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## Disclaimer

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

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Convenor, Care for Advanced Disease Consortium
Immediate Past President
The Federation of Medical Societies of Hong Kong
Editor

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 professed 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, prognosticating, 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, that an issue of Medical Diary is now also devoted to this important notion. Palliative care is also seen as 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 professed 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.

Acknowledgement is also due to Professor Richard Yu, for contributing a good end-of-life sharing with us his treasured insights and vision towards active ageing and illness. Many grateful thanks are to be given to Dr Leong Che-hung, for his high symptom burden and complications. Prognosis 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.

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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.
Advance in Therapeutics Course 2020

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

B 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 HO
  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

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

Enquiries and Registration:
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Advanced Heart Failure: Updates on the Latest Treatment Options

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 inotropics 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-HF³.

PARADIGM-HF was a multicentre, international, randomised trial that compared standard-of-care enalapril with the combined drug of ARB (valsartan) and nepriylsin 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 nepriylsin 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 therapy². 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 not receive ARNI during hospitalisation if they are already on sufficiently stabilised with sufficient renal function as gauged by estimated glomerular filtration rate (eGFR) above 30 ml/min/1.73 m². When eGFR falls below 30 ml/min/1.73 m², 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-HF⁴, 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%.¹ 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)¹. 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. 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. The EMPA-REG OUTCOME, CANVAS, and DECLARE-TIMI 58 trials have shown cardiorenal benefits of SGLT2 inhibitors. EMPA-REG OUTCOME first reported that empagliflozin could reduce cardiovascular mortality by 38%. Similar mortality benefits were seen in CANVAS and DECLARE-TIMI 58 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 peptide-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 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.

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 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. 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. 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.

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. 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) or weekly administration of 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.
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 signif. adverse reactions: Disorientation; dysgeusia, dizziness, somnolence, headache, epistaxis, rhinorrhea, 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.

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BTCP management: standard treatment (classical opioids) and ideal treatment

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

References:
of life should be primary goals in the management of end-stage HF. According to international guidelines, 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

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(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% (IRR: 0.89, p<0.001). Annual rate reduction of severe exacerbations: ULTIBRO® BREEZHALER™ vs. fluticasone/salmeterol was 13% (IRR: 0.87, p<0.001).

References:
Management of Advanced Airway and Lung Diseases

Dr Hon-cheung FAN
MBBS, FRCP(Edin), FHKCP, FHKAM(Medicine)
Consultant, Department of Medicine & Geriatrics, Ruttonjee Hospital

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 mortality1-5. 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 ventilation1. 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 world6. Globally, the COPD burden is projected to increase in the coming decades because of continued exposure to COPD risk factors and population ageing7. 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 cancer2-3. 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 diagnosis8,9. The 5-year survival rate of 20 - 40% is worse than that of many cancers8,9. IPF is the most common idiopathic interstitial lung disease (ILD), affecting about 5 million persons worldwide11. Progression of IPF is characterised by a decline in lung function, worsening symptoms of dyspnoea and cough, and deterioration in QOL12.

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 death2,3. The clinical course of IPF is progressive, highly variable and unpredictable and is frequently associated with a significant symptom burden10. 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 mortality12.

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 pain13,14. Advanced COPD patients experience poor HRQOL comparable to or worse than that of advanced lung cancer patients3,14. 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>
<thead>
<tr>
<th>Symptoms</th>
<th>Advanced COPD</th>
<th>PIF-ILD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dyspnoea</td>
<td>56-98%</td>
<td>58-98%</td>
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<tr>
<td>Cough</td>
<td>59-80%</td>
<td>59-94%</td>
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<td>Tiredness</td>
<td>49-96%</td>
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<td>Insomnia</td>
<td>55-77%</td>
<td>6-47%</td>
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<td>9%</td>
</tr>
<tr>
<td>Dry Mouth</td>
<td>59-67%</td>
<td>-</td>
</tr>
<tr>
<td>Constipation</td>
<td>27-44%</td>
<td>-</td>
</tr>
<tr>
<td>Heartburn</td>
<td>-</td>
<td>29-48%</td>
</tr>
<tr>
<td>Depression</td>
<td>17-77%</td>
<td>10-49%</td>
</tr>
<tr>
<td>Anxiety</td>
<td>32-57%</td>
<td>22-58%</td>
</tr>
</tbody>
</table>

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. The vicious cycle of physical, social, psychological symptoms and decreasing quality of life 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. Pharmacological treatment includes anti-depressive medications such as methylphenidate, serotonin selective reuptake inhibitors, tricyclic antidepressants, and anxiolytic medications such as benzodiazepines.

![Image](image.png)

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

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 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. Moreover, nintedanib and pirfenidone may reduce the risk of severe acute deteriorations which are associated with high mortality.

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. For ILD, PR improves functional exercise capacity, dyspnoea and QOL, with benefits also evident in IPF.

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

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. 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. Moreover, no serious adverse effects (hospitalisations, respiratory depression, or CO2 retention) were reported. The possible mechanism seems to be mediated mainly by a reduction in central ventilatory demand and altered perception of breathlessness.

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. 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.

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. 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. Benzodiazepines caused less drowsiness compared to morphine. 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. Long term oxygen therapy has significant survival benefit when used for at least 15 hours per day in hypoxaemic COPD patients. Supplemental oxygen is also recommended for patients with advanced IPF with significant resting hypoxaemia, commonly defined as a resting SpO2 of < 88%.
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\(^6\). 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\(^7\). And it should be withdrawn if the patient does not report relief of breathlessness within a few days\(^8\).

**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)\(^9\). A recent RCT has found that 12 months of high-intensity home NIV prolonged the time to readmission or death (a survival benefit)\(^10\).

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%\(^11\).

**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 to 100%) 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\(^12\). 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>
<thead>
<tr>
<th>Table 2. Referral criteria for pulmonary palliative care (essential criteria*: 1 &amp; 2; supportive criteria: 3, 4, 5)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1* Severe pulmonary diseases as documented by both (a) and (b)</td>
</tr>
<tr>
<td>a Disabling dyspnoea at rest, poorly or unresponsive to bronchodilators, resulting in decreased functional capacity (FEV1 post-bronchodilator &lt;30% predicted is supportive evidence of disabling dyspnoea, but is not necessary to obtain)</td>
</tr>
<tr>
<td>b Progression of advanced pulmonary disease, as evidenced by increasing hospitalisations for acute exacerbations and/or respiratory failure</td>
</tr>
<tr>
<td>2* Hypoxaemia at rest on room air (pO2 &lt;55 mmHg or oxygen saturation &lt;88%) OR Hypercapnia (pCO2 &gt;50 mmHg)</td>
</tr>
<tr>
<td>3 Cor pulmonale</td>
</tr>
<tr>
<td>4 Unintentional progressive weight loss &gt;10% over the preceding six months</td>
</tr>
<tr>
<td>5 Resting tachycardia &gt;100/min</td>
</tr>
</tbody>
</table>

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\(^13\).

The importance of collaboration model between palliative and respiratory medicine has been recognised in several international guidelines\(^14\). This model includes respiratory and palliative care physicians,
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.

References


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?

Dermatology Quiz

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

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

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

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Honorary Clinical Assistant Professor, The Chinese University of Hong Kong

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Associate Consultant, Palliative Care Unit, Shatin Hospital
Honorary Clinical Associate Professor, Department of Medicine and Therapeutics, The Chinese University of Hong Kong

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 dimensions 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/1.73m² 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/1.73m² 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.
Continuous activity. Targeted stability.

Superior Hb stability

Five dosages to suit every patient

Improved patient care and quality of life

Truly once monthly

References:

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

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

Dosage & Administration: Can be administered subcutaneously or intravenously in order to increase hemoglobin (Hb) to not greater than 12 g/dL (120 mmol/L). Subcutaneous use is preferable in patients who are not receiving hemodialysis to avoid punctures of peripheral veins. Hb variability should be monitored through dose management, with consideration for the Hb target range of 11.0 g/dL (110 mmol/L) to 12.0 g/dL (120 mmol/L). A rise in Hb of greater than 2 g/dL (20 mmol/L) every 2 weeks is recommended. Patients should be reassessed and the dose adjusted as necessary. If Hb levels remain above 12 g/dL (120 mmol/L) for more than 1 week, the dose should be decreased.

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) in all the possible causative factors excluded. Discontinue MIRCERAN and do not switch to another ESA in case PRCA is diagnosed. PRCA caused by anti-erythropoiesis 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 anemia associated with hepatitis C. Adequately control blood pressure in all patients before, at initiation of, and during treatment with MIRCERAN. Consider dose reduction or withholding treatment if high blood pressure is difficult to control by drug treatment or dietary measures. Withdraw MIRCERAN immediately and an alternative treatment should be considered if signs and symptoms of skin reactions appear. Discontinue MIRCERAN if SCAL and ESA use is not tolerated in patients with chronic kidney disease, maintenance Hb concentration should not exceed the upper limit of the target hemoglobin 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 hemoglobinopathies, telangiectases or with plateau levels > 100 g/dL (1000 mmol/L). MIRCERAN should be administered at the dose recommended in the UK. This may be associated with a lower incidence of cardiovascular complications.

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

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

Undesirable effects: Common: Hypertension. Uncommon: vasculitis, access thrombosis, headache. Rare: hypersensitivity, hypertensive encephalopathy, rash (maculopapular), hot flush.

Date of preparation: Dec 2017

Full prescribing information should be viewed prior to prescribing.
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, prioritisising 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.

Fatigue, skin pruritus, nausea and vomiting, oedema, dyspnoea, muscles cramping, sleep disturbance, pain and depression are among the frequently reported symptoms in advanced CKD. 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. 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. 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.

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 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 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

Table 1: Symptom and Function assessment tools

<table>
<thead>
<tr>
<th>Assessment Tools</th>
</tr>
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<tbody>
<tr>
<td>Edmonton Symptom Assessment System Revised Renal (ESAS-r: Renal)</td>
</tr>
<tr>
<td>(<a href="https://www.albertahealthservices.ca/frm-20351.pdf">https://www.albertahealthservices.ca/frm-20351.pdf</a>)</td>
</tr>
<tr>
<td>Integrated Palliative Care Outcome Scale Renal (IPoS-Renal)</td>
</tr>
<tr>
<td>Karnofsky Performance Status (KPS) score</td>
</tr>
<tr>
<td>Eastern Cooperative Oncology Group (ECOG)</td>
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<td>(<a href="https://ecog-acrin.org/resources/ecog-performance-status">https://ecog-acrin.org/resources/ecog-performance-status</a>)</td>
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</tbody>
</table>
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. Hyperuricaemia. 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. Close monitoring of blood fluid & electrolyte balance, renal function & BP, serum creatinine conc & CrCl. Clinically significant adverse reactions: increased BP, short thrombosis/occlusion, headache, malaise. PIP: (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.
irradiation therapy has demonstrated efficacy and can be considered\textsuperscript{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\textsuperscript{16,17,18}. 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 treatment, 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 mortality\textsuperscript{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\textsuperscript{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\textsuperscript{21}. A more recent study, in addition, suggested that ESA benefits patients under renal palliative care in lowering their needs for hospitalisation and blood transfusion by 2-3 fold reductions respectively\textsuperscript{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

Palliative Treatment for Metastatic Cancers: Recent Advances

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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)\(^1,2\)

<table>
<thead>
<tr>
<th>Rank</th>
<th>Site</th>
<th>Number (Worldwide 2018)</th>
<th>Rank</th>
<th>Site</th>
<th>Number (Hong Kong 2017)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Lung</td>
<td>2.09 million</td>
<td>1</td>
<td>Colorectal</td>
<td>5,635</td>
</tr>
<tr>
<td>2</td>
<td>Breast</td>
<td>2.09 million</td>
<td>2</td>
<td>Lung</td>
<td>5,178</td>
</tr>
<tr>
<td>3</td>
<td>Colorectal</td>
<td>1.80 million</td>
<td>3</td>
<td>Breast</td>
<td>4,391</td>
</tr>
<tr>
<td>4</td>
<td>Prostate</td>
<td>1.28 million</td>
<td>4</td>
<td>Prostate</td>
<td>2,240</td>
</tr>
<tr>
<td>5</td>
<td>Skin cancer</td>
<td>1.04 million (non-</td>
<td>5</td>
<td>Liver</td>
<td>1,834</td>
</tr>
<tr>
<td></td>
<td>melanoma)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>Stomach</td>
<td>1.03 million</td>
<td></td>
<td>Stomach</td>
<td>1,314</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>7</td>
<td>Non-melanoma</td>
<td>1,101</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Rank</th>
<th>Site</th>
<th>Number (Deaths Worldwide 2018)</th>
<th>Rank</th>
<th>Site</th>
<th>Number (Deaths in Hong Kong 2017)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Lung</td>
<td>1.76 million</td>
<td>1</td>
<td>Lung</td>
<td>3,890</td>
</tr>
<tr>
<td>2</td>
<td>Colorectal</td>
<td>862,000</td>
<td>2</td>
<td>Colorectal</td>
<td>2,138</td>
</tr>
<tr>
<td>3</td>
<td>Stomach</td>
<td>783,000</td>
<td>3</td>
<td>Liver</td>
<td>1,552</td>
</tr>
<tr>
<td>4</td>
<td>Liver</td>
<td>782,000</td>
<td>4</td>
<td>Breast</td>
<td>724</td>
</tr>
<tr>
<td>5</td>
<td>Breast</td>
<td>627,000</td>
<td>5</td>
<td>Pancreas</td>
<td>690</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(total cancer mortality: n~9.6 million)</td>
<td>6</td>
<td>Stomach</td>
<td>682</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>7</td>
<td>Prostate</td>
<td>443</td>
</tr>
</tbody>
</table>

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
Examples of cancer immunotherapy include preventive and therapeutic cancer vaccines, immune checkpoint inhibitors, and 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. The approved clinical indications now cover multiple malignancies.

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. 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, 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, acting by harnessing the human immune response to break down the escaping mechanism of the cancer cells to achieve treatment effect.

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 illustrative example, the sensitisation of the immune system is associated with a unique side effect profile. Integrated cross-disciplinary care involving endocrinologists, rheumatologists, etc. has become more common on managing the toxicities.
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.
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 unanswerable. 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.

Initiated and Edited by

Partner Institution:

CUHK Centre for Bioethics
The Chinese University of Hong Kong

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

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+852 3943 9450 ioa@cuhk.edu.hk
<table>
<thead>
<tr>
<th>Disease</th>
<th>Biomarker (predicting response) &amp; Drug Target</th>
<th>Targeted Drugs as the standard systemic treatment</th>
<th>Pivotal Trial Intervention Efficacy with statistical significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lung Cancer (non-small cell) driver EGFR mutation positive non-small cell lung cancer</td>
<td>1st line Biomarker: Driver EGFR mutation positivity e.g., Exon 19 deletions, Exon 21 L858R substitutions Target: EGFR &amp; the mediated signaling pathway</td>
<td>EGFR TKIs 1st and 2nd generation e.g.: Gefitinib, Erlotinib, Afatinib 3rd generation: e.g. Osimertinib</td>
<td>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</td>
</tr>
<tr>
<td>Breast Cancer HER2 positive 1st line Biomarker: HER2 positivity Target: HER2 &amp; the mediated signaling pathway</td>
<td>Anti-HER2 Monoclonal Antibodies(MAbs) e.g. Pertuzumab, Trastuzumab</td>
<td>Pertuzumab + Trastuzumab + Docetaxel (chemo) vs Docetaxel (chemo)</td>
<td>mPFS (mo): 19 vs 12 mOS (mo): 56.5 vs 40.8</td>
</tr>
<tr>
<td></td>
<td>2nd line Biomarker: HER2 positivity Target: HER2 &amp; the mediated signaling pathway</td>
<td>Anti-HER2 MAbs-chemo conjugate e.g. Ado-trastuzumab emtansine (T-DM1)</td>
<td>TDM-1 vs Lapatinib + Capecitabine(chemo)</td>
</tr>
<tr>
<td></td>
<td>2nd line Biomarker: HER2 positivity Target: HER2 &amp; the mediated signaling pathway</td>
<td>HER2 Tyrosine Kinase Inhibitor (TKI) e.g Lapatinib</td>
<td>Lapatinib + Capecitabine (chemo) vs Capecitabine (chemo)</td>
</tr>
<tr>
<td>Breast Cancer ER/PR positive &amp; HER2 negative 1st line Biomarker: ER/PR positivity Target: CDK4 and CDK6 for cell division</td>
<td>CDK4/6 inhibitor (CDK4/6i) e.g. Palbociclib, Ribociclib, Abemaciclib</td>
<td>CDK 4/6i + non-steroidal aromatase inhibitor(AI) (hormone therapy) vs Non-steroidal AI (hormone therapy) alone</td>
<td>mPFS (mo): (25-28) vs (14-17)</td>
</tr>
<tr>
<td>Colorectal Cancer RAS wild type 1st line Biomarker: RAS non-mutant Target: EGFR and the mediated signaling pathway</td>
<td>Anti-EGFR MAbs e.g. Cetuximab, Panitumumab</td>
<td>Cetuximab + combination chemo FOLFIRI vs FOLFIRI alone Panitumumab + combination chemo FOLFOX4 vs FOLFOX4 alone</td>
<td>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</td>
</tr>
<tr>
<td>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), FIt3 and c-Kit, and also targets Raf kinases involved in the MAPK/ERK pathway</td>
<td>Sorafenib – a multi-kinase inhibitor</td>
<td>Sorafenib vs Placebo</td>
<td>mPFS (mo): (2.8-5.5) vs (1.4 -2.8) mOS (mo): (6.5-10.7) vs (4.2-7.9)</td>
</tr>
</tbody>
</table>

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)
KEYTRUDA: HELPING TO REDEFINE SURVIVAL EXPECTATIONS FOR MORE PATIENTS WITH NONSQUAMOUS mNSCLC

Regardless of PD-L1 Expression Level

22 MONTHS MEDIAN OS WITH KEYTRUDA + plat/pem

9 MONTHS MEDIAN PFS WITH KEYTRUDA + plat/pem

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

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

Reference:

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

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There are now more than 200 US FDA approvals of unique new oncology drugs over the past 70 years after the year 1949. 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 RADIOThERAPY**

**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. 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.

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. 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)
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**

![Graph showing pain relief over time](image)

- **Improved Dissolution and Absorption by Oragescent® Technology**
  - Modifies pH levels to facilitate Fentora® delivery across the buccal mucosa
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  - Absolute bioavailability = 65% ± 20%*

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* p < 0.0001 compared with placebo

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Further information is available on request.

**References**

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 alone22,23.

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 benefit24.

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

Radionuclide therapy (RNT) is another rapidly growing field concerning precision radiotherapy for advanced malignancies25. 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 (131I) for thyroid cancers, and strontium-90 (90Sr) for bone metastases. Recent developments include Yttrium-90 (90Y) microspheres for hepatocellular carcinoma (HCC), peptide receptor radionuclide therapy (PRRT) such as Lutetium-177 (177lu)-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 90Y-ibritumomabtiuxetan for refractory non-Hodgkin’s lymphoma26.

**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 spiritual27,28. 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 symptoms29,30. 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 satisfaction30,35.

![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](image)

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 preferences34,35. 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 doctors37,38, and they were prepared to attempt clinical trials using experimental therapies of mortality rates of 10% with uncertainty on the clinical benefit39.
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 an effective and honest communication between the oncologists and patients regarding the disease prognosis, benefits and toxicities of the treatment options and what the patients value the most in the context.

References

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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

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. 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:

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. This decline seemingly the best recommended option. It is always important to clarify how involved a patient chooses to be during decision-making. Efforts should be devoted to partnership with patients and families to reach the best consensus. 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. 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 need to be interpreted and acknowledged. 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. 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. 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. 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 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 prerequisite, 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. Plenty of many other barriers remain to be overcome, ranging from time, resources, professional engagement and public education.

LETING 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. 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 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. 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:

- 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 bereaved12.

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.

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1 Cardiovascular disease

* Relative to the healthy counterparts

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, the elderly may try to develop a habit of treating the younger family members as friends.
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.” \(^3,4\)

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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.
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Help her move forward with the relentless protection of Prolia®

Start strong with Prolia® for long-term fracture protection and continuous BMD gains for up to 10 years!

Prolia® (denosumab) Abbreviated Prescribing Information

Prolia® (denosumab) is indicated for the treatment of postmenopausal women with osteoporosis at high risk for fracture, defined as a history of advanced fracture or high-risk factors for fracture or patients who have been treated with estrogen replacement therapy (ERT) for at least 5 years. Prolia® is indicated for the treatment of patients with multiple myeloma who express bone disease. Prolia® is indicated for the treatment of patients with Paget's disease of bone. Prolia® is indicated for the treatment of patients with breast cancer who have bone metastases. Prolia® is indicated for the treatment of patients with prostate cancer who have bone metastases.

Prolia® is prescribed by a healthcare provider who has assessed the patient’s risk factors for fracture. If fracture occurs, Prolia® should be continued. Prolia® should be administered by a trained healthcare provider.

Prolia® is contraindicated in patients with known hypersensitivity to Prolia® or any of its components, or within 14 days of a glucocorticoid injection. Prolia® is not indicated for use in women with active bone cancer or men with prostate cancer with bone metastases who are receiving androgen deprivation therapy (ADT).

The most common adverse reactions were back pain, arthralgia, and nasopharyngitis. The most common adverse reactions leading to discontinuation were back pain, arthralgia, and nasopharyngitis. The incidence of back pain was greater in patients with advanced bone disease.

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<td>College of Surgeons of Hong Kong Enquiry: Dr Calvin MAK Tel: 2965 4061 Fax: No.: 2965 4061</td>
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<td>Refresher Course for Health Care Providers 2019/2020 - Common eye symptoms/signs/treatment from young to old for primary health care and new eye procedures</td>
<td>Ms. Clara TSANG Tel: 2534 2440 2 CME Point</td>
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Answers to Dermatology Quiz

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 follicle; thereby, the scalp looks 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 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
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 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)‡

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)†

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

70% of patients were NYHA Class II²

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

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

Enalapril (N=4212)

ENTRESTO (N=4187)

Kaplan-Meier estimate of cumulative failure rate (%)

Time since randomisation (days)

4.7% ABR

P<0.001

HR (95% CI): 0.84 (0.74-0.94; P=0.003)

References:

ENTRESTO helps keep HFrEF patients out of the hospital and living longer.

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)†

ENTRESTO helped slow the clinical progression of HF vs enalapril 4

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By slowing disease progression, ENTRESTO helps keep HF patients out of the hospital and living longer.
Once-daily TRESIBA®: Ultra-long duration of action

WHEN IT IS TIME FOR BASAL INSULIN

CHOOSE TRESIBA® FIRST

- Successful reductions in HbA1c
- Lower risk of hypoglycaemia versus glargine U100
- Flexibility in day-to-day dosing time when needed...delivered in a once-daily dose.
- Significantly lower day-to-day variability in glucose-lowering effect vs glargine U100 and U300
- Approved for a broad range of patients

Abbreviated prescribing information

Tresiba® (insulin degludec 1000 U/ml), insulin subcutaneous injection (human recombinant DNA origin) is administered by injection into subcutaneous tissue. Treatment of diabetes mellitus in adults, adolescents, and children from the age of 1 year and in combination with oral antidiabetic agents.

Study Design

A phase IIIA, a multicenter, randomized, parallel-group, comparative, active-controlled, safety-assessor-blinded study of 98 adult surgical patients. At the reappearance of T2c after the last dose of rocuronium, patients were randomly assigned to receive 2mg/kg of BRIDION vs 50/uni03BCg/kg of neostigmine with 10/uni03BCg/kg of glycopyrrolate. Primary endpoint was the time from start of BRIDION or neostigmine administration to a TOFa ratio of 0.9.

Study objective:
The study compared the efficacy of BRIDION vs neostigmine in reversing moderate rocuronium-induced NMB at reappearance of T2c.

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:

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

2mg/kg
Immediate reversal approx 3 minutes following administration of 1.2mg/kg Rocuronium (ESMERON)
1 to 2 PTCs if spontaneous recovery has reached reappearance of T2c in response to TOF stimulation if no twitch responses to TOF stimulation
16mg/kg

a TOF, Train of Four; b NMB, neuromuscular block; c T2, second twitch; d CI, confidence interval; e PTCs, Post-tetanic count

Reversal time to TOFa ratio of 0.9 from rocuronium-induced NMB

Median time to recovery from reappearance of T2c (min)

13 times more rapid than neostigmine

40% significant rate reduction (p<0.001)

53% significant rate reduction (p<0.001)

DEVOTE Trial

In 687 patients with type 2 diabetes at high risk of cardiovascular events at baseline, mean age was 65 years, diabetes duration was 16.4 years, HbA1c was 9.4%, and 63.3% were on insulin therapy.

Severe hypoglycaemia

40% significant rate reduction (p<0.001)

Nocturnal severe hypoglycaemia

53% significant rate reduction (p<0.001)

* Once daily (OD) plus standard anti-diabetic treatment in accordance with standard of care.

† Treatment of diabetes mellitus in adults, adolescents, and children from the age of 1 year, elderly patients, and insulin-dependent patients.

 Further information is available from

Nuo 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

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Further information is available from

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Further information is available from
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)

| Dosing (mg/kg) | Reappearance of T\(_2\)\(^c\)
if spontaneous recovery has reached reappearance of T\(_2\) in response to TOF\(^a\) stimulation | 1 to 2 PTCs* if spontaneous recovery of twitch response has reached 1-2 PTCs\(^e\) and no twitch responses to TOF\(^a\) stimulation | Immediate reversal approx 3 minutes following administration of 1.2mg/kg Rocuronium [ESMERON] |
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\(^a\) TOF, Train of Four; \(^b\) NMB, neuromuscular block; \(^c\) T\(_2\), second twitch; \(^d\) CI, confidence interval; \(^e\) PTCs, Post-tetanic count

**BRIDION** dosing guide\(^3\) for the reversal of neuromuscular blockade induced by Rocuronium [ESMERON]

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

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

13 times more rapid than neostigmine

\(^p<0.0001\)

References:
ESMERON® (rocuronium bromide) Selected Safety Information:

Indications:
- An adjunct to general anaesthesia to facilitate tracheal intubation during induction and rapid sequence intubation, and for 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 initial rates of ESMERON® during long-lasting procedures.

Surgical Procedures
- Tracheal intubation:
  - The standard intubating dose of ESMERON® is 0.6 mg/kg rocuronium bromide. If nerve block is required, an additional 0.6 mg/kg rocuronium bromide should be administered immediately before intubation.
  - The standard intubating dose is adequate for facilitating tracheal intubation conditions during rapid sequence intubation of anesthetized, after which adequate intubation conditions are established within 60 seconds in nearly all patients.
  - If a dose of 0.6 mg/kg rocuronium bromide is used for rapid sequence intubation in anesthetized patients, it is recommended to intubate the patient 90 seconds after administration of rocuronium bromide.

- Cessation Section:
  - 0.5 mg/kg-1 rocuronium bromide does not affect the Appar scores; fentanyl does appear to reduce respiratory depression.
  - Since 0.5 mg/kg-1 were investigated during rapid sequence induction of anaesthesia, and not in general anaesthesia patients.
  - Higher doses:
    - Intubation doses up to 2 mg/kg rocuronium bromide have been administered during surgery without adverse CV effects being noted.
    - The peak plasma high doses of rocuronium bromide decreases as the time increases and the duration of action.
  - Maintenance dosing:
    - The recommended maintenance dose is 0.15 mg/kg-1 rocuronium bromide, in the case of long-term intravenous anaesthesia, this should be reduced to 0.05 mg/kg-1 rocuronium bromide.
    - The intubation dose should be given when the patient is ready to be intubated.

Contraindications:
- First degree heart block.
- Proarrhythmic drugs such as 
- Other conditions that are likely to induce a life-threatening arrhythmia.
- Use of specific populations:
- Use in patients with history of arrhythmia.
- Use in patients with clinical indication for cardiology.
- Use in patients with clinical indication for cardiology.
- Use in patients with clinical indication for cardiology.

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 pancuronium bromide in adults undergoing surgery.

Contraindications:
- Pre-existing hypersensitivity to sugammadex or any of its excipients.

Warnings/Precuations:
- Anaphylaxis and Hypersensitivity:
  - Anaphylactic events have occurred in some patients with rocuronium bromide and pancuronium bromide, including cases of anaphylactic reactions.
  - Rare cases of anaphylactic reactions have occurred in patients with prior exposure to sugammadex.

- Respiratory Function Monitoring During Recovery:
  - Ventilatory support is mandatory for patients until adequate spontaneous respiration is restored and the ability to maintain the airway has been ascertained.

- Risk of Prolonged Neuromuscular Blockade:
  - In clinical trials, very small numbers of patients experienced a delayed or transient response to the administration of sugammadex.

- Waiting Times for Re-Administration of Neuromuscular Blocking Agents for Intubation Following Reversal with BRIDION:
  - A minimum of 60 minutes is recommended prior to re-administration of a 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 neuromuscular blocking from the site of action.

- Interactions Potentially Affecting the Effect of Other Drugs:
  - Due to the administration of BRIDION, certain drugs, including benzodiazepines, could become less effective due to a lowering of the blood plasma concentrations. In this situation, consider the use of alternative agents or use higher doses of the alternative agent.

- Adverse Events:
  - The most commonly occurring adverse drug reactions include urticaria, skin reactions, and reactions of the skin and mucous membranes.

- Drug Interactions:
  - Nitroglycerin, a direct-acting coronary vasodilator, has been shown to be safe and effective when used in combination with sugammadex.

- Use in Specific Populations:
  - Use in patients with respiratory disease.
  - Use in patients with cardiac disease.
  - Use in patients with renal disease.

- Dosing:
- The usual dosage is 2.5 mg/kg of the concentrate for infusion 200 mg.

- Before prescribing, please consult the full prescribing information.