin-chung; Venue: Conference Room, F2, Department of Neurosurgery, Queen Elizabeth Hospital; or via Zoom meeting	CME Accreditation College: 1.5 points College of Surgeons of Hong Kong Enquiry: Dr Calvin MAK Tel: 2595 6456 Fax. No.: 2965 4061
7:00 PM	**Certificate Course on Update in Clinical Sleep Medicine 2020 (Video Lectures)** Organiser: The Federation of Medical Societies of Hong Kong; Speaker: Dr Crover HO	Ms. Vienna LAM Tel: 2527 8898
9 THU 7:00 PM	**Certificate Course in Allergy 2020 (Video Lectures)** Organiser: The Federation of Medical Societies of Hong Kong; Speaker: Dr Adrian Yong-yuen WU	Ms. Vienna LAM Tel: 2527 8898
10 FRI 7:00 PM	**Certificate Course on Ultrasound Diagnosis of Fetal Anomalies (Video Lectures)** Organiser: The Federation of Medical Societies of Hong Kong; Speaker: Dr Anita Sik-yau KAN	Ms. Vienna LAM Tel: 2527 8898
11 SAT 2:15 PM	**Refresher Course for Health Care Providers 2019/2020 -** **Common eye sympoms/signs/treatment from young to old for primary health care and new eye procedures** Organiser: Hong Kong Medical Association, HK College of Family Physicians & HA-Our Lady of Maryknoll Hospital; Speaker: Dr Nai-man LAM; Venue: Lecture Halls A&B, 4/F, Block G, Wong Tai Sin Hospital	Ms. Clara TSANG 2354 2440 2 CME Point
13 MON 7:00 PM	**Certificate Course on Ultrasound Diagnosis of Fetal Anomalies (Video Lectures)** Organiser: The Federation of Medical Societies of Hong Kong; Speaker: Chev. CHAN Wing-kwong	Ms. Vienna LAM Tel: 2527 8898
14 TUE 9:00 PM	**HKMA Annual General Meeting** Organiser: The Hong Kong Medical Association; Chairman: Dr. HO Chung-ping, MH, JP. Venue: The HKMA Wanchai Premises, 5/F, Duke of Windsor Social Service Building, 15 Hennessy Road, Wanchai	Ms. Christine WONG Tel: 2527 8285
15 WED 7:00 PM	**Certificate Course on Update in Clinical Sleep Medicine 2020 (Video Lectures)** Organiser: The Federation of Medical Societies of Hong Kong; Speaker: Dr Joyce LAM	Ms. Vienna LAM Tel: 2527 8898
16 THU 7:00 PM	**Certificate Course in Allergy 2020 (Video Lectures)** Organiser: The Federation of Medical Societies of Hong Kong; Speaker: Dr Jaime S ROSA DUQUE	Ms. Vienna LAM Tel: 2527 8898
20 MON 7:00 PM	**Certificate Course in Clinical Cytogenetics and Genetics 2020 (Video Lectures)** Organiser: The Federation of Medical Societies of Hong Kong; Speaker: Dr Edmond Shiu-kwan MA	Ms. Vienna LAM Tel: 2527 8898
21 TUE 1:00 PM	**HKMA-GHK CME Programme 2020** **Topic: Treatment on Breast Cancer** Organiser: Hong Kong Medical Association, Gleneagles Hong Kong Hospital; Speaker: Dr Roger NGAN, Dr Lorraine CHOW; Venue: The HKMA Wanchai Premises, 5/F, Duke of Windsor Social Service Building, 15 Hennessy Road, Wanchai	HKMA CME Department 2527 8285 1 CME Point
22 WED 7:00 PM	**Certificate Course on Update in Clinical Sleep Medicine 2020 (Video Lectures)** Organiser: The Federation of Medical Societies of Hong Kong; Speaker: Dr Steve WONG	Ms. Vienna LAM Tel: 2527 8898
23 THU 7:00 PM	**Certificate Course in Allergy 2020 (Video Lectures)** Organiser: The Federation of Medical Societies of Hong Kong; Speaker: Dr Agnes Sze-yin LEUNG	Ms. Vienna LAM Tel: 2527 8898
27 MON 7:00 PM	**Certificate Course in Clinical Cytogenetics and Genetics 2020 (Video Lectures)** Organiser: The Federation of Medical Societies of Hong Kong; Speaker: Dr Stephen Tak-sum LAM	Ms. Vienna LAM Tel: 2527 8898
29 WED 7:00 PM	**Certificate Course on Update in Clinical Sleep Medicine 2020 (Video Lectures)** Organiser: The Federation of Medical Societies of Hong Kong; Speaker: Dr Kah-lin CHOO	Ms. Vienna LAM Tel: 2527 8898
30 THU 7:00 PM	**Certificate Course in Allergy 2020 (Video Lectures)** Organiser: The Federation of Medical Societies of Hong Kong Speaker: Dr June King-chi CHAN	Ms. Vienna LAM Tel: 2527 8898

Answers to Dermatology Quiz

Answers:

1. Folliculitis Deculvans
   The diagnosis is folliculitis deculvans. It is a form of alopecia associated with scarring – scarring alopecia. Any hairy area like scalp, underarm, pubis can be involved; however, the disease is commonly confined to the scalp. Typically, several hairs get off from a single hair follicule; thereby, the scalp looks like tufted as a toothbrush. The cause is unknown. Although bacteria, especially Staphylococcus aureus is commonly isolated from the affected area, its role in the pathogenesis is uncertain.

2. Folliculitis deculvans is a cicatricial scarring alopecia in which a chronic inflammatory process is causing destruction of hair follicles. Clinical suspicion with scalp skin biopsy can reach the definitive diagnosis. Histologically, there is a folliculitis; otherwise, it is not specific. The dermis of adjacent follicles is also destroyed by infiltration of mixed inflammatory cells. Neutrophilic infiltration is dominant in the early lesions and additionally lymphocytes and plasma cells in advanced lesions. Bacterial culture may show secondary bacterial infection. Fungal culture should be ordered and the positive result may suggest other diagnosis particularly kerion, a kind of fungal infection.

3. There is no definite treatment for folliculitis deculvans. The management is mainly aimed at controlling the symptoms and inflammation. Oral antibiotic such as tetracycline group, rifampicin, cloxacillin, clindamycin and even quinolones have been tried with variable results. In some severe cases, the addition of systemic corticosteroids may be helpful. Oral isotretinoin may result in long-term control in some patients. Methyl aminolevulinate photodynamic therapy is reported to be efficacious.

Dr Chi-keung KWAN
MBBS(HK), MRCP(UK), FRCP(Lond, Glasg), Dip Derm(Glasg), PDipID(HK), FHKCP, FHKAM(Medicine)
Specialist in Dermatology and Venereology

Entresto®
sacubitril/valsartan

THE SOONER, THE BETTER.

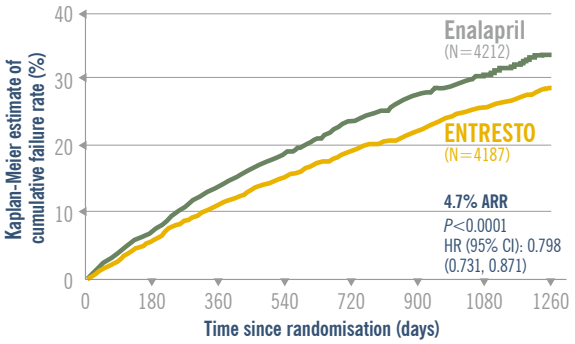
Keep HFrEF patients alive, out of the hospital, and on the right path

The path to slowing disease progression starts with ENTRESTO. Improve survival by reducing the risk of HF events, and give them more time to keep doing what they love.

In the PARADIGM-HF study,

ENTRESTO reduced the risk of CV death or HF hospitalisation as a first event by 20%

vs enalapril (primary end point)[1*]



70% of patients were NYHA Class II[2]

In post hoc analyses of the PARADIGM-HF study,

ENTRESTO reduced the risk of sudden cardiac death in HF patients by 20% vs enalapril ($P=0.0082$)[1†]

ENTRESTO reduced the risk of a primary end point event in both the most and least stable HF patients[3‡]

ENTRESTO helped slow the clinical progression of HF vs enalapril[4§]

- ⬇ **16%** fewer CV hospitalisations ($P<0.001$)
- ⬇ **30%** lower rate of ED visits ($P=0.017$)
- ⬇ **16%** less likely to require intensification of outpatient HF therapy

By slowing disease progression, ENTRESTO helps keep HF patients out of the hospital and living longer.

ARR = absolute risk reduction; EF = ejection fraction; ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; HF = heart failure; HFrEF = heart failure with reduced ejection fraction

*PARADIGM-HF was a multinational, randomised, double-blind, active-controlled, 2-arm event-driven trial comparing the long-term efficacy and safety of enalapril and ENTRESTO in 8442 patients in NYHA classes II–IV with chronic symptomatic HF and reduced EF (LVEF ≤40%. This was changed to ≤35% by an amendment to the protocol on 15 December, 2010). Patients were required to discontinue their existing ACE inhibitor or ARB therapy and entered a sequential single-blind run-in period during which patients received treatment with enalapril 10 mg twice daily, followed by treatment with ENTRESTO 49 mg/51 mg twice daily, increasing to 97 mg/103 mg twice daily. Patients were then randomised to the double-blind period of the study to receive either ENTRESTO 97 mg/103 mg (n=4209) or enalapril 10 mg twice daily (n=4233). Patients received treatment for up to 4.3 years, with a median duration of follow-up of 27 months; 3271 ENTRESTO patients were treated for more than 1 year.[1] †This post hoc analysis of PARADIGM-HF examined the effect of ENTRESTO compared with enalapril on mode of death in HF patients (a total of 1546 patients died, including 711 in the ENTRESTO group and 835 in the enalapril group [17% and 19.8% of total patients, respectively]). The majority of deaths were cardiovascular (80.9%; n=1251), and the majority of these CV deaths were categorised as sudden (44.8%) or HF related (26.5%).[1] ‡This post hoc analysis of PARADIGM-HF examined the risk of the primary outcome based on presence of and time from a prior HF hospitalisation as a measure of clinical stability. Patients having their most recent HF hospitalisation within 3 months of screening (n=1611) were defined as least stable, while patients who had no prior HF hospitalisation (n=3125) were defined as the most stable. Compared to patients in the enalapril group, patients in the ENTRESTO group, regardless of presence of and time from a prior HF hospitalisation, had a reduction of at least 19% in the risk of a primary end point event.[1,3] §This post hoc analysis of PARADIGM-HF focused on prespecified measure of nonfatal clinical deterioration. In comparison with the enalapril group, fewer ENTRESTO patients required intensification of medical treatment for HF (520 for ENTRESTO vs 604 for enalapril; HR, 0.84; 95% CI, 0.74-0.94; P=0.003) or an ED visit for worsening HF (HR, 0.66; 95% CI, 0.52-0.85; P=0.001).[1,4]

References: 1. ENTRESTO Core Data Sheet, Version 1.2. Novartis Pharmaceuticals, July 2017. **2.** McMurray JJ, et al. *N Engl J Med*. 2014;371(11):993-1004. **3.** Solomon SD, et al. *JACC Heart Fail*. 2016;4(10):816-822. **4.** Packer M, et al. [Abstract P1705]. *Circulation*. 2015;131(1):54-61.

ENTRESTO tablets Important note: Before prescribing, consult full prescribing information. **Presentation: ENTRESTO 50 mg film-coated tablets** Each film-coated tablet contains 24.3 mg sacubitril and 25.7 mg valsartan (as sacubitril valsartan sodium salt complex). **ENTRESTO 100 mg film-coated tablets** Each film-coated tablet contains 48.6 mg sacubitril and 51.4 mg valsartan (as sacubitril valsartan sodium salt complex). **ENTRESTO 200 mg film-coated tablets** Each film-coated tablet contains 97.2 mg sacubitril and 102.8 mg valsartan (as sacubitril valsartan sodium salt complex). **Indications:** Treatment of symptomatic chronic heart failure (NYHA class II–IV) in adult patients with reduced ejection fraction to reduce the risk of cardiovascular death and hospitalization due to heart failure. **Dosage and administration: Adults:** •The recommended starting dose of ENTRESTO is 100 mg twice daily. The dose should be doubled at 2-4 weeks to the target dose of one tablet of 200 mg twice daily, as tolerated by the patient. • A starting dose of 50 mg twice daily is recommended for patients not currently taking an angiotensin-converting enzyme (ACE) inhibitor or an angiotensin II receptor blocker (ARB), and should be considered for patients previously taking low doses of these agents. **•Geriatric patients:** The dose should be in line with the renal function. **•Pediatric patients:** ENTRESTO has not been studied. Use of ENTRESTO is not recommended. **•Renal impairment:** No dose adjustment is required in patients with mild renal impairment(Estimated Glomerular Filtration Rate [eGFR] 60-90 ml/min/1.73 m2); A starting dose of 50 mg twice daily is recommended in patients with moderate renal impairment(eGFR 30-60 ml/min/1.73 m2). A starting dose of 50 mg twice daily and caution is recommended in patients with severe renal impairment (eGFR <30 ml/min/1.73 m2). Not recommended for patients with end-stage renal disease. **•Hepatic impairment:** No dose adjustment is required in patients with mild hepatic impairment (Child-Pugh A classification). A starting dose of 50 mg twice daily is recommended in patients with moderate hepatic impairment (Child-Pugh B classification) or with AST/ALT values more than twice the upper limit of the normal range. In patients with severe hepatic impairment use of ENTRESTO is not recommended. **•Method of administration** For oral use. May be administered with or without food. **Contraindications:** •Hypersensitivity to the active substance, sacubitril, valsartan, or to any of the excipients. • Concomitant use with ACE inhibitors. ENTRESTO must not be administered until 36 hours after discontinuing ACE inhibitor therapy. • Known history of angioedema related to previous ACE inhibitor or ARB therapy. •Concomitant use with aliskiren in patients with diabetes mellitus or in patients with renal impairment (eGFR <60 ml/min/1.73 m2). • Second and third trimester of pregnancy. •Hereditary or idiopathic angioedema •Severe hepatic impairment, biliary cirrhosis and cholestasis **Warnings and precautions: • Dual blockade of the Renin-Angiotensin-Aldosterone System (RAAS):** ENTRESTO must not be administered with an ACE inhibitor due to the risk of angioedema. ENTRESTO must not be initiated until 36 hours after taking the last dose of ACE inhibitor therapy. If treatment with ENTRESTO is stopped, ACE inhibitor therapy must not be initiated until 36 hours after the last dose of ENTRESTO. • The combination of ENTRESTO with direct renin inhibitors such as aliskiren is not recommended. The combination of ENTRESTO with aliskiren-containing products is contraindicated in patients with diabetes mellitus or in patients with renal impairment (eGFR <60 ml/min/1.73 m2). • ENTRESTO contains valsartan, and therefore should not be co-administered with another ARB containing product. **•Hypotension:** If hypotension occurs, temporary down-titration or discontinuation of ENTRESTO is recommended. Dose adjustment of diuretics, concomitant antihypertensive drugs, and treatment of other causes of hypotension (e.g. hypovolemia) should be considered. Sodium and/or volume depletion should be corrected before starting treatment with ENTRESTO. **•Impaired renal function:** • Evaluation of patients with heart failure should always include assessment of renal function. Down titration of ENTRESTO should be considered in patients who develop a clinically significant decrease in renal function. Caution should be exercised when administering ENTRESTO in patients with severe renal impairment (eGFR <30 ml/min/1.73 m2). **•Hyperkalemia:** Treatment should not be initiated if the serum potassium level is >5.4 mmol/l. Medications known to raise potassium levels (e.g. potassium-sparing diuretics, potassium supplements) should be used with caution. If clinically significant hyperkalemia occurs, measures such as adjustment of concomitant medicinal products, temporary down-titration or discontinuation should be considered. Monitoring of serum potassium is recommended especially in patients with risk factors such as renal impairment, diabetes mellitus, hypoaldosteronism, receiving a high potassium diet or mineralocorticoid antagonists. If serum potassium level is >5.4 mmol/l discontinuation should be considered. **•Angioedema:** If angioedema occurs, ENTRESTO should be immediately discontinued and appropriate therapy and monitoring should be provided until complete and sustained resolution of signs and symptoms has occurred. ENTRESTO must not be re-administered. Patients with a prior history of angioedema were not studied. As they may be at higher risk for angioedema, caution is recommended if ENTRESTO is used in these patients. ENTRESTO must not be used in patients with a known history of angioedema related to previous ACE inhibitor or ARB therapy. Black patients may have increased susceptibility to develop angioedema. **• Patients with renal artery stenosis:** Caution is required in patients with renal artery stenosis and monitoring of the renal function is recommended. **• Patients with NYHA functional classification IV:** Caution should be exercised. **• B-type natriuretic peptide (BNP):** BNP is not a suitable biomarker of heart failure in patients treated with ENTRESTO. **• Hepatic impairment:** Caution is recommended when using ENTRESTO in patients with moderate hepatic impairment (Child-Pugh B classification) or with AST/ALT values more than twice the upper limit of the normal range. ENTRESTO is contraindicated in patients with severe hepatic impairment, biliary cirrhosis or cholestasis (Child-Pugh C classification). **Pregnancy:** The use of ENTRESTO is not recommended during the first trimester of pregnancy and is contraindicated during the second and third trimesters of pregnancy. **Breast-feeding:** It is not known whether ENTRESTO is excreted in human milk. Because of the potential risk for adverse drug reactions in breastfed newborns/infants, ENTRESTO is not recommended during breastfeeding. **Adverse drug reactions:** ***Very common (≥ 1/10):*** Hyperkalemia, hypotension, renal impairment. ***Common (≥ 1/100 to < 1/10):*** Anaemia, hypokalemia, Hypoglycaemia, Dizziness, Cough, Headache, Syncope, Vertigo, Orthostatic hypotension, Diarrhoea, Nausea, Gastritis, Renal failure (renal failure, acute renal failure), Fatigue, Asthenia ***Uncommon (≥ 1/1,000 to < 1/100):*** Hypersensitivity, Dizziness postural, Pruritis, Rash, Angioedema. **Interactions:** ***• Concomitant use contraindicated:*** aliskiren in patients with diabetes mellitus or in patients with renal impairment (eGFR <60 ml/min/1.73 m2); Use with ACE inhibitors: ENTRESTO must not be started until 36 hours after taking the last dose of ACE inhibitor therapy. ACE inhibitor therapy must not be started until 36 hours after the last dose of ENTRESTO. ***• Concomitant use not recommended:*** ARB containing products ***• Caution when used concomitantly*** with OAT1B1 and OATP1B3 substrates(e.g. statins), PDE5 inhibitors (e.g. sildenafil), lithium, potassium-sparing diuretics (triamterene, amiloride) , mineral corticoid antagonists (e.g. spironolactone, eplerenone), potassium supplements, salt substitutes containing potassium, other agents that may lead to increased serum potassium level (e.g. heparin), non-steroidal anti-inflammatory agents (NSAIDs) including selective cyclooxygenase-2 inhibitors (COX-2 Inhibitors), inhibitors of OATP1B1, OATP1B3, OAT3 (e.g. rifampin, cyclosporine) OAT1 (e.g. tenofovir, cidofovir) or MPR2 (e.g. ritonavir), furosemide, nitrates (e.g. nitroglycerine), metformin. **Packs:** 50mg: 28's; 100mg: 28's and 56's; 200mg: 56's. Not all pack sizes may be marketed. **Legal classification:** P1S1S3. **Ref:** EMA Nov 2015. **FULL PRESCRIBING INFORMATION IS AVAILABLE UPON REQUEST.**

HK1907026/4

NOVARTIS
Novartis Pharmaceuticals (HK) Ltd
7/F, Citi Tower, One Bay East, 83 Hoi Bun Road, Kwun Tong, Kowloon, Hong Kong
Tel: 2882 5222 Fax: 2577 0274

TRESIBA®

insulin degludec [rDNA origin] injection

Once-daily TRESIBA®: Ultra-long duration of action[1,2]

WHEN IT IS TIME FOR BASAL INSULIN

CHOOSE TRESIBA® FIRST

- **Successful reductions in HbA_{1c}**[3,4]
- **Lower risk of hypoglycaemia versus glargine U100** [5-7]
- **Flexibility in day-to-day dosing time when needed**
  ...delivered in a once-daily dose.[1]
- **Significantly lower day-to-day variability in glucose-lowering effect vs glargine U100 and U300** [8,9]
- **Approved for a broad range of patients**[1#]

Tresiba® OD* VS Glargine U100 OD*

DEVOTE Trial[5]

In **7,637** patients with type 2 diabetes at high risk of cardiovascular events[5]

At baseline: mean age was 65 years, diabetes duration was 16.4 years, HbA_{1c} was 8.4%, and 83.9% were on insulin therapy[6]

Severe hypoglycaemia	40% significant rate reduction (p<0.001)	-40%
Nocturnal severe hypoglycaemia	53% significant rate reduction (p<0.001)	-53%

* Once daily (OD) plus additional antidiabetic treatments in accordance with standard of care.
\# Treatment of diabetes mellitus in adults, adolescents and children from the age of 1 year, elderly patients, renal and hepatic impairment patients.

Abbreviated prescribing information

Tresiba® (insulin degludec) 100U (100 units/mL insulin solution for injection) in a prefilled pen (FlexTouch®) Consult Summary of Product Characteristics before prescribing.

Presentation: Tresiba® FlexTouch®. All presentations contain insulin degludec. Tresiba® 100 units/mL – 1 mL of solution contains 100 units insulin degludec (equivalent to 3.66 mg). One pre-filled device or one cartridge contains 300 units of insulin degludec in 3 mL solution. Indications: Treatment of diabetes mellitus in adults, adolescents and children from the age of 1 year, Posology and administration: Tresiba® is a basal insulin for once-daily subcutaneous administration any time of the day, preferably at the same time of day. On occasions when administration at the same time of the day is not possible, Tresiba® allows for flexibility in the timing of insulin administration, A minimum of 8 hours between injections should be ensured. In patients with type 2 diabetes mellitus, Tresiba® can be administered alone, or in any combination with oral antidiabetic medicinal products, GLP-1 receptor agonists and bolus insulin. In type 1 diabetes mellitus, Tresiba® must be used with short-/rapid-acting insulin. Administration by subcutaneous injection only. Tresiba® is available in 100 units/mL. For Tresiba® 100 units/mL a dose of 1–80 units per injection, in steps of 1 unit, can be administered. The dose counter shows the number of units regardless of strength. No dose conversion should be done when transferring a patient to a new strength. When initiating patients with type 2 diabetes mellitus the recommended daily starting dose is 10 units followed by individual dosage adjustments. Transferring from other insulins; in type 2 diabetes changing the basal insulin to Tresiba® can be done unit-to-unit, based on the previous basal insulin component, and when transferring from a twice daily regimen or from insulin glargine (300 units/ml) a dose reduction of 20% should be considered; in type 1 diabetes a dose reduction of 20% based on the previous insulin dose or basal component of a continuous subcutaneous insulin infusion should be considered with subsequent individual dosage adjustments. Doses and timing of concomitant treatment may require adjustment, Using Tresiba® in combination with GLP-1 receptor agonists in patients with type 2 diabetes mellitus; when adding Tresiba® to GLP-1 receptor agonists, the recommended daily starting dose is 10 units; when adding GLP-1 receptor agonists to Tresiba®, it is recommended to reduce the dose of Tresiba® by 20% to minimize the risk of hypoglycaemia, In all cases doses should be adjusted based on individual patients' needs; fasting plasma glucose is recommended to be used for optimising basal insulin doses. In elderly patients and patients with renal/hepatic impairment glucose monitoring should be intensified and the dose adjusted on an individual basis. In paediatric population; when changing basal insulin to Tresiba®, dose reduction of basal and bolus insulin needs to be considered on an individual basis in order to minimise the risk of hypoglycaemia, Tresiba® comes in a pre-filled pen, FlexTouch®, designed to be used with NovoFine® needles, Contraindications: Hypersensitivity to the active substance or any of the excipients, Special warnings and precautions: Too high insulin dose, omission of a meal or unplanned strenuous physical exercise may lead to hypoglycaemia, In children care should be taken to match insulin doses (especially in basal-bolus regimens) with food intake and physical activities in order to minimize the risk of hypoglycaemia. Reduction of warning symptoms of hypoglycaemia may be seen upon tightening control and also in patients with long-standing diabetes. Administration of rapid acting insulin is recommended in situations with severe hyperglycaemia, Inadequate dosing and/or discontinuation of treatment in patients requiring insulin may lead to hyperglycaemia and potentially to diabetic ketoacidosis, Concomitant illness, especially infections, may lead to hyperglycaemia and thereby cause an increased insulin requirement, Transferring to a new type, brand or manufacturer of insulin should be done under medical supervision and may result in a change in dosage. When using insulin in combination with pioglitazone, patients should be observed for signs and symptoms of heart failure, weight gain and oedema. Pioglitazone should be discontinued if any deterioration in cardiac symptoms occurs. Patients must be instructed to always check the insulin label before each injection to avoid accidental mix-ups between the two strengths of Tresiba® and other insulins, Hypoglycaemia may constitute a risk when driving or operating machinery, Pregnancy and lactation: There is no clinical experience with use of Tresiba® in pregnant women and during breastfeeding, Animal reproduction studies have not revealed any difference between insulin degludec and human insulin regarding embryotoxicity and teratogenicity. Undesirable effects: Refer to SmPC for complete information on side effects. Very common (≥1/10); common (≥1/100 to < 1/10); uncommon (≥1/1,000 to < 1/100); rare (≥ 1/10,000 to < 1/1,000); very rare (< 1/10,000); not known (cannot be estimated from the available data). Very common: Hypoglycaemia. Common: Injection site reactions. Uncommon: Lipodystrophy and peripheral oedema. Rare: Hypersensitivity and urticaria. With insulin preparations, allergic reaction may occur; immediate-type allergic reactions may potentially be life threatening. Injection site reactions are usually mild, transitory and normally disappear during continued treatment, FlexTouch®, NovoFine®, Penfill®, and Tresiba® are registered trademarks of Novo Nordisk A/S.

References

1. Tresiba® Packing Insert, **2.** Jonassen I, Havelund S, Hoeg-Jensen T, et al. Design of the novel protraction mechanism of insulin degludec, an ultra-long-acting basal insulin. Pharmaceutical Research 2012;29(8):2104-14, **3.** Rodbard HW, Cariou B, Zinman B, Handelsman Y, Philis-Tsimikas A, Skjoth TV, Rana A, Mathieu C on behalf of the BEGIN Once Long Trial Investigators. Comparison of insulin degludec with insulin glargine in insulin-naive subjects with Type 2 diabetes: a 2-year randomized, treat-to-target trial. DIABETIC Medicine 2013;30(11):1298–304. **4.** Bode BW, Buse JB, Fisher M, Garg SK, Marre M, Merker L, Renard E,Russell-Jones DL, Hansen CT, Rana A, Heller SR on behalf of the BEGIN® Basal–Bolus Type 1 Trial Investigators. Insulin degludec improves glycaemic control with lower nocturnal hypoglycaemia risk than insulin glargine in basal–bolus treatment with mealtime insulin aspart in Type 1 diabetes (BEGIN® Basal–Bolus Type 1): 2-year results of a randomized clinical trial. DIABETIC Medicine 2013;30(11):1293–297. **5.** Marso SP, McGuire DK, Zinman B, Poulter NR, Emerson SS, Pieber TR, Pratley RE, Haahr P-M, Lange M, Brown Frandsen K, Moses A, Skibsted S, Kvist K, Buse JB for _the DEVOTE Study Group. Efficacy and safety of degludec versus glargine in type 2 diabetes. New England Journal of Medicine 2017; 377:723–732. **6.** Wysham C,Bhargava A, Chaykin L, de la Rosa R, Handelsman Y, Troelsen L, Kvist K, Norwood P. Effect of Insulin Degludec vs Insulin Glargine U100 on Hypoglycemia in Patients With Type 2 Diabetes: The SWITCH 2 Randomized Clinical Trial. JAMA 2017; 318(1):45–56. **7.** Lane W, Bailey TS, Gerety G, Gumprecht J, Philis-Tsimikas A, Hansen CT, Nielsen TSS, Warren M. Effect of Insulin Degludec vs Insulin Glargine U100 on Hypoglycemia in Patients With Type 1 Diabetes: The SWITCH 1 Randomized Clinical Trial. JAMA 2017; 318(1):33–44. **8.** Heise T, Hermanski L, Nosek L, Feldman A, Rasmussen S, Haahr H, Insulin degludec: four times lower pharmacodynamic variability than insulin glargine under steady-state conditions in type 1 diabetes, Diabetes, Obesity and Metabolism 2012; 14:859–864, **9.** Heise T, Norskov M, Nosek L, Kaplan K, Famulla S, Haahr HL. Insulin degludec: lower day-to-day and within-day variability in pharmacodynamic response compared to insulin glargine 300 U/mL in type 1 diabetes. Diabetes, Obesity and Metabolism 2017; 19(7):1032–1039.

novo nordisk®

Further information is avaliable from
Novo Nordisk Hong Kong Ltd.
Unit 923A-928, 9/F, Trade Square, 681 Cheung Sha Wan Road, Kowloon, Hong Kong SAR, China Tel: (852) 2387 8555 Fax: (852) 2386 0800 www.novonordisk.com

TRE-D-20200302

Insert

bridion® sugammadex

COMPLETE[1,2] PREDICTABLE[3] RAPID[1,2,4]

Reversal time to TOF[a] ratio of 0.9 from rocuronium-induced NMB[b,1]

Median time to recovery from reappearance of T_2[c] (min)

BRIDION (2mg/kg; n=47)
(Mean=1.5min; 95% CI[d], 1.3-1.6min)

p<0.0001

Neostigmine (50µg/kg; n=45)
(Mean=18.6min; 95% CI[d], 14.2-24.4min)

13 times more rapid than neostigmine

BRIDION® dosing guide[3] for the reversal of neuromuscular blockade induced by Rocuronium [ESMERON]

2mg/kg — Reappearance of T_2[c]
if spontaneous recovery has reached reappearance of T_2[c] in response to TOF[a] stimulation

4mg/kg — 1 to 2 PTCs[e]
if spontaneous recovery of twitch response has reached 1-2 PTCs[e] and no twitch responses to TOF[a] stimulation

16mg/kg — Immediate reversal
approx 3 minutes following administration of 1.2mg/kg **Rocuronium (ESMERON)**

[a] TOF, Train of Four; [b] NMB, neuromuscular block; [c] T_2, second twitch; [d] CI, confidence interval; [e] PTCs, Post-tetanic count

Study Design[1]

A phase IIIA, a multicenter, randomized, parallel-group, comparative, active-controlled, safety-assessor-blinded study of 98 adult surgical patients. At the reappearance of T_2[c] after the last dose of rocuronium, patients were randomly assigned to receive 2mg/kg of BRIDION vs 50µg/kg of neostigmine with 10µg/kg of glycopyrrolate. Primary endpoint was the time from start of BRIDION or neostigmine administration to a TOF[a] ratio of 0.9.

Study objective:
The study compared the efficacy of BRIDION vs neostigmine in reversing moderate rocuronium-induced NMB[b] at reappearance of T_2[c].

Safety:
Five patients (two treated with BRIDION and three treated with neostigmine) had serious adverse events, but none of these were considered related to study drug. No patient discontinued the trial because of an adverse event.

References:

1. Blobner, M. et al. Reversal of rocuronium- induced neuromuscular blockade with sugammadex compared with neostigmine during sevoflurane anaesthesia: results of a randomised, controlled trial. Eur J Anaesthesiol 27, 874–881 (2010). **2.** Jones, R. K. et al. Reversal of profound rocuronium-induced blockade with sugammadex: a randomized comparison with neostigmine. Anesthesiology 109, 816–824 (2008). **3.** Hong Kong Product Circular, BRIDION (2019). **4.** Flockton, E. A. et al. Reversal of rocuronium- induced neuromuscular block with sugammadex is faster than reversal of cisatracurium-induced block with neostigmine. Br J Anaesth 100, 622–630 (2008).

MSD

ESMERON® (rocuronium bromide) Selected Safety Information:

Indications:
- an adjunct to general anesthesia to facilitate tracheal intubation during routine and rapid sequence induction, and to provide skeletal muscle relaxation during surgery
- an adjunct in the intensive care unit (ICU) to facilitate intubation and mechanical ventilation.

Dosing:
- Individualized in each patient
- adjustments with Esmeron® should be made by administering smaller maintenance doses at less frequent intervals or by using lower infusion rates of Esmeron® during long lasting procedures (longer than 1 hour) under inhalational anesthesia

Surgical Procedure
- Tracheal intubation:
  - The standard intubating dose during routine anesthesia is 0.6 mg.kg-1 rocuronium bromide, after which adequate intubation conditions are established within 60 seconds in nearly all patients.
  - A dose of 1.0 mg.kg-1 of rocuronium bromide is recommended for facilitating tracheal intubation conditions during rapid sequence induction of anesthesia, after which adequate intubation conditions are established within 60 seconds in nearly all patients.
  - If a dose of 0.6 mg.kg-1 rocuronium bromide is used for rapid sequence induction of anesthesia, it is recommended to intubate the patient 90 seconds after administration of rocuronium bromide.
- Cesarean-Section:
  - Doses of 0.6mg.kg-1 rocuronium bromide do not affect the Apgar score, fetal muscle tone nor cardiorespiratory adaptation
  - Doses of 1.0mg.kg-1 have been investigated during rapid sequence induction of anesthesia, but not in Cesarean section patients.
- Higher doses:
  - Initial doses up to 2 mg.kg-1 rocuronium bromide have been administered during surgery without adverse CV effects being noted.
  - The use of these high dosages of rocuronium bromide decreases the onset time and increases the duration of action
- Maintenance dosing:
  - The recommended maintenance dose is 0.15 mg.kg-1 rocuronium bromide; in the case of long-term inhalational anesthesia, this should be reduced to 0.075-0.1 mg.kg-1 rocuronium bromide. The maintenance doses should best be given when twitch height has recovered to 25% of control twitch height, or when 2 to 3 responses to TOF-stimulation (train of four) are present.
- Continuous infusion:
  - It is recommended to give a loading dose of 0.6 mg.kg-1 rocuronium bromide. When neuromuscular block starts to recover, administration by infusion can be started.
  - The infusion rate should be adjusted to maintain twitch response at 10% of control twitch height or to maintain 1 to 2 responses to train of four stimulation.
  - In adults under intravenous anesthesia, the infusion rate required to maintain neuromuscular block at this level ranges from 0.3-0.6 mg.kg-1.h-1 and under inhalational anesthesia the infusion rate ranges from 0.3-0.4 mg.kg-1.h-1.

ICU
- Tracheal intubation: same doses as surgical procedures
- Maintenance dosing:
  - The use of an initial loading dose of 0.6 mg.kg-1 rocuronium is recommended, followed by a continuous infusion as soon as twitch height recovers to 10% or upon reappearance of 1 to 2 twitches to TOF-stimulation. Dosage should always be titrated to effect in the individual patient.
  - The recommended initial infusion rate for the maintenance of a neuromuscular block of 80 - 90% (1 to 2 twitches to TOF-stimulation) in adult patients is 0.3 - 0.6 mg.kg-1.h-1 during the first hour of administration, which will need to be decreased during the following 6-12 hours, according to the individual response. Thereafter, individual dose requirements remain relatively constant.
- Special population:
  - Esmeron® is not recommended for the facilitation of mechanical ventilation in the intensive care in pediatric and geriatric patients due to a lack of data on safety and efficacy.

Contraindications:
- Hypersensitivity to rocuronium or to the bromide ion or to any of the excipients.

Warnings and Precautions:
- Residual Curarization: It is recommended to extubate only after the patient has recovered sufficiently from neuromuscular block. Caution in geriatric patients (65 years or older) or other factors which could cause residual curarization after extubation in the post-operative phase (such as drug interactions or patient condition). If not used as part of standard clinical practice, the use of a reversal agent should be considered.
- Anaphylactic reactions: allergic cross-reactivity to neuromuscular blocking agents has been reported, inducing histamine release both locally at the site of injection and/or generalized histaminoid (anaphylactoid) reactions should always be taken in to consideration.
- Prolonged paralysis and/or skeletal muscle weakness (long-term use in ICU): neuromuscular transmission is monitored throughout the use of muscle relaxants. In addition, patients should receive adequate analgesia and sedation.
- Myopathy (long-term combination use with corticosteroid in ICU): should limit such combination use. Delay the administration of Esmeron® until the patients has clinically recovered from the neuromuscular block induced by vecuronium.

Adverse Events:
- The most commonly occurring adverse drug reactions include injection site pain/reaction, changes in vital signs and prolonged neuromuscular block. The most frequently reported serious adverse drug reactions during post-marketing surveillance is 'anaphylactic and anaphylactoid reactions' and associated symptoms.

Drug interactions:
- Increased effect: halogenated volatile anesthetics, suxamethonium, long-term concomitant use of corticosteroids, antibiotics (aminoglycoside, lincosamide and polypeptide antibiotics, acylamino-penicillin antibiotics), diuretics, quinidine, Mg^{2+} salts, CCB, Li^{+} salts, local anesthetics (lidocaine i.v, bupivacaine epidural) and acute administration of phenytoin or ß-blocking agents
- Decreased effect: chronic administration of phenytoin or carbamazepine and protease inhibitors (gabexate, ulinastatin)

Use in specific populations:
- Pregnancy and Lactation:
  - no clinical data on exposed pregnancies are available. It is unknow whether Esmeron® is excreted in human breast milk. Physicians decides the benefits outweigh the risks.
- Surgical procedure - pediatric patients (28 days to 18 years): similar dosing to adults.
  - For continuous infusion: For children higher infusion rates might be necessary. For children the same initial infusion rates as for adults are recommended and this should be adjusted to maintain twitch response at 10% of control twitch height or to maintain 1 or 2 responses to TOF-stimulation during the procedure. Rocuronium bromide is not recommended for facilitating tracheal intubation conditions during rapid sequence induction in pediatric patients.
- Surgical procedure - Geriatric patients and patients with hepatic and/or biliary tract disease and/or renal failure:
  - The standard intubation dose for geriatric patients and patients with hepatic and/or biliary tract disease and/or renal failure during routine anesthesia is 0.6 mg.kg-1 rocuronium bromide. A dose of 0.6 mg.kg-1 should be considered for rapid sequence induction of anesthesia in patients in which a prolonged duration of action is expected. Regardless of the anesthetic technique used, the recommended maintenance dose for these patients is 0.075-0.1 mg.kg-1 rocuronium bromide, and the recommended infusion rate is 0.3-0.4 mg.kg-1.h-1.
- Surgical procedure - overweight and obese patients:
  - When used in overweight or obese patients (defined as patients with a body weight of 30% or more above ideal body weight) doses should be reduced taking into account a lean body mass.
- ICU: Esmeron® is not recommended for the facilitation of mechanical ventilation in the intensive care in pediatric and geriatric patients due to a lack of data on safety and efficacy.

Before prescribing, please consult the full prescribing information.

BRIDION® (sugammadex, MSD) Concentrate for solution for infusion 200mg (IV) – Selected Safety Information:

Indication:
BRIDION is indicated for the reversal of neuromuscular blockade induced by rocuronium bromide and vecuronium bromide in adults undergoing surgery.

Contraindications: Contraindicated in patients with known hypersensitivity to sugammadex or any of its components. Hypersensitivity reactions that occurred varied from isolated skin reactions to serious systemic reactions (i.e., anaphylaxis, anaphylactic shock) and have occurred in patients with no prior exposure to sugammadex.

Warnings/Precautions:

Anaphylaxis and Hypersensitivity:
Clinicians should be prepared for the possibility of drug hypersensitivity reactions (including anaphylactic reactions) and take the necessary precautions. Potentially serious hypersensitivity reactions, including anaphylaxis, have occurred in patients treated with BRIDION.

Marked Bradycardia:
Cases of marked bradycardia, some of which have resulted in cardiac arrest, have been observed within minutes after the administration of BRIDION. Patients should be closely monitored for hemodynamic changes during and after reversal of neuromuscular blockade.

Respiratory Function Monitoring During Recovery:
Ventilatory support is mandatory for patients until adequate spontaneous respiration is restored and the ability to maintain a patent airway is assured.

Risk of Prolonged Neuromuscular Blockade:
In clinical trials, a small number of patients experienced a delayed or minimal response to the administration of BRIDION.

Waiting Times for Re-Administration of Neuromuscular Blocking Agents for Intubation Following Reversal with BRIDION:
A minimum waiting time is necessary before administration of a steroidal neuromuscular blocking agent after administration of BRIDION.

Risk of Recurrence of Neuromuscular Blockade Due to Displacement Interactions:
Recurrence of neuromuscular blockade may occur due to displacement of rocuronium or vecuronium from BRIDION by other drugs.

Interactions Potentially Affecting the Efficacy of Other Drugs:
Due to the administration of BRIDION, certain drugs, including hormonal contraceptives, could become less effective due to a lowering of the (free) plasma concentrations. In this situation, consider the re-administration of the other drug, the administration of a therapeutically equivalent drug (preferably from a different chemical class), and/or non-pharmacological interventions as appropriate.

Risk of Recurrence of Neuromuscular Blockade with Lower Than Recommended Dosing:
The use of lower than recommended doses of BRIDION may lead to an increased risk of recurrence of neuromuscular blockade after initial reversal and is not recommended.

Risk of Recurrence of Neuromuscular Blockade Due to the Administration of Drugs that Potentiate Neuromuscular Blockade:
When drugs which potentiate neuromuscular blockade are used in the post-operative phase, special attention should be paid to the possibility of recurrence of neuromuscular blockade.

Risk of Coagulopathy and Bleeding:
Doses up to 16 mg/kg were associated with increases in the coagulation parameters activated partial thromboplastin time (aPTT) and prothrombin time/International normalized ratio (PT/INR) of up to 25% for up to 1 hour in healthy volunteers.

Renal Impairment:
Not recommended for use in patients with severe renal impairment, including those requiring dialysis.

Light Anesthesia:
When neuromuscular blockade was reversed intentionally in the middle of anesthesia in clinical trials, e.g., when investigating urgent reversal, signs of light anesthesia were noted occasionally (movement, coughing, grimacing and sucking of the tracheal tube).

Reversal after Rocuronium or Vecuronium Administration in the ICU:
Has not been studied for reversal following rocuronium or vecuronium administration in the ICU.

Reversal of Neuromuscular Blocking Agents Other Than Rocuronium or Vecuronium:
Do not use BRIDION to reverse blockade induced by nonsteroidal neuromuscular blocking agents such as succinylcholine or benzylisoquinolinium compounds.

Adverse Events:
The following serious adverse reactions are described elsewhere in the labeling:
- Anaphylaxis and Hypersensitivity
- Marked Bradycardia

For drug interaction, use in special population and other details, please consult the full prescribing information.

MSD
Merck Sharp & Dohme (Asia) Ltd.
27/F., Lee Garden Two, 28 Yun Ping Road, Causeway Bay, Hong Kong.
Tel: (852) 3971 2800 Fax: (852) 2834 0756 Website: www.msd.com.hk

HK-XBR-00058 06/20