THE HONG KONG 香港醫訊
MEDICAL DIARY
www.fmshk.org
VOL.23 NO.8 August 2018

Urology

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

Enantone® DPS

Leuprorelin acetate 3.75 mg, 11.25 mg & 30mg

SEE THE REAL PERSON BEHIND THE PATIENT

Enantone has proven benefits

Well-established efficacy in all stages of prostate cancer

- **Immediate therapy with Enantone minimises the risk of progression.**[1]
- **Enantone adjuvant to radiotherapy improves overall survival.**[2]
- **Enantone adjuvant to radical prostatectomy decreases the risk of relapse.**[3,4]
- **Enantone controls disease after biochemical relapse.**[5]
- **Enantone has good response rates in patients with advanced disease.**[6,7]

Abridged Prescribing Information

Active Ingredient: Leuprorelin acetate Indication: Enantone 1-Month DPS 3.75 mg Endometriosis; decrease of myoma vol &/or amelioration of symptoms in uterine myoma w/ hypermenorrhea, hypogastralgia, low back pain, anemia, etc (conservative treatment); premenopausal breast cancer (negative hormone receptor expression);fibroids. Childn: Precocious puberty (before 8 yr in females & before 10 yr in males). Enantone 6- Month DPS 30 mg Palliative treatment of advanced hormone-dependent prostate carcinoma. **Dosage/Administration:** Enantone 1-Month DPS 3.75 mg Endometriosis Adult 3.75 mg SC once every 4 wk. Patient weighing <50 kg 1.88 mg may be used. Initiate administration on 1st-5th day after the start of the menstrual period. Uterine myoma Adult 1.88 mg SC once every 4 wk. Patients w/ heavy wt or those w/ markedly enlarged uterus Administer 3.75 mg. Initiate administration on 1st-5th day after the start of the menstrual period. Prostate cancer & premenopausal breast cancer Adult 3.75 mg SC once every 4 wk. Central precocious puberty 30 mcg/kg SC once every 4 wk, may be increased up to 180 mcg/kg. Enantone 3-Month DPS 11.25 mg Male & female 11.25 mg once every 3 mth. Childn <20 kg 5.63 mg once every 3 mth; ≥20 kg 11.25 mg once every 3 mth. Endometriosis & uterine fibroids 6 mth treatment duration. Enantone 6- Month DPS 30 mg SC once every 6 mth w/ interval of 168 days to max 182 days. **Contraindication:** Enantone 1-Month DPS 3.75 mg Hypersensitivity to synthetic LH-RH or LH-RH derivatives. Abnormal genital bleeding of indeterminable nature. Women having possibilities of being pregnant. Pregnancy & lactation. Enantone 3-Month DPS 11.25 mg Hypersensitivity. In case of not diagnosed vag bleeding. Pregnancy & lactation.Enantone 6-Month DPS 30 mg Hypersensitivity to leuprorelin or other GnRH analogues, polylactic acid. Undiagnosed abnormal genital bleeding. Pregnancy, lactation. **Special Precaution:** Enantone 1-Month DPS 3.75 mg Patients w/ submucous myoma; renal dysfunction due to spinal cord compression or ureteral obstruction or those who may be at a risk of developing such manifestations. Discontinue treatment in case of growing phyma or no improvement is seen. Transient aggravation of clinical condition, bone pain. Depressed state-like climacteric disturbance. Perform LH-RH test at regular intervals. Enantone 3-Month DPS 11.25 mg Male: Transitory worsening of clinical symptomatology eg, bone pain, urinary tract obstruction & haematuria, weakness of the lower extremities & paresthesia due to temporary increase of serum testosterone level. Patients w/ neurological signs of spinal cord compression or in those w/ ureteric obstruction. Verify testosterone levels, PSA & acid phosphatase periodically. Female: Eventual onset of severe metrorrhagia; onset of serious vag bleeding during treatment. Use non-hormonal contraceptive methods during treatment. Fertile women. Verify periodically the values of bone densitometry in case of prolonged treatment. Temporary worsening of clinical status. Girls: May require additional adequate treatment if little genital hemorrhages after the 1st inj goes on beyond the 1st mth of treatment. Childn: Gonadotropin-pituitary inhibition. Check regularly that the estradiol/testosterone levels are low in case the wt is near 20 kilos. Increased risk of incident depression (which may be severe).Enantone 6-Month DPS 30 mg Patients at risk of ureteric obstruction or spinal cord compression. Prostate cancer patients w/ vertebral metastasis. Women w/ high risk in metabolic bone disease. Monitor potential neurological complications, spinal metastases, or urinary tract obstruction during the 1st few weeks of treatment. Increased risk of diabetes & certain cardiovascular diseases in men undergoing treatment of prostate cancer. **Adverse Reaction:** Enantone 1-Month DPS 3.75 mg Hot flushes, feeling of warmth, feeling of hot flushes, shoulder stiffness, headache, insomnia, dizziness or diaphoresis. Pains eg, arthralgia & bone pain. Enantone 3-Month DPS 11.25 mg Hot flushes. Male: Decrease of the libido, loss of bone mass, impotence, gynecomastia & reduction of testicular vol, testicular atrophy. Initial worsening of the urinary obstructive symptomatology (dysuria, haematuria, lumbar pain), of the muscoloskeletal symptomatology (bone pain), or of the neurological compression signs (weakness feeling, paresthesia of the lower extremities). Female: Libido reduction, menstrual disorders, vaginitis w/ hematic spotting, vag dryness, breast size decrease, arthralgia, myalgia. Girls: Occurrence of genital spots after the 1st inj.Enantone 6-Month DPS 30 mg Anaphylactic symptoms. Pituitary apoplexy may develop after initial administration in patients w/ pituitary adenoma. Women: Transient aggravation of pelvic pain, dysmenorrhea. Hot flushes, vag dryness, libido decrease, dyspareunia. Depression. Men: Transient aggravation of bone pain, ureteral obstruction or spinal cord compression. Hot flushes, impotence, decrease in testes size, nausea, vomiting, edema of lower limbs, general pain, gynaecomastia. Depression. Loss of appetite, headache, joint or back pain, muscle weakness, nocturia, dysuria, inj site reactions, increased sweating, tiredness peripheral edema, paraesthesia, sleep disturbances, wt gain. **Drug interaction:** Enantone 1-Month DPS 3.75 mg Reduced effect w/ sex hormone prep eg, estradiol derivatives, estriol derivatives, conjugated estrogen prep, combined prep of estrogen & progesteron, mixed sex hormones. **Presentation/Packing:** Enantone 1-Month DPS 3.75 mg pre-filled syringe. Enantone 3-Month DPS 11.25 mg pre-filled syringe. Enantone 6-Month DPS 30 mg pre-filled syringe.

ADT, androgen deprivation therapy; LHRH, luteinising hormone-releasing hormone; PSA, prostate-specific antigen.

References: 1. Tunn UW et al. Prostate Cancer Prostatic Dis 2009;12 83–7. **2.** D'Amico AV, et al. JAMA 2004;292:821–7. **3.** Zincke H, et al. J Urol 2001;166:2208–15. **4.** Inman BA, et al. Cancer 2008;113:1544–51. **5.** Moul JW, et al. J Urol 2004;171:1141–7. **6.** Kienle E, et al. Urol Int 1996;56(51):23–30. **7.** Bischoff W. J Int Med Res 1990;18:103–13.

Further information is available upon request. Before prescribing, please consult local prescribing information.

Takeda Pharmaceuticals (Hong Kong) Limited
23/F & 24/F East Exchange Tower, 38 Leighton Road, Causeway Bay, Hong Kong
Tel : 2133 9800 Fax : 2856 2728

Enantone® DPS
Leuprorelin acetate 3.75 mg, 11.25 mg & 30mg

Takeda

HK/LEU/2016-00023

Contents

Scan the QR-code

To read more about The Federation of Medical Societies of Hong Kong

Disclaimer

The Cover Shot

Peacock

The cover shot was taken from a March 2018 painting by Stephanie Wong, an 11-year-old local artist. This piece of artwork was created on a square piece of canvas, which was first covered with patching paste to recreate the texture and 3D feel of a peacock's feathers. After the patching paste has dried up, it is then covered with a layer of "Gesso", which makes the texture stand out more and makes the patching paste slightly stiffer. After the "Gesso" has dried up, acrylic paint is used to add colour to the artwork, the colours being blue, green, turquoise, white, black and, as the final touch, a few speckles of gold.

Dr Martin Kwok-tin WONG
MBBS(HK), FRCSEd, FCSHK, FRCSEd(Urol), FHKAM(Surgery)
Specialist in Urology
Founder & Chairman, Hong Kong Prostate Foundation
Immediate Past President, The Hong Kong Society of Practising Urologists

Published by
The Federation of Medical Societies of Hong Kong

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

Editorial

Dr Martin Kwok-tin WONG

MBBS(HK), FRCSEd, FCSHK, FRCSEd(Urol), FHKAM(Surgery)

Specialist in Urology
Founder & Chairman, Hong Kong Prostate Foundation
Immediate Past President,
The Hong Kong Society of Practising Urologists

Editor

Dr Martin Kwok-tin WONG

Urology is well recognised to be an innovative and fast-growing specialty in medicine. The endoscope, an instrument that allows us to peek inside the human body, was used as early as the ancient Greek and Roman periods. An instrument considered a prototype of endoscopes was evidenced and discovered in the ruins of Pompeii. It was Philipp Bozzini, a German, who in 1805 made the first attempt to observe the living human body directly through a tube he created known as a Lichtleiter (light-guiding instrument) to examine the urinary tract. In 1853, Antoine Jean Desormeaux of France developed an instrument specially designed to examine the urinary tract and the bladder. He named it the "endoscope", and it was the first time this term was used in history. Nowadays, many urological diseases can be treated effectively with endoscopes and laparoscopes. Modern energy sources enable urologists to perform lithotripsy or tissue ablation with flexible and very fine endourological instruments. Advances in surgical skills and techniques also enable urologists to perform partial nephrectomy with highly selective clamping of renal arterial branches. When the era of robotic-assisted surgery arrived, radical prostatectomy was one of the earliest and most popularly performed robotic-assisted operations, readily benefitting from such state-of-the-art technology. Modern approach to multi-disciplinary management also opens up opportunities for urologists to collaborate with clinical oncologists in treating patients with urological malignancies.

In Hong Kong, we are proud to have world-famous urologists who contributed so much to the field of urology. Dr Che-hung Leong is the one who has pioneered the use of the stomach as the material for augmentation cystoplasty in humans. His paper on gastrocystoplasty published in 1978 is still widely cited by many authors. Dr Leong also introduced the technology of TURP (transurethral resection of the prostate) to Hong Kong when he was teaching at the Faculty of Medicine, the University of Hong Kong.

In this issue, we have invited five local experts to share with us their respective knowledge on and experience in five topics of modern urology. Dr Eddie Chan shows us how he pioneers a minimally invasive approach to treating bladder tumours. Dr Darren Poon enlightens us on the advances in immunotherapy in the treatment of advanced urothelial malignancies. Dr Jeremy Teoh has contributed a comprehensive review on the management of lower urinary tract symptoms in the primary care setting. Dr Ka-lun Chui shows us how urologists use laser to treat various urological disease entities, and Dr Francis Lee provides an update on the management of small renal masses.

Lastly, we always talk about "the art and science of medicine"; art enriches the life of a doctor too. This is the reason why I take this opportunity to share with you, on the front cover, an acrylic painting on canvass by a local young artist; and a casual article, written by myself, about Chinese music. Hopefully, this relaxing yet enlightening issue of the Medical Diary will give our readers a cool breeze in the hot summer months.

DUODART
(dutasteride/tamsulosin HCl) Capsules

gsk

Dual Action
Dual PROtection

DUAL ACTION:

- **Superior symptoms improvement**[1]
  (adjusted mean change in IPSS from baseline to year 4 was **-6.3** points for combination therapy versus **-3.8** points for tamsulosin)
- **Reduce prostate size up to 27%**#

DUAL PROTECTION:

Reduce relative risk of
- AUR by **68%**
- BPH related surgery by **71%**

vs tamsulosin monotherapy[1]

*The **ONLY** fixed-dose combination in relieving BPH symptoms and reduce risk of AUR or BPH-related surgery*

BPH: Benign Prostatic Hyperlasia
AUR: Acute Urinary Retention

DUODART (Dutasteride-tamsulosin) abbreviated prescribing information[2]

Indications Treatment of moderate to severe symptoms of benign prostatic hyperplasia (BPH). Limitations of use: Dutasteride-containing products, including DUODART, are not approved for the prevention of prostate cancer. **Dosage and Administration** The recommended dose of DUODART (Dutasteride-tamsulosin) is one capsule (0.5 mg/ 0.4 mg) taken once daily. The capsules should be swallowed whole and not chewed or opened. Contact with the contents of the dutasteride capsule contained within the hard-shell capsule may result in irritation of the oropharyngeal mucosa. **Contraindications** Patients with known hypersensitivity to dutasteride, other 5 alphareductase inhibitors, tamsulosin (including tamsulosin- induced angio-edema), soya, peanut or any of the excipients; history of orthostatic hypotension; with severe hepatic impairment; women and children and adolescents. **Warnings and Precautions** *Cardiac Failure* In two 4-year clinical study, the incidence of cardiac failure (a composite term of reported events, primarily cardiac failure and congestive cardiac failure) was higher among subjects taking the combination of dutasteride and an alpha1- adrenoceptor antagonist, primarily tamsulosin, than it was among subjects not taking the combination. In these two trials, the incidence of cardiac failure was low (≤1%) and variable between the studies. *Effect on prostate-specific antigen (PSA) and prostate cancer detection* Digital rectal examination, as well as other evaluations for prostate cancer or other conditions which can cause the same symptoms as BPH, must be performed on patients with BPH prior to initiating therapy with DUODART and periodically thereafter. Serum prostate-specific antigen (PSA) concentration is an important component in the detection of prostate cancer. DUODART causes a decrease in mean serum PSA levels by approximately 50% after six months of treatment. Patients receiving Duodart should have a new PSA baseline established after 6 months of treatment with Duodart. It is recommended to monitor PSA values regularly thereafter. Any confirmed increase from lowest PSA level while on DUODART may signal the presence of prostate cancer (particularly high grade cancer) or noncompliance to therapy with DUODART and should be carefully evaluated, even if those values are still within the normal range for men not taking a 5α-reductase inhibitor. In the interpretation of a PSA value for a patient taking DUODART, previous PSA values while on dutasteride treatment should be sought for comparison. Total serum PSA levels return to baseline within 6 months of discontinuing treatment. The ratio of free to total PSA remains constant even under the influence of DUODART. If clinicians elect to use percent free PSA as an aid in the detection of prostate cancer in men undergoing DUODART therapy, no adjustment to its value appears necessary. *Prostate cancer and high grade tumours* Results of one clinical study (the REDUCE study) in men at increase risk of prostate cancer revealed a higher incidence of Gleason 8 – 10 prostate cancers in dutasteride treated men compared to placebo. The relationship between dutasteride and high grade prostate cancer is not clear. Men taking DUODART should be regularly evaluated for prostate cancer risk including PSA testing. *Renal impairment* The treatment of severely renally impaired patients should be approached with caution as these patients have not been studied. *Hypotension* Orthostatic: As with other alpha1-adrenoceptor antagonists, a reduction in blood pressure can occur during treatment with tamsulosin, as a result of which, rarely, syncope can occur. Patients beginning treatment with DUODART should be cautioned to sit or lie down at the first signs of orthostatic hypotension (dizziness, weakness) until the symptoms have resolved. Symptomatic: Caution is advised when alpha adrenergic blocking agents including tamsulosin are co-administered with PDE5 inhibitors. Alpha1-adrenoceptor antagonists and PDE5 inhibitors are both vasodilators that can lower blood pressure. Concomitant use of these two drug classes can potentially cause symptomatic hypotension. *Intraoperative Floppy Iris Syndrome* (IFIS, a variant of small pupil syndrome) has been observed during cataract surgery in some patients on or previously treated with tamsulosin. IFIS may increase the risk of eye complications during and after the operation. The initiation of therapy with DUODART in patients for whom cataract surgery is scheduled is therefore not recommended. During pre-operative assessment, cataract surgeons and ophthalmic teams should consider whether patients scheduled for cataract surgery are being or have been treated with DUODART in order to ensure that appropriate measures will be in place to manage the IFIS during surgery. Discontinuing tamsulosin 1 – 2 weeks prior to cataract surgery is anecdotally considered helpful, but the benefit and duration of stopping therapy prior to cataract surgery has not yet been established. *Leaking Capsule* Dutasteride is absorbed through the skin, therefore women and children and adolescents must avoid contact with leaking capsules. If contact is made with leaking capsules, the contact area should be washed immediately with soap and water. *Inhibitors of CYP3A4 and CYP2D6* Concomitant administration of tamsulosin hydrochloride with strong inhibitors of CYP3A4, or to a lesser extent, with strong inhibitors of CYP2D6 can increase tamsulosin exposure. Tamsulosin hydrochloride is therefore not recommended in patients taking a strong CYP3A4 inhibitor and should be used with caution in patients taking a moderate CYP3A4 inhibitor, a strong or moderate CYP2D6 inhibitor, a combination of both CYP3A4 and CYP2D6 inhibitors, or in patients known to be poor metabolisers of CYP2D6. *Hepatic Impairment* DUODART has not been studied in patients with liver disease Caution should be used in the administration of DUODART to patients with mild to moderate hepatic impairment. *Expients* This medicinal product contains the colouring agent Sunset Yellow (E110), which may cause allergic reactions. *Breast neoplasia* Breast cancer has been reported in men taking dutasteride in clinical trials and during the post-marketing period. Prescribers should instruct their patients to promptly report any changes in their breast tissue such as lumps or nipple discharge. It is not clear if there is a causal relationship between the occurrence of male breast cancer and long term use of dutasteride. **Interactions** *Tamsulosin* Concomitant administration of tamsulosin hydrochloride with drugs which can reduce blood pressure, including anaesthetic agents, PDE5 inhibitors and other alpha1- adrenoceptor antagonists could lead to enhanced hypotensive effects. Dutasteride-tamsulosin should not be used in combination with other alpha1- adrenoceptor antagonists. Concomitant administration of tamsulosin hydrochloride and ketoconazole (a strong CYP3A4 inhibitor) resulted in an increase of the Cmax and AUC of tamsulosin hydrochloride by a factor of 2.2 and 2.8 respectively. Concomitant administration of tamsulosin hydrochloride and paroxetine (a strong CYP2D6 inhibitor) resulted in an increase of the Cmax and AUC of tamsulosin hydrochloride by a factor of 1.3 and 1.6 respectively. A similar increase in exposure is expected in CYP2D6 poor metabolisers as compared to extensive metabolisers when co-administered with a strong CYP3A4 inhibitor. The effects of co-administration of both CYP3A4 and CYP2D6 inhibitors with tamsulosin hydrochloride have not been evaluated clinically, however there is a potential for significant increase in tamsulosin exposure. Concomitant administration of tamsulosin hydrochloride (0.4 mg) and cimetidine (400 mg every six hours for six days) resulted in a decrease in the clearance (26%) and an increase in the AUC (44%) of tamsulosin hydrochloride. Caution should be used when dutasteride-tamsulosin is used in combination with cimetidine. A definitive drug-drug interaction study between tamsulosin hydrochloride and warfarin has not been conducted. Results from limited in vitro and in vivo studies are inconclusive. Diclofenac and warfarin, however, may increase the elimination rate of tamsulosin. Caution should be exercised with concomitant administration of warfarin and tamsulosin hydrochloride. **Fertility, pregnancy and lactation** DUODART is contraindicated for use by women. There have been no studies to investigate the effect of DUODART on pregnancy, lactation and fertility. As with all 5 alpha reductase inhibitors, when the patient's partner is or may potentially be pregnant it is recommended that the patient avoids exposure of his partner to semen by use of a condom. As with other 5 alpha reductase inhibitors, dutasteride inhibits the conversion of testosterone to dihydrotestosterone and may, if administered to a woman carrying a male foetus, inhibit the development of the external genitalia of the foetus. Dutasteride has been reported to affect semen characteristics (reduction in sperm count, semen volume, and sperm motility) in healthy men. The possibility of reduced male fertility cannot be excluded. Effects of tamsulosin hydrochloride on sperm counts or sperm function have not been evaluated. The effects of dutasteride 0.5 mg/day on semen characteristics were evaluated in healthy volunteers aged 18 to 52 (n=27 dutasteride, n=23 placebo) throughout 52 weeks of treatment and 24 weeks of post-treatment follow-up. At 52 weeks, the mean percent reduction from baseline in total sperm count, semen volume and sperm motility were 23%, 26% and 18%, respectively, in the dutasteride group when adjusted for changes from baseline in the placebo group. Sperm concentration and sperm morphology were unaffected. After 24 weeks of follow-up, the mean percent change in total sperm count in the dutasteride group remained 23% lower than baseline. While mean values for all parameters at all time points remained within the normal ranges and did not meet the predefined criteria for a clinically significant change (30%), two subjects in the dutasteride group had decreases in sperm count of greater than 90% from baseline at 52 weeks, with partial recovery at the 24 week follow-up. The possibility of reduced male fertility cannot be excluded. It is not known whether dutasteride or tamsulosin are excreted in human milk. **Adverse Reactions** *Clinical Trial Data* (Dutasteride and tamsulosin co-administration): Impotence, altered (decreased) libido, ejaculation disorders, breast disorders (includes breast tenderness and breast enlargement), dizziness and cardiac failure. (Dutasteride monotherapy): Impotence, altered (decreased) libido, ejaculation disorders, breast disorders (includes breast tenderness and breast enlargement), alopecia (primarily body hair loss), hypertrichosis. (Tamsulosin Monotherapy): Dizziness, abnormal ejaculation, palpitations, constipation, diarrhoea, vomiting, asthenia, rhinitis, rash, pruritis, urticaria, orthostatic hypotension, syncope, headache, nausea, angioedema, priapism, Stevens-Johnson syndrome. During postmarketing surveillance, reports of Intraoperative Floppy Iris Syndrome (IFIS), a variant of small pupil syndrome, during cataract surgery have been associated with alpha1- adrenoceptor antagonists, including tamsulosin. In addition atrial fibrillation, arrhythmia, tachycardia, dyspnoea, epistaxis, vision blurred, visual impairment, erythema multiforme, dermatitis exfoliative, ejaculation disorder, retrograde ejaculation, ejaculation failure and dry mouth have been reported in association with tamsulosin use. The frequency of events and the role of tamsulosin in their causation cannot be reliably determined.
Abbreviated PI based on HK092016(GDS11v3/MHRA20160901). Please refer to the full prescribing information before prescribing. Full prescribing information is available upon request.

At month 48, the adjusted mean percentage change from baseline in total prostate volume was -27.3% for combination therapy, +4.6% (p<0.001) for tamsulosin, and -28.0% (p=0.42) for dutasteride.

References: 1. Roehrborn CG, *et al. Eur Urol* 2010;57(1):123–31 **2.** DUODART Hong Kong Full Prescribing Information 2016. Version number: HK092016(GDS11v3/MHRA20160901)

GlaxoSmithKline Limited 23/F, Tower 6, The Gateway, 9 Canton Road, TsimShaTsui, Kowloon, Hong Kong Tel. (852) 3189 8989 Fax.(852) 3189 8931

HKRX/DUTT/0015/18 (05/2020)
Date of preparation: 12/06/2018

Managing Lower Urinary Tract Symptoms with Special Attention to Overactive Bladder in the Primary Care Setting

Dr Jeremy Yuen-chun TEOH

MBBS (HK), FRCSEd (Urol), FCSHK, FHKAM (Surgery)

Assistant Professor
SH HO Urology Centre, Department of Surgery, Prince of Wales Hospital,
The Chinese University of Hong Kong

Dr Jeremy Yuen-chun TEOH

This article has been selected by the Editorial Board of the Hong Kong Medical Diary for participants in the CME programme of the Medical Council of Hong Kong (MCHK) to complete the following self-assessment questions in order to be awarded 1 CME credit under the programme upon returning the completed answer sheet to the Federation Secretariat on or before 31 August 2018.

Introduction

Lower urinary tract symptoms (LUTS) are common urological complaints in both men and women, and the prevalence of LUTS increases substantially with age[1]. Broadly speaking, LUTS can be divided into storage, voiding and post-micturition symptoms[2]. Storage symptoms include urinary frequency, urgency and nocturia. Voiding symptoms include poor stream, hesitancy, intermittency and terminal dribbling. Post-micturition symptoms include sensation of incomplete emptying following urination and post-micturition dribbling. In our clinical practice, LUTS are often overlapping. The causes of LUTS are often multi-factorial[3] and we may encounter difficulties in the diagnosis and management of patients presenting with LUTS. In this paper, we shall discuss LUTS with special attention to overactive bladders (OAB), and how we can manage them appropriately in the primary care setting.

Local data on the prevalence of LUTS

A cross-sectional survey on the pattern of LUTS has been conducted in Hong Kong (unpublished data, CH Yee et al). A total of 1,000 subjects (302 males and 698 females) were randomly sampled from the general population, and phone interviews were conducted. It was noted that the severity of both storage and voiding symptoms increased with age, and they were in general more severe in the male population. Of note, 14.6% of the male population and 12.9% of the female population aged 60-79 years had urgency with urinary incontinence. The number of nocturia episodes also increased with age, with a median of 3 times in male patients and 2 times in female patients aged 80 years or above. Upon multivariate analysis, old age, hypertension and diabetes were associated with more severe storage symptoms, while male sex, hypertension, diabetes, ischaemic heart disease and stroke were associated with more severe voiding symptoms. The results confirmed that LUTS are indeed a common urological problem in both the male and female populations in Hong Kong, and the severity of LUTS could be associated with multiple underlying medical conditions.

Understanding the development of LUTS

We should always be aware that the development of LUTS could be due to many different causes[4]. In managing male patients presenting with LUTS, it is often presumed that LUTS is due to underlying benign prostatic hyperplasia (BPH). However, this presumption is often incorrect and could lead to suboptimal management of LUTS[5,6]. For male patients, the presentation of LUTS is often an end result of the interaction between the bladder and the bladder outlet, which is represented by BPH in most of the cases[7]. When there is bladder outlet obstruction due to underlying BPH, patients would present with voiding symptoms including slow stream, hesitancy, intermittency and terminal dribbling. The presence of BPH and ineffective voiding mechanism could lead to post-micturition symptoms including sensation of incomplete emptying and post-micturition dribbling. With a prolonged period of bladder outlet obstruction, patients could develop secondary detrusor hypertrophy[8]. Normal functional bladder capacity is about 300 to 500 mL[9,10]. In patients with detrusor hypertrophy, they may have the urge to void before reaching their usual bladder capacities and develop storage symptoms including urinary frequency, urgency and nocturia. In such cases, the occurrence of storage symptoms is a result of a bladder problem (detrusor hypertrophy) secondary to bladder outlet obstruction (BPH); BPH treatment alone is unlikely to lead to complete resolution of storage symptoms[11,12]. On the other hand, we should always be aware that the development of storage symptoms could be caused by primary bladder dysfunction, which by definition would have no relationship with bladder outlet obstruction even in male patients with BPH[13]. In such cases, the management of storage LUTS should be primarily focused in the bladder part instead of BPH. In female patients, in the absence of the prostate gland, the possibility of bladder outlet obstruction is very low, and the presence of storage symptoms would often be indicative of a primary bladder dysfunction. On the other hand, medical conditions including diabetes mellitus could lead to a hypo-contractile bladder resulting in voiding symptoms, and the presentation of LUTS in female patients could still be overlapping. In patients presenting with LUTS, we should always try to explore the types of symptoms that they are suffering from; we might gather some hints regarding the underlying aetiologies and they can be managed accordingly.

Diagnosing LUTS in the primary care setting

In female patients, bladder outlet obstruction is very rare and the diagnosis of LUTS is usually more straightforward. In male patients, the diagnosis of LUTS could be more complicated. Clinical evaluation is most important in diagnosing patients presenting with LUTS. Mixed storage and voiding symptoms are not uncommon, but it is often useful to enquire which type of symptoms is predominant. Male patients who complain of predominantly voiding symptoms are likely to suffer from BPH. This could be supported by the presence of an enlarged prostate gland upon digital rectal examination (DRE), a high voiding domain score from the International Prostate Symptom Score (IPSS) questionnaire, and a poor maximum urinary flow rate of less than 10 mL/second upon uroflowmetry. For male patients who complain of predominantly storage symptoms, this would raise the alarm of an OAB syndrome. OAB is a clinical syndrome defined as urgency (with or without urge incontinence) usually accompanied by frequency and nocturia. The diagnosis of primary OAB could be supported by a high storage domain score from the IPSS questionnaire, a high score from the Overactive Bladder Symptom Score (OABSS) questionnaire and the presence of frequent voiding with a small amount of urine per void as recorded in the voiding diary. For male patients who complain of both voiding and storage symptoms, BPH with secondary detrusor hypertrophy should be considered. This could be supported by the presence of an enlarged prostate gland, high storage and voiding domain scores from the IPSS questionnaire, a high score from the OABSS questionnaire, the presence of frequent voiding with a small amount of urine per void as recorded in the voiding diary, and a poor maximum urinary flow rate of less than 10 mL/second upon uroflowmetry. Common presentations of the above hypothetical cases in male patients are summarised in Fig. 1. In real-life practice, however, the presentation of LUTS could vary between different patients and the development of LUTS could be multi-factorial. We should always remember other causes of LUTS such as nocturnal polyuria, congestive heart failure and neurological disorders, which could give rise to similar presentations. We must therefore exercise our expertise in making the most likely diagnosis and manage accordingly.

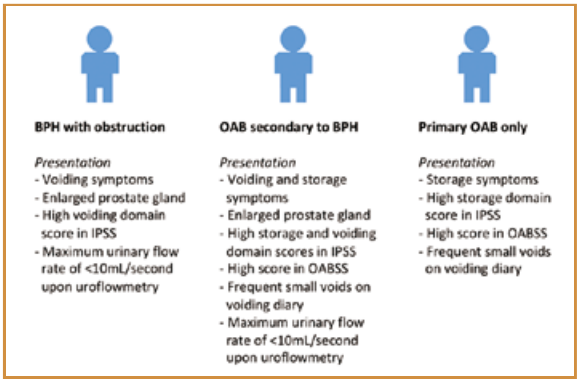


Fig. 1. Schematic diagram showing the common clinical presentations of LUTS in male patients

Management of LUTS

Patient education, reassurance and periodic monitoring of urinary symptoms should be offered to all patients with LUTS[4]. Dietary advice including the avoidance of caffeine or alcohol intake, and the reduction of fluid intake before sleep at night could improve urinary frequency, urgency and nocturia[14,15]. Double-voiding technique and urethral milking could improve sensation of incomplete emptying and post-micturition dribbling. Bladder training encourages men to hold their urgency in the hope of increasing their functional bladder capacities, and this could result in improvements in storage symptoms.

The need for pharmacological treatment would depend on the degree of bothersome symptoms. Generally speaking, there are four common types of medications that we could consider in the primary care setting, namely alpha-1 blockers, 5-alpha reductase inhibitors (5-ARI), anti-cholinergic medications and beta-3 agonists. The type of medication to be given would depend on the type of symptoms that the patient complains of primarily.

For male patients with predominantly voiding symptoms, they are likely to suffer from bladder outlet obstruction because of BPH. An alpha-1 blocker is commonly used in these patients. Alpha-1 blockers aim to inhibit the effect of endogenously released noradrenaline on smooth muscle cells in the prostate gland and therefore reduce the prostate tone[16]. Previous studies have shown that the use of alpha-1 blockers could improve IPSS by 30-40% and the maximum urinary flow rate by 16-25%[17]. Alpha-1 blockers act on the dynamic component of the prostate gland. Therefore, one would expect a fast onset of action, but it would have reached its maximal effect by 4 weeks' time. For patients not responding to alpha-1 blockers beyond 4 weeks, we should review our treatment plan and decide whether any change is needed[17]. Common side effects of alpha-1 blockers include asthenia, dizziness and orthostatic hypotension. Among the different types of alpha-1 blockers, tamsulosin appears to have the best vascular-related safety profile[18], presumably due to its preferential selective action on alpha-1A receptors (prostate and bladder neck) over alpha-1B receptors (blood vessel).

5-ARI is another class of medications that we can consider in male patients with BPH and predominantly voiding symptoms. Androgens, namely testosterone and dihydrotestosterone (DHT), play complementary roles in the development of BPH[19]. In normal male physiology, testosterone is converted into DHT by 5-alpha reductase. As DHT is 2.4 to 10 times more potent than testosterone[20,21], the inhibition of DHT could lead to apoptosis of the prostate gland and therefore reduction in the prostate size. To the contrary of alpha-1 blockers, it takes a longer time period for 5-ARI to lead to a reduction of prostate size, but its effect tends to increase with longer treatment durations. Compliance with long-term treatment is therefore important for this medication. After 2 to 4 years of treatment, 5-ARI could improve IPSS by a mean of 2.6, and maximum urinary flow rate by 1.5-2.0 mL/second, reduce the prostate size by 18 to 28%, and reduce the risk of acute

Betmiga®
mirabegron

THE *1ST* β_3-AGONIST FOR **OAB* PATIENTS**
WITH PROMISING SAFETY PROFILE
PLACEBO-LIKE DRY MOUTH(1.7%) SIDE EFFECT[1]

Harnal OCAS®
tamsulosin

YOUR *1ST* STEP FOR **MALE LUTS+ PATIENTS**
WITH PROMISING SAFETY PROFILE#
PLACEBO-LIKE DIZZINESS(1.4%) SIDE EFFECT[2]

A *FRESH* STEP IN LUTS+ MANAGEMENT

*OAB: Overactive Bladder + LUTS: Lower Urinary Tract Symptoms
α_1-blockers are often considered the first line drug treatment of male LUTS[3]

Reference: **1.** Chapple C.R. et al. Neurourol Urodynam 2013 [doi 10.1002/nau22505] **2.** Chapple C.R. et al. Eur Urol Supp. 2005; 4:33-44
3. Gravas S, et al. EAU Guidelines on the Treatment of Non-neurogenic Male LUTS. European Association of Urology. 2017.

Abbreviated prescribing information of Harnal OCAS® 0.4 mg Tablets
Version: 002 PI version: Sep 2013. **Composition:** Tamsulosin HCl **Indication:** Lower urinary tract symptoms (LUTS) associated with benign prostatic hyperplasia (BPH). **Dosage:** 1 tab daily, can be taken independently of food. **Administration:** Swallow whole, do not chew/crunch. **Contraindications:** Hypersensitivity to tamsulosin hydrochloride or to any of the excipients. **Special warnings and special precaution for use:** As with other α1-adrenoceptor antagonists, a reduction in blood pressure can occur in individual cases during treatment with Harnal OCAS® 0.4 mg Tablets, as a result of which, rarely, syncope can occur. At the first signs of orthostatic hypotension (dizziness, weakness), the patient should sit or lie down until the symptoms have disappeared. Before therapy with Harnal OCAS® 0.4 mg Tablets is initiated, the patient should be examined in order to exclude the presence of other conditions, which can cause the same symptoms as benign prostatic hyperplasia. Digital rectal examination and, when necessary, determination of prostate specific antigen (PSA) should be performed before treatment and at regular intervals afterwards. Treatment of patients with a history of orthostatic hypotension should be approached with caution. The treatment of patients with severe renal impairment (creatinine clearance of <10 ml/min) should be approached with caution, as these patients have not been studied. The treatment of patients with severe hepatic dysfunction should be approached with caution. The 'Intraoperative Floppy Iris Syndrome' (IFIS, a variant of small pupil syndrome) has been observed during cataract and glaucoma surgery in some patients on or previously treated with tamsulosin hydrochloride. IFIS may increase the risk of eye complications during and after the operation. Discontinuing tamsulosin hydrochloride 1-2 weeks prior to cataract or glaucoma surgery is anecdotally considered helpful, but the benefit of treatment discontinuation has not been established. IFIS has also been reported in patients who had discontinued tamsulosin for a longer period prior to the surgery. The initiation of therapy with tamsulosin hydrochloride in patients for whom cataract or glaucoma surgery is scheduled is not recommended. During pre-operative assessment, surgeons and ophthalmic teams should consider whether patients scheduled for cataract or glaucoma surgery are being or have been treated with tamsulosin in order to ensure that appropriate measures will be in place to manage the IFIS during surgery. Tamsulosin hydrochloride should not be given in combination with strong inhibitors of CYP3A4 in patients with poor metaboliser CYP2D6 phenotype. Tamsulosin hydrochloride should be used with caution in combination with strong and moderate inhibitors of CYP3A4. Cases of allergic reaction to tamsulosin in patients with a past history of sulfonamide allergy have been reported. If a patient reports a previously experienced sulfa allergy, caution is warranted when administrating tamsulosin hydrochloride. **Undesirable effects:** *Common (>1%, <10%), Uncommon (>0.1%, <1%), Rare (>0.01%, <0.1%), Very rare (<0.01%). Cardiac disorder: Uncommon:* Palpitations. *Gastrointestinal disorders: Uncommon:* Constipation, diarrhoea, nausea, vomiting. *General disorders and administration site conditions: Uncommon:* Asthenia. *Nervous systems disorders: Common:* Dizziness (1.3%). *Uncommon:* Headache. *Rare: Syncope. Reproductive system and breast disorders: Common:* Ejaculation disorders. *Very rare:* Priapism. *Respiratory, thoracic and mediastinal disorders: Uncommon:* Rhinitis. *Skin and subcutaneous tissue disorders: Uncommon:* Rash, pruritus, urticaria. *Rare:* Angioedema. *Vascular disorders: Uncommon:* Orthostatic hypotension. ***Post-marketing experience:*** The following events have also been reported during the post-marketing period. These events are reported voluntarily from a population of uncertain size, therefore it is not possible to reliably estimate their frequency: visual disorders (e.g. blurred vision, visual impairment), dermatitis exfoliative, erythema multiforme and epistaxis. During cataract and glaucoma surgery a small pupil situation, known as Intraoperative Floppy Iris Syndrome (IFIS), has been reported. **Full prescribing information is available upon request.**

Abbreviated prescribing information of Betmiga® prolonged-release tablets
Version: 003 PI version: Apr 2016. **Composition:** Mirabegron **Indication:** Symptomatic treatment of urgency, increased micturition frequency and/or urgency incontinence as may occur in adult patients with overactive bladder (OAB) syndrome. **Dosage:** Adult including elderly 50 mg once daily with or without food. **Administration:** Swallow whole with liquids. Do not chew/divide/crush. **Contraindications:** Mirabegron is contraindicated in patients with - Hypersensitivity to the active substance or to any of the excipients. - Severe uncontrolled hypertension defined as systolic blood pressure ≥ 180 mm Hg and/or diastolic blood pressure ≥ 110 mm Hg. **Special warnings and precautions for use:** Renal impairment: Betmiga has not been studied in patients with end stage renal disease (GFR < 15 mL/min/1.73 m2 or patients requiring haemodialysis) and, therefore, it is not recommended for use in this patient population. Data are limited in patients with severe renal impairment (GFR 15 to 29 mL/min/1.73 m2); based on a pharmacokinetic study a dose reduction to 25 mg is recommended in this population. Betmiga is not recommended for use in patients with severe renal impairment (GFR 15 to 29 mL/min/1.73 m2) concomitantly receiving strong CYP3A inhibitors. Hepatic impairment: Betmiga has not been studied in patients with severe hepatic impairment (Child-Pugh Class C) and, therefore, it is not recommended for use in this patient population. Betmiga is not recommended for use in patients with moderate hepatic impairment (Child-Pugh B) concomitantly receiving strong CYP3A inhibitors. Hypertension: Mirabegron can increase blood pressure. Blood pressure should be measured at baseline and periodically during treatment with Betmiga, especially in hypertensive patients. Data are limited in patients with stage 2 hypertension (systolic blood pressure ≥ 160 mm Hg or diastolic blood pressure ≥ 100 mm Hg). Patients with congenital or acquired QT prolongation: Betmiga, at therapeutic doses, has not demonstrated clinically relevant QT prolongation in clinical studies. However, since patients with a known history of QT prolongation or patients who are taking medicinal products known to prolong the QT interval were not included in these studies, the effects of mirabegron in these patients is unknown. Caution should be exercised when administering mirabegron in these patients. Patients with bladder outlet obstruction and patients taking antimuscarinics medications for OAB: Urinary retention in patients with bladder outlet obstruction (BOO) and in patients taking antimuscarinic medications for the treatment of OAB has been reported in postmarketing experience in patients taking mirabegron. A controlled clinical safety study in patients with BOO did not demonstrate increased urinary retention in patients treated with Betmiga; however, Betmiga should be administered with caution to patients with clinically significant BOO. Betmiga should also be administered with caution to patients taking antimuscarinic medications for the treatment of OAB. **Undesirable effects:** Summary of the safety profile: The safety of Betmiga was evaluated in 8,433 patients with OAB, of which 5,648 received at least one dose of mirabegron in the phase 2/3 clinical program, and 622 patients received Betmiga for at least 1 year (365 days). In the three 12-week phase 3 double blind, placebo controlled studies, 88% of the patients completed treatment with Betmiga, and 4% of the patients discontinued due to adverse events. Most adverse reactions were mild to moderate in severity. The most common adverse reactions reported for patients treated with Betmiga 50 mg during the three 12-week phase 3 double blind, placebo controlled studies are tachycardia and urinary tract infections. The frequency of tachycardia was 1.2% in patients receiving Betmiga 50 mg. Tachycardia led to discontinuation in 0.1% patients receiving Betmiga 50 mg. The frequency of urinary tract infections was 2.9% in patients receiving Betmiga 50 mg. Urinary tract infections led to discontinuation in none of the patients receiving Betmiga 50 mg. Serious adverse reactions included atrial fibrillation (0.2%). Adverse reactions observed during the 1-year (long term) active controlled (muscarinic antagonist) study were similar in type and severity to those observed in the three 12-week phase 3 double blind, placebo controlled studies. List of adverse reactions: The table below reflects the adverse reactions observed with mirabegron in the three 12-week phase 3 double blind, placebo controlled studies. The frequency of adverse reactions is defined as follows: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness. Infections and infestations: Common: Urinary tract infection. Uncommon: Vaginal infection, Cystitis. Psychiatric disorders: Not known (cannot be estimated from the available data): Insomnia*. Eye disorders: Rare: Eyelid oedema. Cardiac disorders: Common: Tachycardia. Uncommon: Palpitation, Atrial fibrillation. Vascular disorders: Very rare: Hypertensive crisis*. Gastrointestinal disorders: Common: Nausea*, Constipation*, Diarrhoea*. Uncommon: Dyspepsia, Gastritis. Rare: Lip oedema. Skin and subcutaneous tissue disorders: Uncommon: Urticaria, Rash, Rash macular, Rash popular, Pruritus. Rare: Leukocytoclastic vasculitis, Purpura, Angioedema*. Musculoskeletal and connective tissue disorders: Uncommon: Joint swelling. Reproductive system and breast disorders: Uncommon: Vulvovaginal pruritus. Investigations: Uncommon: Blood pressure increased, GGT increased, AST increased, ALT increased. Renal and urinary disorders: Rare: Urinary retention*. Nervous system disorders: Common: Headache*, Dizziness*. *observed during post-marketing experience. **Full prescribing information is available upon request.**

Astellas Pharma Hong Kong Co., Ltd. Unit 1103-08, 11/F, Tower 1, Grand Century Place, 193 Prince Edward Road West, Mongkok, Kowloon.
Tel: (852) 2377 9801 Fax: (852) 2856 1440

astellas | UROLOGY Commitment in Urology

BET-MAD-05011 8-0001

urinary retention as well as the need of BPH surgery by 51%[4,22,23]. Understandably, the use of 5-ARI would be more effective for larger prostate glands due to a greater mass reduction by the same percentage. A meta-analysis showed that the use of 5-ARI would be more effective in prostate glands larger than 40 mL in size[24]. Common side effects would include loss in libido, erectile dysfunction and ejaculatory dysfunction[25].

For patients presenting with predominantly storage symptoms, we should consider the possibility of underlying bladder dysfunction. Anti-cholinergic medications are commonly used in patients with OAB. Detrusor muscle contraction is controlled by the parasympathetic nervous system. Acetylcholine is the main neurotransmitter which stimulates muscarinic receptors on smooth muscle cells. There are 5 subtypes of muscarinic receptors (M1 to M5), but only the M2 and M3 subtypes are predominantly expressed in the detrusor muscle[26]. Previous studies have shown that anti-cholinergic medications could improve OAB symptoms including urinary frequency, urgency and urge urinary incontinence[27-29]. However, anti-cholinergic medications are associated with side effects including dry eyes, dry mouth and constipation. The use of anti-cholinergic medications may also worsen cognitive function in elderly patients[30,31]. Although anti-cholinergic medications have long been described as a precipitating factor of urinary retention, it is generally safe to give these medications in men with post-void residual urine of <200 mL at baseline[32].

Mirabegron, a beta-3 agonist, is another type of medication which we can consider in patients with OAB symptoms. It primarily acts on beta-adrenoceptors which play an important role in the relaxation of bladder smooth muscle. There are 3 beta-adrenoceptor subtypes in detrusor muscle, but it is the beta-3 adrenoceptor that is responsible for promoting its relaxation and urine storage[33]. Pre-clinical studies have shown beta-3 agonists carry no significant negative effects on voluntary detrusor contraction, therefore limiting the risk of urinary retention[34]. Clinical studies have shown that mirabegron improves OAB symptoms including urinary frequency, urgency and urge urinary incontinence[35,36]. As beta-3 agonists work through a distinct mechanism of action from anti-cholinergic medications, there were no increased risks of anti-cholinergic side effects being observed[35,36]. We should be aware that beta-3 agonists are contraindicated in patients with severe uncontrolled hypertension (systolic blood pressure ≥180mmHg or diastolic blood pressure ≥110mmHg, or both). However, previous studies actually did not demonstrate any increased risks of cardiovascular side effects (including hypertension and cardiac arrhythmia) [35,36]. There was also no increased risk of urinary retention following the use of beta-3 agonists[35,36].

In summary, alpha-1 blockers, 5-ARI, anti-cholinergic medications and beta-3 agonists are the common medications used to treat patients with LUTS. For male patients with BPH and predominantly voiding symptoms representing obstruction, alpha-blockers and 5-ARI can be considered. For patients with predominantly storage symptoms representing OAB (both primary and secondary), anti-cholinergic medications and beta-3 agonists can be considered. Monotherapy or combination therapy (E.g. alpha-1 blocker + 5-ARI, alpha-1 blocker + anti-cholinergic, alpha-1 blocker + beta-3 agonist, anti-cholinergic + beta-3 agonist, etc.) can be considered as soon as they fit in appropriately to the patients' clinical presentations and diagnoses[23,32,37,38]. A schematic diagram on the overview of the management of LUTS in male patients is shown in Fig. 2. Although the clinical pathway is usually straightforward in most cases, we must always be aware of other causes of LUTS to avoid misdiagnosis and suboptimal treatment.

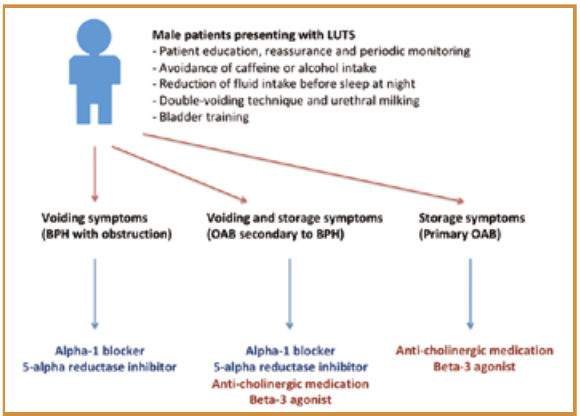


Fig. 2. Overview of the management of LUTS in male patients

Treatment pattern in patients with LUTS

In the old days, we used to think that every type of LUTS could be explained by BPH alone, hence the term 'prostatism'. With more understanding of the underlying pathophysiology, we realise that this is not true, and a more general term, 'lower urinary tract symptoms', is used instead. An observational study was conducted in the United Kingdom to investigate the treatment pattern for men presenting with both storage and voiding symptoms[39]. A total of 8,964 men were included in this study. Although all men presented with both storage and voiding symptoms, the majority of them received alpha-1 blockers (90.3%), and only 24.9% of them received anti-cholinergic medications over a median of 2.1 years. Combination therapy of alpha-1 blockers and anti-cholinergic medications was only given to 14.8% of the patients. Another similar study was conducted to investigate the treatment patterns of 16,998 male patients with OAB, with or without concomitant BPH[40]. Among the 4,806 patients who had both OAB and BPH, 9% received OAB medication, 36% received BPH medication, 8% received both and the rest did not receive either of the treatment. Among the 12,192 patients who had OAB without BPH, 11% received OAB medication, 22% received BPH medication, 6% received both, and 61% did not receive either of the treatment. The above two studies showed that the majority of male patients who had OAB symptoms did not receive any OAB medications. On the other hand, BPH medications such as an alpha-1 blocker is the commonest medication being used to treat patients presenting with LUTS, regardless of their types of symptoms. Such pattern could be explained by two main reasons. First, doctors may not be well aware of the importance of bladder function in LUTS. More

HONG KONG SANATORIUM & HOSPITAL

LI SHU PUI SYMPOSIUM 2018

MANAGEMENT OF URGENT CLINICAL CONDITIONS

Date : Sunday, 9 September 2018
Venue : Ballroom, JW Marriott Hotel Hong Kong

08:50 – 09:00	Welcome		Dr. Walton LI
09:00 – 09:30	**Keynote Lecture 1: Stroke Service at HKSH – Our Progress**		Dr. Patrick LI
Symposium 1	**Medical Emergency Conditions**	Chairperson	Dr. Henry TONG | Dr. Axel HSU
09:30 – 09:45	Acute Retrosternal Pain		Dr. Raymond CHAN
09:45 – 10:00	Wheezing and Shortness of Breath		Dr. LAM Bing
10:00 – 10:15	Acute Renal Failure – Call Nephrologist		Dr. LAI Kar Neng
10:15 – 10:30	Critical Care Physician in ICU, Any Difference?		Dr. Raymond LEE
10:30 – 10:40	Q & A		
10:40 – 11:00	Coffee Break		
Symposium 2	**Emergency Surgical Conditions**	Chairperson	Dr. SIU Wing Tai | Dr. CHAN See Ching
11:00 – 11:15	Acute Abdomen		Dr. Daniel TONG
11:15 – 11:30	Epistaxis, Stridor and Sudden Hearing Loss		Dr. Ambrose HO
11:30 – 11:45	Acute Aortic Emergencies		Dr. LAW Yuk (HKU)
11:45 – 12:00	Common Sports Injuries		Dr. Jimmy WONG
12:00 – 12:10	Q & A		
12:10 – 13:00	**Li Shu Pui Lecture** **Acute Stroke Services and Management Strategies**	Chairperson	Dr. TSOI Tak Hong **Dr. Mark ALBERTS**
13:00 – 14:00	Lunch		
Symposium 3	**Other Emergency Clinical Services**	Chairperson	Dr. Eric MAN | Dr. Natalie LEE
14:00 – 14:15	Critical Conditions in Obstetrics		Dr. CHAN Wan Pang
14:15 – 14:30	Pancytopenia – Management Strategies		Dr. Raymond LIANG
14:30 – 14:45	Neonatal Emergency Conditions		Dr. KO Lee Yuen
14:45 – 15:00	Interventional Radiology and the Critically Ill		Dr. Jimmy YUEN
15:00 – 15:10	Q & A		
15:10 – 15:40	**Keynote Lecture 2 :** **Endocrine Emergencies – Immediate and Follow Up Management**		Dr. LO Kwok Wing
15:40 – 16:00	Coffee Break		
Symposium 4	**GP Forum**	Chairperson	Dr. YAU Wah Hon | Dr. Cynthia SHUM
16:00 – 16:15	Radiophobia – Facts and Fallacies		Dr. Garrett HO
16:15 – 16:30	Sudden Loss of Vision		Dr. Marcus MARCET
16:30 – 16:45	Dental Emergencies		Dr. Walter LI | Dr. Raymond CHOW
16:45 – 17:00	Pain Management: Current Concepts		Dr. LEE Tsun Woon

**Content is subject to change without prior notice*

REGISTRATION IS ON A FIRST COME, FIRST SERVED BASIS

Reserve your place by phone: 2835 8800 or at www.hksh.com/lsp2018

CME Accreditation Pending | CNE 5.5 Points | CPD (Allied Health) Pending

Registration Deadline: Friday, 24 August 2018 or Once the Quota is Full | For Medical Professionals

work is needed for doctors to understand the changing paradigm in the evaluation and treatment of LUTS, and to pay extra attention to the bladder condition. Secondly, doctors may not be comfortable to give OAB medications because of safety and tolerability issues. To address this concern, we shall discuss the safety concerns of giving OAB medications in the following scenarios.

1. Men with OAB symptoms and co-existing bladder outlet obstruction

Anti-cholinergic medications are well known to be a precipitating factor of acute urinary retention. Therefore, a history of acute urinary retention by itself is a contraindication to the use of anti-cholinergic treatment. However, a significant proportion of men develop OAB symptoms secondary to BPH with obstruction. Is it then safe to give anti-cholinergic medications to these men?

A multi-centre study on the use of anti-cholinergic medications for 222 men aged ≥40 years with urodynamically confirmed detrusor overactivity and bladder outlet obstruction was conducted[41]. It was found that the use of anti-cholinergic medications did not affect any urodynamic parameters. The use of anti-cholinergic medications also did not increase the risk of urinary retention. Another randomised controlled trial investigated the use of anti-cholinergic medications plus alpha-1 blockers with LUTS and OAB[32]. Patients with post-void residual volume of >200mL and maximum urinary flow rate of <5mL/second were excluded. The results showed that anti-cholinergic medications did not result in any increased risk of acute urinary retention. Therefore, apart from patients with a history of acute urinary retention, large post-void residual volume and/or slow maximum urinary flow rate, it is considered safe to give anti-cholinergic medications, even in patients with proven bladder outlet obstruction.

The use of beta-3 agonists in men with bladder outlet obstruction has also been investigated[42]. In this study, urodynamic study was performed for every man before and after the use of mirabegron. It was shown that the use of beta-3 agonists, when compared to placebo, did not lead to any worsening of the urinary flow rate nor of the detrusor pressure at maximum urinary flow (an index for bladder outlet obstruction). The overall incidence of adverse events was also comparable between mirabegron and placebo. No increased risk of acute urinary retention was noted after the use of mirabegron. This is in line with other studies which also did not show any increased risk of acute urinary retention following the use of beta-3 agonists[35,36]. It is considered safe to give beta-3 agonists to men with OAB symptoms and concomitant bladder outlet obstruction. A recent study investigated the efficacy of adding beta-3 agonists to alpha-1 blockers in men with BPH and OAB[38]. It was shown that the addition of beta-3 agonists improved the number of micturition per 24 hours, the mean voided volume and the OABSS total score. There were no major safety concerns regarding urinary retention or cardiovascular events.

2. Elderly patients with OAB symptoms

There have been increasing concerns about the anti-cholinergic burden in elderly patients. A number of studies have shown that a high anti-cholinergic burden was associated with cognitive impairment and the risk of dementia in elderly patients[31,43]. Clinical studies investigating the use of anti-cholinergic medications usually focus on younger patients and involve a relatively short period of follow-up. Clinical data regarding the use of anti-cholinergic medications in elderly men, and long-term data on safety and efficacy are limited. Therefore, in elderly patients, we must take note of their anti-cholinergic burden before prescribing any anti-cholinergic medication. Regular evaluation of their symptoms and possible side effects is also advised. On the other hand, since beta-3 agonists work through a mechanism of action distinct from anti-cholinergic medications, beta-3 agonists do not lead to any anti-cholinergic side effect. In patients in whom the anti-cholinergic burden is a concern, beta-3 agonists may serve as an excellent alternative.

3. Patients with pre-existing cardiovascular problems

Anti-cholinergic medications can lead to tachycardia and arrhythmia by blocking the M2 receptors in the heart. However, clinical trials did not demonstrate any increased risk of cardiovascular adverse events following the use of anti-cholinergic medications, although these are mostly rather short-term data. Beta-3 agonists act primarily on beta-3 adrenoceptors. However, previous studies have shown that beta-3 agonists could also work on beta1-adrenoceptors, therefore raising the concern of cardiovascular side effects in patients receiving this medication. We should be aware that beta-3 agonists are contraindicated in patients with severe uncontrolled hypertension. However, in clinical trial settings, no increased risks of cardiovascular side effects (including hypertension and cardiac arrhythmia) were observed[35,36]. Mirabegron appears to be a safe drug for treating OAB symptoms in carefully selected patients, i.e. those without severe uncontrolled hypertension. In a Japanese study, the safety of beta-3 agonists in patients with OAB and a known history of mild to moderate cardiovascular disease (New York Heart Association Class I or II) was investigated. A total of 236 patients were included in the study. The mean heart rate only increased by 1.24 beats per minute after the use of mirabegron. There were no significant electrocardiographic changes. No unexpected cardiovascular safety concerns were observed. Therefore, the use of mirabegron appears to be safe in patients with OAB and co-existing mild to moderate cardiovascular disease.

Management of patients who fail to respond to medical treatment

For patients who have persistent LUTS despite medications, they should be reassessed to see if they carry the correct diagnoses. Special investigations such as cystometrogram may be needed in difficult cases. Some other medications including desmopressin and phosphodiesterase 5 inhibitors have been used to treat patients with LUTS. However, they are not commonly used to treat LUTS alone in the primary care setting

Certificate Course For Nurses And Allied Health Professionals • CME/CNE Course • Course No. C319

Certificate Course on

Respiratory Medicine 2018

Jointly organised by

The Federation of Medical Societies of Hong Kong
香港醫學組織聯會

Hong Kong Thoracic Society
香港胸肺學會

CHEST

Date	Topics	Speakers
6 Sep	Non-invasive Ventilation and Troubleshooting	Dr Kah-lin CHOO Consultant (MED), NDH
13 Sep	Lung Malignancy from the Medical Oncologist's Perspective	Dr Yim-kwan LAM Consultant (M&G), UCH
20 Sep	Updates on the Management of Pulmonary Infections	Dr Man-po LEE Consultant (MED), QEH
27 Sep	Interventional Pulmonology	Dr Jones KWOK AC (M&G), PMH
4 Oct	Diagnostic Investigations & Pharmacotherapy for Chronic Airway Disease	Dr Maureen WONG COS(MG/ICU), CMC
11 Oct	Alternative Therapy for Dyspnoea	Dr David YU SPT(PHYSIO), QEH

Date : 6, 13, 20, 27 September, 2018 & 4, 11, October 2018 (Every Thursday)
Time : 7:00 p.m. – 8:30 p.m.
Venue : Lecture Hall, 4/F., Duke of Windsor Social Service Building, 15 Hennessy Road, Wanchai, Hong Kong
Course Fee : HK$750 (6 sessions)
Enquiry : The Secretariat of The Federation of Medical Societies of Hong Kong
Tel.: 2527 8898 Fax: 2865 0345 Email: info@fmshk.org

Application form can be downloaded from website: http://www.fmshk.org

Certificate Course for doctors, nurses, and health care providers • CME/CNE Course • Course No. C324

Certificate Course on

Disease in Otorhinolaryngology, Head & Neck Surgery (ENT)

Jointly organised by

The Federation of Medical Societies of Hong Kong

Hong Kong Society of Otorhinolaryngology, Head & Neck Surgery

Date	Topics	Speakers
24 Oct	Diagnosis and surgical management of common facial lesions	Dr. FUNG Tai Hang, Thomas Consultant Department of Ear, Nose & Throat Pamela Youde Nethersole Eastern Hospital
31 Oct	Management of obstructive sleep apnea syndrome - a surgeon's perspective	Dr. CHAN Kin Ming Specialist in Otorhinolaryngology Private Practice
7 Nov	Endoscopic management of sinonasal diseases	Dr. LEE Chi Wai Specialist in Otorhinolaryngology Private Practice
14 Nov	Liquid Biopsy – its role in NPC screening	Dr. LAM Wai Kei Clinical lecturer Department of otorhinolaryngology, head and neck surgery The Chinese University of Hong Kong
21 Nov	How to approach a vertigo patient	Dr. WONG Ka Fai Associate Consultant Department of Ear, Nose & Throat Queen Mary Hospital
28 Nov	Minimal invasive surgery in head and neck disease	Dr. CHUNG Chun Kit, Joseph Associate Consultant Department of Ear, Nose & Throat Queen Mary Hospital

Date : 24, 31 October 2018 & 7, 14, 21, 28 November, 2018 (Every Wednesday)
Time : 7:00 pm – 8:30 pm
Venue : Lecture Hall, 4/F., Duke of Windsor Social Service Building,15 Hennessy Road, Wanchai, Hong Kong
Course Fee : HK$750 (6 sessions)
Enquiry : The Secretariat of The Federation of Medical Societies of Hong Kong
Tel.: 2527 8898 Fax: 2865 0345 Email: info@fmshk.org

Application form can be downloaded from website: http://www.fmshk.org

and are therefore not discussed in this paper. Surgical intervention for BPH would be indicated in patients who have LUTS refractory to medications, or those who developed BPH-related complications including urinary retention, obstructive uropathy, recurrent urinary tract infections, recurrent haematuria (after ruling out other salient pathologies) and bladder stone. Referral to a urology specialist's clinic should be considered.

Conclusion

LUTS is a common urological presentation in the primary setting. OAB is common condition which is often neglected in our clinical practice. Classifying the types of LUTS, storage and voiding symptoms in particular, is useful to guide the subsequent management. Monotherapy or combination therapy can be considered, and the choice of treatment should be determined in an individualised approach.

References

1. Kupelian V, Wei JT, O'Leary MP, et al. Prevalence of lower urinary tract symptoms and effect on quality of life in a racially and ethnically diverse random sample: the Boston Area Community Health (BACH) Survey. Arch Intern Med 2006; 166(21):2381-2387.
2. Abrams P, Cardozo L, Fall M, et al. The standardisation of terminology of lower urinary tract function: report from the Standardisation Sub-committee of the International Continence Society. Am J Obstet Gynecol 2002; 187(1):116-126.
3. Sexton CC, Coyne KS, Kopp ZS, et al. The overlap of storage, voiding and postmicturition symptoms and implications for treatment seeking in the USA, UK and Sweden: EpiLUTS. BJU Int 2009; 103 Suppl 3:12-23.
4. Gratzke C, Bachmann A, Descazeaud A, et al. EAU Guidelines on the Assessment of Non-neurogenic Male Lower Urinary Tract Symptoms including Benign Prostatic Obstruction. Eur Urol 2015; 67(6):1099-1109.
5. Holtgrewe HL. Current trends in management of men with lower urinary tract symptoms and benign prostatic hyperplasia. Urology 1998; 51(4A Suppl):1-7.
6. Abrams P. New words for old: lower urinary tract symptoms for "prostatism". BMJ 1994; 308(6934):929-930.
7. Knutson T, Edlund C, Fall M, Dahlstrand C. BPH with coexisting overactive bladder dysfunction--an everyday urological dilemma. Neurourol Urodyn 2001; 20(3):237-247.
8. Sibley GN. The physiological response of the detrusor muscle to experimental bladder outflow obstruction in the pig. Br J Urol 1987; 60(4):332-336.
9. Fitzgerald MP, Stablein U, Brubaker L. Urinary habits among asymptomatic women. Am J Obstet Gynecol 2002; 187(5):1384-1388.
10. Latini JM, Mueller E, Lux MM, Fitzgerald MP, Kreder KJ. Voiding frequency in a sample of asymptomatic American men. J Urol 2004; 172(3):980-984.
11. Abrams PH, Farrar DJ, Turner-Warwick RT, Whiteside CG, Feneley RC. The results of prostatectomy: a symptomatic and urodynamic analysis of 152 patients. J Urol 1979; 121(5):640-642.
12. Seaman EK, Jacobs BZ, Blaivas JG, Kaplan SA. Persistence or recurrence of symptoms after transurethral resection of the prostate: a urodynamic assessment. J Urol 1994; 152(3):935-937.
13. Hyman MJ, Groutz A, Blaivas JG. Detrusor instability in men: correlation of lower urinary tract symptoms with urodynamic findings. J Urol 2001; 166(2):550-552; discussion 553.
14. Brown CT, Yap T, Cromwell DA, et al. Self management for men with lower urinary tract symptoms: randomised controlled trial. BMJ 2007; 334(7583):25.
15. Yap TL, Brown C, Cromwell DA, van der Meulen J, Emberton M. The impact of self-management of lower urinary tract symptoms on frequency-volume chart measures. BJU Int 2009; 104(8):1104-1108.
16. Michel MC, Vrydag W. Alpha1-, alpha2- and beta-adrenoceptors in the urinary bladder, urethra and prostate. Br J Pharmacol 2006; 147 Suppl 2:S88-119.
17. Djavan B, Marberger M. A meta-analysis on the efficacy and tolerability of alpha1-adrenoceptor antagonists in patients with lower urinary tract symptoms suggestive of benign prostatic obstruction. Eur Urol 1999; 36(1):1-13.
18. Nickel JC, Sander S, Moon TD. A meta-analysis of the vascular-related safety profile and efficacy of alpha-adrenergic blockers for symptoms related to benign prostatic hyperplasia. Int J Clin Pract 2008; 62(10):1547-1559.
19. Andriole G, Bruchovsky N, Chung LW, et al. Dihydrotestosterone and the prostate: the scientific rationale for 5alpha-reductase inhibitors in the treatment of benign prostatic hyperplasia. J Urol 2004; 172(4 Pt 1):1399-1403.
20. Wright AS, Thomas LN, Douglas RC, Lazier CB, Rittmaster RS. Relative potency of testosterone and dihydrotestosterone in preventing atrophy and apoptosis in the prostate of the castrated rat. J Clin Invest 1996; 98(11):2558-2563.
21. Deslypere JP, Young M, Wilson JD, McPhaul MJ. Testosterone and 5 alpha-dihydrotestosterone interact differently with the androgen receptor to enhance transcription of the MMTV-CAT reporter gene. Mol Cell Endocrinol 1992; 88(1-3):15-22.
22. McConnell JD, Roehrborn CG, Bautista OM, et al. The long-term effect of doxazosin, finasteride, and combination therapy on the clinical progression of benign prostatic hyperplasia. N Engl J Med 2003; 349(25):2387-2398.
23. Roehrborn CG, Siami P, Barkin J, et al. The effects of combination therapy with dutasteride and tamsulosin on clinical outcomes in men with symptomatic benign prostatic hyperplasia: 4-year results from the CombAT study. Eur Urol 2010; 57(1):123-131.
24. Boyle P, Gould AL, Roehrborn CG. Prostate volume predicts outcome of treatment of benign prostatic hyperplasia with finasteride: meta-analysis of randomized clinical trials. Urology 1996; 48(3):398-405.
25. Naslund MJ, Miner M. A review of the clinical efficacy and safety of 5alpha-reductase inhibitors for the enlarged prostate. Clin Ther 2007; 29(1):17-25.
26. Yamanishi T, Chapple CR, Chess-Williams R. Which muscarinic receptor is important in the bladder? World J Urol 2001; 19(5):299-306.
27. Herschorn S, Jones JS, Oelke M, MacDiarmid S, Wang JT, Guan Z. Efficacy and tolerability of fesoterodine in men with overactive bladder: a pooled analysis of 2 phase III studies. Urology 2010; 75(5):1149-1155.
28. Roehrborn CG, Abrams P, Rovner ES, Kaplan SA, Herschorn S, Guan Z. Efficacy and tolerability of tolterodine extended-release in men with overactive bladder and urgency urinary incontinence. BJU Int 2006; 97(5):1003-1006.
29. Reynolds WS, McPheeters M, Blume J, et al. Comparative Effectiveness of Anticholinergic Therapy for Overactive Bladder in Women: A Systematic Review and Meta-analysis. Obstet Gynecol 2015; 125(6):1423-1432.
30. Lechevallier-Michel N, Molimard M, Dartigues JF, Fabrigoule C, Fourrier-Reglat A. Drugs with anticholinergic properties and cognitive performance in the elderly: results from the PAQUID Study. Br J Clin Pharmacol 2005; 59(2):143-151.
31. Pfistermeister B, Tumena T, Gassmann KG, Maas R, Fromm MF. Anticholinergic burden and cognitive function in a large German cohort of hospitalized geriatric patients. PLoS One 2017; 12(2):e0171353.
32. Kaplan SA, Roehrborn CG, Rovner ES, Carlsson M, Bavendam T, Guan Z. Tolterodine and tamsulosin for treatment of men with lower urinary tract symptoms and overactive bladder: a randomized controlled trial. JAMA 2006; 296(19):2319-2328.
33. Yamaguchi O. Beta3-adrenoceptors in human detrusor muscle. Urology 2002; 59(5 Suppl 1):25-29.
34. Michel MC, Ochodnicky P, Homma Y, Igawa Y. beta-adrenoceptor agonist effects in experimental models of bladder dysfunction. Pharmacol Ther 2011; 131(1):40-49.
35. Nitti VW, Khullar V, van Kerrebroeck P, et al. Mirabegron for the treatment of overactive bladder: a prespecified pooled efficacy analysis and pooled safety analysis of three randomised, double-blind, placebo-controlled, phase III studies. Int J Clin Pract 2013; 67(7):619-632.
36. Chapple CR, Kaplan SA, Mitcheson D, et al. Randomized double-blind, active-controlled phase 3 study to assess 12-month safety and efficacy of mirabegron, a beta(3)-adrenoceptor agonist, in overactive bladder. Eur Urol 2013; 63(2):296-305.
37. Herschorn S, Chapple CR, Abrams P, et al. Efficacy and safety of combinations of mirabegron and solifenacin compared with monotherapy and placebo in patients with overactive bladder (SYNERGY study). BJU Int 2017; 120(4):562-575.
38. Kakizaki H, Lee K-S, Yamamoto O, et al. LBA13 EFFICACY AND SAFETY OF ADD-ON MIRABEGRON VS. PLACEBO TO TAMSULOSIN IN MEN WITH OVERACTIVE BLADDER SYMPTOMS (MATCH STUDY). The Journal of Urology 2018; 199(4, Supplement):e988.
39. Hakimi Z, Johnson M, Nazir J, Blak B, Odeyemi IA. Drug treatment patterns for the management of men with lower urinary tract symptoms associated with benign prostatic hyperplasia who have both storage and voiding symptoms: a study using the health improvement network UK primary care data. Curr Med Res Opin 2015; 31(1):43-50.
40. Jumadilova Z, Harris H, Aguila M, Wagner S, Boccuzzi S, Bavendam T. Agent selection for overactive bladder patients with and without documented comorbid benign prostatic hyperplasia (Read By Title). Presented at: International Continence Society; Aug 28–Sept 2, 2005; Montreal, Canada.
41. Abrams P, Kaplan S, Millard R. Tolterodine treatment is safe in men with bladder outlet obstruction (BOO) and symptomatic detrusor overactivity (DO). 2001; 20(4):547-548.
42. Nitti VW, Rosenberg S, Mitcheson DH, He W, Fakhoury A, Martin NE. Urodynamics and safety of the beta(3)-adrenoceptor agonist mirabegron in males with lower urinary tract symptoms and bladder outlet obstruction. J Urol 2013; 190(4):1320-1327.
43. Naharci MI, Cintosun U, Ozturk A, et al. Effect of anticholinergic burden on the development of dementia in older adults with subjective cognitive decline. Psychiatry and Clinical Psychopharmacology 2017; 27(3):269-276.

Certificate Course for Medical and Healthcare Professionals

● Course No. C320 ● CME/CNE Course

Certificate Course on

Renal Medicine 2018

Jointly organised by

The Federation of Medical Societies of Hong Kong

Hong Kong Society of Nephrology

Objectives:

To update the participants on new advances in renal medicine and clinical practice of common renal problems, and to help the participants to interpret results of common renal investigations.

Date	Topics	Speakers
5 Sep	Common Investigation Tests for Renal Disease Including Approach to Proteinuria & Haematuria	Dr Sze-kit YUEN Associate Consultant Department of Medicine & Geriatrics Caritas Medical Centre
	Update & Management of Glomerular Disease	Dr Elaine Tsz-ling HO Associate Consultant Department of Medicine Tsueng Kwan O Hospital
12 Sep	Update & Management of Acute Kidney Injury	Dr Chun-hay TAM Associate Consultant Department of Medicine & Geriatrics United Christian Hospital
	Nutritional Management in Kidney Diseases	Ms Cherry LAW Dietitian Pamela Youde Nethersole Eastern Hospital
19 Sep	Update & Management of Hypertension	Dr Wai-yan LAU Associate Consultant Department of Medicine Alice Ho Miu Ling Nethersole Hospital
	Drug Prescribing in Renal Failure	Dr Anthony Kai-ching HAU Associate Consultant Department of Medicine & Geriatrics Tuen Mun Hospital
26 Sep	Kidney Involvement in Multi-System Disorders	Dr Desmond Yat-hin YAP Clinical Assistant Professor Department of Medicine, Queen Mary Hospital Hong Kong University
	ABC of Hemodialysis Therapy	Dr Gensy Mei-wah TONG Consultant in Nephrology Renal Centre Hong Kong Baptist Hospital
3 Oct	ABC of Peritoneal Dialysis Therapy	Dr Joseph Ho-sing WONG Associate Consultant Department of Medicine Queen Elizabeth Hospital
	Update on Diabetic Nephropathy	Dr Maggie Ma Associate Consultant Department of Medicine Queen Mary Hospital
10 Oct	Update & Management of Chronic Kidney Disease	Dr Wing-fai PANG Associate Consultant Department of Medicine & Therapeutics Prince of Wales Hospital
	ABC of Renal Transplantation	Dr Ka-fai YIM Associate Consultant Department of Medicine & Geriatrics Princess Margaret Hospital

Dates : 5, 12, 19, 26 September 2018 & 3, 10 October, 2018 (Every Wednesday)
Time : 7:00 pm – 8:30 pm
Venue : Lecture Hall, 4/F., Duke of Windsor Social Service Building, 15 Hennessy Road, Wanchai, Hong Kong
Language Media : Cantonese (Supplemented with English)
Course Fee : HK$750 (6 sessions)
Certificate : Awarded to participants with a minimum attendance of 70%
Enquiry : The Secretariat of The Federation of Medical Societies of Hong Kong
Tel: 2527 8898 Fax: 2865 0345 Email: info@fmshk.org

CME / CNE Accreditation in application
Application form can be downloaded from website: http://www.fmshk.org

MCHK CME Programme Self-assessment Questions

Please read the article entitled "Managing Lower Urinary Tract Symptoms with Special Attention to Overactive Bladder in the Primary Care Setting" by Dr Jeremy Yuen-chun TEOH 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 August 2018 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. Terminal dribbling is one of the storage symptoms.
2. The severity of both storage and voiding symptoms increases with age.
3. Anti-cholinergic medications are effective for treating BPH patients with predominantly voiding symptoms.
4. 5-ARI is effective in treating BPH irrespective of its size.
5. Detrusor muscle contraction is controlled by the parasympathetic nervous system.
6. Beta-3 agonists are contraindicated in patients with severe uncontrolled hypertension.
7. Use of mirabegron may increase the risk of urinary retention.
8. Anti-cholinergic drugs can be used in combination with beta-3 agonists.
9. A history of acute urinary retention is a contraindication to the use of anti-cholinergic medications.
10. It is safe to give beta-3 agonists to men with OAB symptoms and concomitant bladder outlet obstruction.

ANSWER SHEET FOR AUGUST 2018

Please return the completed answer sheet to the Federation Secretariat on or before 31 August 2018 for documentation. 1 CME point will be awarded for answering the MCHK CME programme (for non-specialists) self-assessment questions.

Managing Lower Urinary Tract Symptoms with Special Attention to Overactive Bladder in the Primary Care Setting

Dr Jeremy Yuen-chun TEOH

MBBS (HK), FRCSEd (Urol), FCSHK, FHKAM (Surgery)

Assistant Professor
SH HO Urology Centre, Department of Surgery, Prince of Wales Hospital,
The Chinese University of Hong Kong

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.: _____ (for reference only)

Answers to July 2018 Issue

Prevention and Treatment of Sarcopenia

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

Laser Application in Urology

Dr Ka-lun CHUI

FRCSEd(UROL), FHKAM(Surgery)

Specialist in Urology

Dr Ka-lun CHUI

Introduction

Laser, a name coming from the first letters of the words in a phrase "Light Amplification by Stimulated Emission of Radiation", is a tool that emits monochromatic light.

From a medical perspective, the most important phenomenon is the absorption of the laser light by chromophores, on which the light energy is converted into thermal energy. The light in tissues is absorbed by haemoglobin, water or melanin. Depending on the temperature the tissue is heated, undergoes coagulation or vaporisation. In the case of a low tissue absorption coefficient, the laser beam penetrates deeper, whereas a high absorption coefficient results in shallow penetration. The effect, however, is not only medium-dependent. The wavelength of the laser also plays an important role. For lasers emitting shorter wavelengths, a greater amount of energy is converted into heat.[1]

Laser lithotripsy generally involves two basic mechanisms, photo-mechanical and photo-thermal.

An example of photo-mechanical mechanism is formation of cavitation bubbles, which occurs when pulsed types of lasers are used. A cavitation bubble is caused by rapid expansion of water vapour at the laser fibre tip. The bubble then rapidly collapses releasing very strong pressure waves which cause stone fragmentation.[2]

Types of lasers

Ho:YAG laser is a pulsed type of laser that emits energy absorbed by water. It is characterised by a wavelength of 2,140 nm and a pulse duration of 350 ms. The depth of penetration in the prostate tissue is only 0.4 mm. Therefore the depth of necrosis and thermal damages are limited. Ho-laser causes rapid coagulation of small and medium-sized vessels to the depth of about 2 mm.

KTP: YAG laser, also called green light laser, is derived from Nd: YAG laser. Passing the invisible Nd:YAG beam via a KTP crystal, doubles the frequency and halves the wavelength from 1,064 nm to 532 nm. Its energy is selectively absorbed by haemoglobin, but not by water. The penetration depth is about 0.8 mm. The KTP: YAG laser is characterised by a very good coagulation effect, which results in good control of haemostasis. As the energy of KTP laser is absorbed only by haemoglobin, it is possible to perform the operation in noncontact use called photoselective vaporisation of tissue. Due to the shallow absorption rate, necrosis of the tissues localised beneath the vaporised area is limited. An additional advantage is an almost bloodless course of the procedure.

The Tm: YAG laser produces continuous, 2,000 nm waves. As in Ho-laser, energy is absorbed only by water and a slightly shorter wavelength of thulium laser decreases the depth of penetration to 0.25 mm. The Tm-laser is used for transurethral vaporisation, enucleation or resection of the prostate.

Laser applications in treatment of patients with bladder outlet obstruction

Holmium laser is used in patients with narrowing of the bladder neck/benign prostatic hypertrophy. Possible procedures include ablation (HoLAP), enucleation (HoLEP) and resection (HoLRP) of the prostate. Lasers with power of 60W, 80W and 100W are currently in use. A recent study comparing HoLEP with transurethral resection of the prostate (TURP) showed slightly better postoperative results at 12-month follow-up in the HoLEP group, as well as significantly better perioperative results and similarly low complication rates[3].

The need for re-operation after TURP and adenomectomy during 8 years of follow-up observation (re-TURP, bladder neck incision, urethrotomy) is 14.7 and 9.8% respectively[4]. Perioperative complications after laser prostate treatments occur in approximately 20% of patients; however, 80% of these complications are considered low-grade (Clavien grade I-II)[5]. In addition, laser treatments are performed in 0.9% NaCl environment; hence the transurethral resection syndrome, which occurs in 1.4% of patients after TURP, does not occur after laser techniques[4, 6].

Laser applications in treatment of patients with urolithiasis

Modern laser techniques are an indispensable tool for treating patients with urolithiasis[7]. The advancement of the new generation ureteroscopes and the increasing power of the lasers allow lithotripsy of larger concrements to be shorter. Over 90% of lithotripsy procedures are successful[8]. The effectiveness and safety of laser lithotripsy has been proven in multiple studies regarding symptomatic ureteral stones in every location,

treatment of pregnant women, overweight/obese patients and children of all ages[9–11].

It was shown in the literature that the Ho:YAG laser is a suitable tool to disintegrate ureteral calculi irrespective of its location[12]. This type of laser is also an adequate tool for laser lithotripsy of ureteral post-SWL (shock wave lithotripsy) steinstrasse. In some patients with multiple intrarenal calculi, ureteroscopy with Ho:YAG laser lithotripsy can be an alternative to ESWL (please spell out the term in full if not mentioned earlier) or PNL (please spell out in full if not mentioned earlier), with acceptable efficacy and low morbidity[7]. It has been proven that both laser lithotripsy and pneumatic lithotripsy are equally safe and efficient for stone fragmentation. Thus laser lithotripsy is associated with a lower stone migration rate and easier retrieval of stone fragments[3]. It is also shown that laser lithotripsy is a superior method in cost-effectiveness analysis compared to SWL for renal stones <1.5 cm[13].

Conclusions

Laser techniques are versatile tools in urology. Particularly significant is their use in patients with diseases of the prostate. Promising therapeutic effects of laser procedures tend to demonstrate their usage in treatment of patients with other diseases.

References

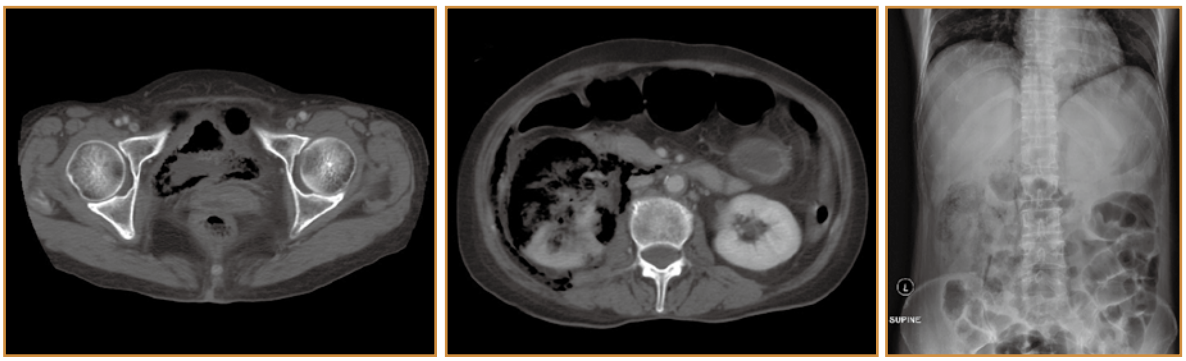
1. Gravas S, Bachmann A, Reich O, Roehrborn CG, Gilling PJ, De La Rosette J. Critical review of lasers in benign prostatic hyperplasia (BPH) BJU Int. 2011;107:1030–1043.
2. Ganesamoni R, Sabnis RB, Mishra S, et al. Prospective randomized controlled trial comparing laser lithotripsy with pneumatic lithotripsy in miniperc for renal calculi. J Endourol. 2013;27:1444–1449.
3. Yin L, Teng J, Huang CJ, Zhang X, Xu D. Holmium laser enucleation of the prostate versus transurethral resection of the prostate: a systematic review and meta-analysis of randomized controlled trials. J Endourol. 2013;27:604–611.
4. Madersbacher S, Lackner J, Brossner C, et al. Reoperation, myocardial infarction and mortality after transurethral and open prostatectomy: a nation-wide, long-term analysis of 23,123 cases. Eur Urol. 2005;47:499–504.
5. Elshal AM, Elmansy HM, Elhilali MM. Transurethral laser surgery for benign prostate hyperplasia in octogenarians: safety and outcomes. Urology. 2013;81:634–639.
6. Reich O, Gratzke C, Bachmann A, et al. Morbidity, mortality and early outcome of transurethral resection of the prostate: a prospective multicenter evaluation of 10,654 patients. J Urol. 2008;180:246–249.
7. Zarrabi A, Gross AJ. The evolution of lasers in urology. Ther Adv Urol. 2011;3:81–89.
8. Kuntz RM. Current role of lasers in the treatment of benign prostatic hyperplasia (BPH) Eur Urol. 2006;49:961–969.
9. Wosnitzer MS, Rutman MP. KTP/LBO laser vaporization of the prostate. Urol Clin North Am. 2009;36:471–483.
10. Heinrich E, Wendt-Nordahl G, Honeck P, et al. 120 W lithium triborate laser for photoselective vaporization of the prostate: comparison with 80 W potassium-titanyl-phosphate laser in an ex-vivo model. J Endourol. 2010;24:75–79.
11. Chiang PH, Chen CH, Kang CH, Chuang YC. GreenLight HPS laser 120-W versus diode laser 200-W vaporization of the prostate: comparative clinical experience. Lasers Surg Med. 2010;42:624–629.
12. de Lucia C, Femminella GD, Rengo G, et al. Risk of acute myocardial infarction after transurethral resection of prostate in elderly. BMC Surg. 2013;13(Suppl 2):S35.
13. Capitan C, Blazquez C, Martin MD, Hernandez V, de la Pena E, Llorente C. GreenLight HPS 120-W laser vaporization versus transurethral resection of the prostate for the treatment of lower urinary tract symptoms due to benign prostatic hyperplasia: a randomized clinical trial with 2-year follow-up. Eur Urol. 2011;60:734–739.

Radiology Quiz

Dr Victor Siang-hua CHAN

FRCR

Department of Radiology, Queen Mary Hospital



Questions

1. What are the imaging findings in this newly diagnosed diabetic patient presenting with acute abdominal pain and fever?
2. What is the diagnosis?
3. What is the classification of this disease entity and the potential underlying causes?
4. What is the treatment?

(See P.36 for answers)

VASCOG 2018

4 DAYS
Cutting-Edge Science

40+ SPEAKERS
Top Scientists and Clinicians from Around the Globe

7 PLENARIES
Presenting the Latest Advances

The 9th International Conference of
The International Society of Vascular Behavioural and Cognitive Disorders

NOVEMBER 14 -17 | HONG KONG SCIENCE PARK

ORGANIZING COMMITTEES:

Vincent Mok
Hong Kong
Chair, Local Organizing Committee

Adrian Wong
Hong Kong
Chair, Scientific Committee

PLENARY SPEAKERS

Suvarna Alladi
India

David Attwell
United Kingdom

Rhoda Au
USA

Miia Kivipelto
Sweden

Julie Schneider
USA

Ingmar Skoog
Sweden

Eric Smith
Canada

PLENARIES & SYMPOSIA

15 - 17 NOVEMBER, THU - SAT

- Potential Mechanisms in VCI
- Vascular-Alzheimer's Spectrum in Multiple Etiologies Dementias
- Neuroimaging and Other Biomarkers in VCI
- Technology in Detection, Assessment and Treatment of VCI
- Prevention and Treatment for VCI
- Vascular Factors and Non-Cognitive Symptoms

PRE-CONFERENCE TEACHING SESSIONS

14 NOVEMBER, WED

- Neuroimaging in VCI
- Clinical Management of VCI: Pharmacological and Lifestyle Approaches
- Neuropsychology
- Basic Neurosciences

FREE Registration for Main Congress Delegates and Current Students

VIBRANT DEBATES

15 - 16 NOVEMBER, THU - FRI

- Should silent stroke and high WMH burden be treated the same as symptomatic stroke?
- "Vessels OR tangles?" Do we really need diagnostic criteria for vascular and Alzheimer's dementias?

LATE-BREAKING CLINICAL TRIALS

16 NOVEMBER, FRI

REGISTER NOW | EARLY REGISTRATION DEADLINE: 10 SEPTEMBER

http://www.mect.cuhk.edu.hk/vascog2018/
vascog2018@cuhk.edu.hk
facebook.com/vascog2018 @vascog2018 @vascog2018

ORGANIZERS

VAS-COG

Division of Neurology
Department of Medicine and Therapeutics
Faculty of Medicine
The Chinese University of Hong Kong

SUPPORTING ORGANIZATIONS

The Hong Kong Geriatrics Society 香港老人科醫學會

The Emerging Role of Immunotherapy in Advanced Urothelial Carcinoma

Dr Darren MC POON

Consultant, Department of Clinical Oncology, Prince of Wales Hospital.

Dr Darren MC POON

Introduction

There were no breakthrough developments in the treatment of metastatic urothelial cancer (UC) for a decade since the establishment of platinum-based chemotherapy as the standard treatment in the early 90s[1]. However, the median survival with cisplatin-based chemotherapy was only 12 to 15 months. Moreover, cisplatin-ineligibility is not uncommon in real-world clinical settings, as defined by renal dysfunction, poor performance status (ECOG 2 or above) or the presence of comorbidities (cardiac dysfunction, neuropathy and hearing loss)[2]. Cisplatin-ineligible patients exhibit a dismal median survival of 8 to 9 months with carboplatin-based combination chemotherapy[3]. Second or later line treatments with taxanes and vinflunine yield disappointing median survivals of 6 to 8 months[4-6]. The emergence of immunotherapy, in particular the immune checkpoint inhibitors (CPI), opens a new chapter of the management of advanced urothelial carcinoma with more durable response and favourable toxicity[7]. In this review, the latest advancement of immunotherapy in locally advanced and metastatic urothelial carcinoma will be discussed.

Immunobiology of urothelial carcinoma

In fact, Bacillus Calmette-Guerin (BCG) is one of the most successful immunotherapies in cancer treatment and remains the gold standard in the treatment of high-risk non-muscle-invasive bladder cancer, with initial response rates of approximately 70%[8]. BCG helps to establish urothelial carcinoma as immunogenic, and CD4 T cells, CD8 cytotoxic T cells, and natural killer cells have been shown to drive antitumour activity in response to BCG[9]. The long-existing success of BCG in urothelial carcinoma provides a strong foundation of exploring new immunotherapeutic approaches. Furthermore, the high prevalence of tumour somatic mutations in advanced urothelial carcinoma, which may generate neoantigens recognised by activated antitumour T cells, provides a rationale for assessing immune checkpoint inhibitors in this disease[10,11].

Mechanism of immune checkpoint inhibitors

The checkpoint molecules inhibit T-cell mediated damage of healthy tissues. However, inhibitory signals from checkpoint molecules may allow cancer cells to evade immune surveillance[12,13]. PD-1 is expressed on T-cells and PD-L1 is expressed on immune and cancer cells. The interaction between PD-1 and PD-L1 inhibits distal T-cell functions within the tumour microenvironment and leads to exhaustion of competent cytotoxic T-cells. By targeting either PD-1 or PD-L1 this inhibitory signal can be overcome allowing for a more effective immune response to cancer[14]. Similarly, cytotoxic T-lymphocyte antigen (CTLA-4) is expressed on T-regulatory cells (Tregs), which inhibit cytotoxic T-cells mostly at the time of early T-cell priming within lymph nodes. In addition to PD-1/PD-L1 and CTLA-4, which are targeted by currently commercially available agents, an expanding list of other co-activating and co-inhibiting T-cell checkpoint molecules have been discovered. Some of the co-activating molecules include OX-40, GITR, CD137, and ICOS, whereas co-inhibiting molecules includeTIM-3, LAG-3, CD73, ITK, and TIGIT. Other non-immune cell specific or metabolic pathways may have immunomodulating properties, for example, IDO-1, CSF-1R, adenosine-R, and TGF-β.

Second or later lines of immune checkpoint inhibitors

Atezolizumab (MPDL3280A) is an engineered, humanised monoclonal IgG1 antibody, with a high affinity for PD-L1 acting as an inhibitor of the interaction between PD-L1 and PD-1/B7.1. It was the first immune agent which was approved by FDA for the treatment of patients with locally advanced or metastatic UC which have progressed during or following platinum-based chemotherapy or whose disease has worsened within 12 months of neoadjuvant or adjuvant platinum-based chemotherapy. The approval was based on the phase II trial (IMvigor 210 trial, NCT02108652) involving two different cohorts (cohort 1, patients with metastatic urothelial cancers ineligible for platinum-based chemotherapy for first line treatment; cohort 2, patients who progressed during or following platinum-based treatment). In this phase II trial, cohort 2 patients (n = 310) who received Atezolizumab showed an objective response rate (ORR) of 15% and a 12-month overall survival (OS) of 37% in the overall population with a median duration of response not reached after a medium of 17.5 months of follow-up[15]. A subsequent phase III study (IMvigor 211), comparing Atezolizumab with chemotherapy (docetaxel, paclitaxel and vinflunine) in patient progressed to platinum-based therapy, failed to confirm phase II findings, and did not meet its primary endpoint of OS. The statistical design and potential interaction between IC PD-L1 expression

and activity of chemotherapy may have influenced the results observed in this trial[16].

KEYNOTE-045 was the only positive phase III study so far to show superior OS and ORR with immune checkpoint inhibitors to chemotherapy. This study compared pembrolizumab, a monoclonal IgG4k anti-PD-1 antibody, with investigator choice of chemotherapy (paclitaxel, docetaxel, or vinflunine) in 542 patients with metastatic or advanced urothelial carcinoma that recurred or progressed after platinum-based chemotherapy, showed an ORR for pembrolizumab of 21% compared to 11% for chemotherapy. The OS, regardless of PD-L1 expression, was superior with pembrolizumab compared to chemotherapy (10.3 vs. 7.4months), and there was a 30% reduction in the risk of death. Pembrolizumab was tolerated better than chemotherapy; 61% of patients in the pembrolizumab arm compared to 90% of patients in the chemotherapy arm experienced treatment-related adverse events (TRAEs) of any grade, including those of grade 3 or higher (17% and 50% for pembrolizumab and chemotherapy, respectively)[16]. Results from KEYNOTE-045 led to full FDA approval for treatment of this patient population with metastatic urothelial carcinoma.

Together with the other CPIs, including Avelumab, Durvulamab, and Nivolumab, there are currently five FDA-approved agents that are indicated for patients with metastatic urothelial carcinoma who had prior platinum-based chemotherapy[17-19] (Table 1). There are no head to head studies among the 5 agents and the selection would probably depend on the availability, familiarity and convenience (q2 vs q3weeks) of these CPIs.

Table 1. Subsequent systemic treatment for patients with locally advanced or metastatic urothelial carcinoma who had prior platinum

Standard regimen options	Alternative options
Pembrolizumab	Paclitaxel
Atezoluzumab	Docetaxel
Nivolumab	Gemcitabine
Avelumab	Pemetrexed
Durvalumab	Ifosafamide
	Methotrexate
	Docetaxel and Ramucirumab

First line immune checkpoint inhibitors

In real-world settings, patients with metastatic urothelial carcinoma who are cisplatin-ineligible as a result of poor renal function (CrCl <60), poor performance status (ECOG >1), or other comorbidities, are not uncommonly encountered[20,21]. Cisplatin in combination with gemcitabine, the current standard of care, would be substituted by carboplatin in these patients. However, the survival outcome was shown to be inferior with carboplatin-based to cisplatin-based treatments[22]. In cohort 1 of the IMVigor 210 phase II study, the efficacy and safety of Atezolizumab in post-platinum cisplatin-ineligible patients was examined[23]. In this cohort (n=119), the response rate was 23% for the entire population. The median progression-free survival (PFS) and OS was 2.7 months and 15.9 months for the entire population. Despite the response rate and PFS are comparatively inferior to the prior carboplatin-based results (Atezo vs carbo, RR, 36% vs 24%), the OS with Atezolizumab compares favourably to the historical data with the carboplatin regimen (Atezo vs carbo, 1 year OS, 57% vs 37%)[3]. Those patients with Atezolizumab who had responses were durable in this study and this could probably explain the result of the modest ORR and PFS but favourable OS with Atezolizumab. Grade 3 to 4 treatment-related AEs occurred in 16% of patients and immune-related AEs occurred in 12%, whereas AEs leading to treatment discontinuation occurred in 8%. Following the release of such result, the FDA extended the accelerated approval for atezolizumab on April 17, 2017 to include treatment-naïve, cisplatin-ineligible patients with metastatic or locally advanced urothelial carcinoma.

KEYNOTE-052, a single-arm, phase II trial evaluated pembrolizumab in treatment-naïve, cisplatin-ineligible patients with locally advanced or metastatic urothelial carcinoma[24]. Similar to the IMVigor 210 phase II study, the ORR (23%) and median PFS (2.7 months) were numerically less to carboplatin-based chemotherapy while the median OS (15.9 months) with Pembrolizumab is similar to Atezolizumab. Grade ≥3 AEs occurred in 18% of patients. Supported by results of the KEYNOTE-052 clinical trial, the FDA granted approval to pembrolizumab at 200mg IV every 3 weeks in post-chemotherapy and cisplatin-ineligible first line therapy patients with locally advanced or metastatic UC on May 18, 2017 (Table 2).

Table 2. First line treatment for patients with locally advanced or metastatic urothelial carcinoma

Treatment options: Cisplatin-eligible	Treatment options: Cisplatin-ineligible
Gemcitabline and cisplatin	Atezoluzumab
Dose-dense M-VAC with GCSF support*	Pembrolizumab
	Gemcitabine and carboplatin

*M-VAC, methotrexate, vinblastine, doxorubicin, cisplatin; GCSF, granulocyte colony stimulating factor

The role of CPIs as first line treatment in patients who are eligible to cisplatin remains uncertain. Multiple first line randomised clinical trials are evaluating novel combinations of PD-1/PD-L1 inhibitors with CTLA-4 inhibitors or PD-1/PD-L1 inhibitors with platinum-based combination chemotherapy. Importantly, these trials allow both cisplatin-eligible and cisplatin-ineligible patients to participate (cisplatin-ineligible patients receive carboplatin-based chemotherapy). However, until the results of these studies are available, cisplatin-based chemotherapy remains the standard treatment for cisplatin-eligible advanced UC patients.

Biomarkers for immune checkpoint inhibitors

The PD-L1 expression is a potential biomarker for CPIs as there are data suggesting that the clinical outcome with CPIs are associated with the level of PD-L1 expression. However, the use of PD-L1 as a biomarker in urothelial carcinoma is sophisticated as a consequence of several factors, including heterogeneity of PD-L1 expression level within tumours, variability in tissue collection requirements across trials (fresh or archival samples), differences among antibody clones used for immunohistochemistry (IHC), definitions of PD-L1

positivity based on protocol-specific staining cutoffs, and use of non-standardised test designs[25]. These issues may explain why some trials have suggested a relationship between PD-L1 status and response, whereas others have not. While a variety of PD-L1 IHC assays are now approved as complementary tests, none of the approved CPIs require PD-L1 expression for use in UC; that is, the assay is not a companion diagnostic test. In addition to PD-L1 expression, other biomarkers are currently being explored, including mutational burden, molecular subtype according to The Cancer Genome Atlas (TCGA), expanded immune gene expression signatures[26-28]. Despite early data suggesting these biomarkers are associated with the clinical outcome with CPIs, until further being validated in prospective study, they remain investigational.

Conclusion

The emergence of immune checkpoint inhibitors in advanced urothelial carcinoma is a long-awaiting breakthrough in this field for more than decades. The CPIs are now the contemporary standard treatment in patients who had prior platinum as supported by various phase II and III studies. In cisplatin-ineligible patients, CPIs reasonable alternative options to carboplatin-based chemotherapy while cisplatin-based chemotherapy remains the standard of care in those who are fit for cisplatin. Despite the enthusiasm about CPIs, we should address the fact that the majority have no response to CPIs. Hence, predictive biomarkers are needed to select appropriate patients for CPIs. Ongoing studies are undertaken to evaluate the combination treatment with CPIs as well as the potential promising biomarkers for CPIs.

References

1. von der Maase H, Sengelov L, Roberts JT, et al. Long-term survival results of a randomized trial comparing gemcitabine plus cisplatin, with methotrexate, vinblastine, doxorubicin, plus cisplatin in patients with bladder cancer. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. Jul 20 2005;23(21):4602-4608.
2. Galsky MD, Hahn NM, Rosenberg J, et al. Treatment of patients with metastatic urothelial cancer "unfit" for Cisplatin-based chemotherapy. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. Jun 10 2011;29(17):2432-2438.
3. De Santis M, Bellmunt J, Mead G, et al. Randomized phase II/III trial assessing gemcitabine/carboplatin and methotrexate/carboplatin/vinblastine in patients with advanced urothelial cancer who are unfit for cisplatin-based chemotherapy: EORTC study 30986. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. Jan 10 2012;30(2):191-199.
4. Bellmunt J, Fougeray R, Rosenberg JE, et al. Long-term survival results of a randomized phase III trial of vinflunine plus best supportive care versus best supportive care alone in advanced urothelial carcinoma patients after failure of platinum-based chemotherapy. Annals of oncology : official journal of the European Society for Medical Oncology. Jun 2013;24(6):1466-1472.
5. McCaffrey JA, Hilton S, Mazumdar M, et al. Phase II trial of docetaxel in patients with advanced or metastatic transitional-cell carcinoma. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. May 1997;15(5):1853-1857.
6. Roth BJ, Dreicer R, Einhorn LH, et al. Significant activity of paclitaxel in advanced transitional-cell carcinoma of the urothelium: a phase II trial of the Eastern Cooperative Oncology Group. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. Nov 1994;12(11):2264-2270.
7. Sonpavde G. PD-1 and PD-L1 Inhibitors as Salvage Therapy for Urothelial Carcinoma. The New England journal of medicine. Mar 16 2017;376(11):1073-1074.
8. Lamm DL, Blumenstein BA, Crawford ED, et al. A randomized trial of intravesical doxorubicin and immunotherapy with bacille Calmette-Guerin for transitional-cell carcinoma of the bladder. The New England journal of medicine. Oct 24 1991;325(17):1205-1209.
9. Fuge O, Vasdev N, Allchorne P, Green JS. Immunotherapy for bladder cancer. Research and reports in urology. 2015;7:65-79.
10. Alexandrov LB, Nik-Zainal S, Wedge DC, et al. Signatures of mutational processes in human cancer. Nature. Aug 22 2013;500(7463):415-421.
11. Chen DS, Mellman I. Oncology meets immunology: the cancer-immunity cycle. Immunity. Jul 25 2013;39(1):1-10.
12. Poschke I, Mougiakakos D, Kiessling R. Camouflage and sabotage: tumor escape from the immune system. Cancer immunology, immunotherapy : CII. Aug 2011;60(8):1161-1171.
13. Boussiotis VA. Molecular and Biochemical Aspects of the PD-1 Checkpoint Pathway. The New England journal of medicine. Nov 3 2016;375(18):1767-1778.
14. Ribas A. Tumor immunotherapy directed at PD-1. The New England journal of medicine. Jun 28 2012;366(26):2517-2519.
15. Rosenberg JE, Hoffman-Censits J, Powles T, et al. Atezolizumab in patients with locally advanced and metastatic urothelial carcinoma who have progressed following treatment with platinum-based chemotherapy: a single-arm, multicentre, phase 2 trial. Lancet. May 7 2016;387(10031):1909-1920.
16. Bellmunt J, de Wit R, Vaughn DJ, et al. Pembrolizumab as Second-Line Therapy for Advanced Urothelial Carcinoma. The New England journal of medicine. Mar 16 2017;376(11):1015-1026.
17. Sharma P, Retz M, Siefker-Radtke A, et al. Nivolumab in metastatic urothelial carcinoma after platinum therapy (CheckMate 275): a multicentre, single-arm, phase 2 trial. The Lancet. Oncology. Mar 2017;18(3):312-322.
18. Massard C, Gordon MS, Sharma S, et al. Safety and Efficacy of Durvalumab (MEDI4736), an Anti-Programmed Cell Death Ligand-1 Immune Checkpoint Inhibitor, in Patients With Advanced Urothelial Bladder Cancer. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. Sep 10 2016;34(26):3119-3125.
19. Heery CR, O'Sullivan-Coyne G, Madan RA, et al. Avelumab for metastatic or locally advanced previously treated solid tumours (JAVELIN Solid Tumor): a phase 1a, multicohort, dose-escalation trial. The Lancet. Oncology. May 2017;18(5):587-598.
20. Dash A, Galsky MD, Vickers AJ, et al. Impact of renal impairment on eligibility for adjuvant cisplatin-based chemotherapy in patients with urothelial carcinoma of the bladder. Cancer. Aug 1 2006;107(3):506-513.
21. Bellmunt J, Mottet N, De Santis M. Urothelial carcinoma management in elderly or unfit patients. EJC supplements : EJC : official journal of EORTC, European Organization for Research and Treatment of Cancer ... [et al.]. Mar 2016;14(1):1-20.
22. De Santis M, Bachner M. New developments in first- and second-line chemotherapy for transitional cell, squamous cell and adenocarcinoma of the bladder. Current opinion in urology. Sep 2007;17(5):363-368.
23. Balar AV, Galsky MD, Rosenberg JE, et al. Atezolizumab as first-line treatment in cisplatin-ineligible patients with locally advanced and metastatic urothelial carcinoma: a single-arm, multicentre, phase 2 trial. Lancet. Jan 7 2017;389(10064):67-76.
24. Balar AV, Castellano D, O'Donnell PH, et al. First-line pembrolizumab in cisplatin-ineligible patients with locally advanced and unresectable or metastatic urothelial cancer (KEYNOTE-052): a multicentre, single-arm, phase 2 study. The Lancet. Oncology. Nov 2017;18(11):1483-1492.
25. Apolo AB. PDL1: The Illusion of an Ideal Biomarker. European urology focus. Feb 2016;1(3):269-271.
26. Schumacher TN, Schreiber RD. Neoantigens in cancer immunotherapy. Science. Apr 3 2015;348(6230):69-74.
27. Cancer Genome Atlas Research N. Comprehensive molecular characterization of urothelial bladder carcinoma. Nature. Mar 20 2014;507(7492):315-322.
28. Herbst RS, Soria JC, Kowanetz M, et al. Predictive correlates of response to the anti-PD-L1 antibody MPDL3280A in cancer patients. Nature. Nov 27 2014;515(7528):563-567.

once-daily tablets
Zytiga®
abiraterone acetate

Redefining Journey for Your High-risk mHSPC Patients

Reduce risk of death by
38%

Extend
33.2 months
of time to PSA progression

Extend
33.0 months
of time to radiographic progression

REFERENCE :

1. Fizazi K, Tran N, Fein L, et al. Abiraterone plus prednisone in metastatic, castration-sensitive prostate cancer. N Engl J Med. 2017;337:352-360.

ZYTIGA® Tablets 250 mg
ABBREVIATED PRESCRIBING INFORMATION

ACTIVE INGREDIENT(S): Abiraterone acetate. **INDICATION(S):** With prednisone or prednisolone for: the treatment of newly diagnosed high risk metastatic hormone sensitive prostate cancer (mHSPC) in adult men in combination with androgen deprivation therapy (ADT); the treatment of metastatic castration resistant prostate cancer (mCRPC) in adult men who are asymptomatic or mildly symptomatic after failure of androgen deprivation therapy in whom chemotherapy is not yet clinically indicated; the treatment of (mCRPC) in adult men whose disease has progressed on or after a docetaxel-based chemotherapy regimen. **DOSAGE & ADMINISTRATION:** 1,000 mg as a single daily dose that must not be taken with food. For mHSPC, ZYTIGA is used with 5 mg prednisone or prednisolone daily. For mCRPC, ZYTIGA is used with 10 mg prednisone or prednisolone daily. ZYTIGA should be taken at least two hours after eating and no food should be eaten for at least one hour after taking the tablets. These should be swallowed whole with water. **CONTRAINDICATIONS:** Hypersensitivity to the product. Women who are or may potentially be pregnant. Severe hepatic impairment (Child-Pugh Class C). **SPECIAL WARNINGS & PRECAUTIONS:** Mineralocorticoid excess: Use with caution in patients whose underlying medical conditions might be compromised by increases in blood pressure, hypokalaemia, or fluid retention. Use with caution in patients with a history of cardiovascular disease. Correct and control hypertension, hypokalaemia and fluid retention before treatment. Monitor blood pressure, serum potassium, fluid retention and other symptoms of congestive heart failure as recommended. Hepatotoxicity and hepatic impairment: Monitor serum transaminase levels and liver function. Modify, interrupt, or discontinue ZYTIGA dosing as recommended. Corticosteroid withdrawal and coverage of stress situations: Monitor for adrenocortical insufficiency if patients are withdrawn from prednisone or prednisolone. Monitor for mineralocorticoid excess if ZYTIGA is continued after corticosteroids are withdrawn. An increased dose of corticosteroids may be indicated before, during and after unusually stressful situations. Bone density: Use of ZYTIGA in combination with glucocorticoid could increase the decrease of bone density. Ketoconazole: Lower rates of response might occur in patients previously treated with ketoconazole for prostate cancer. Hyperglycaemia: Measure blood sugar frequently in patients with diabetes. Intolerance to excipients: This product contains lactose and sodium. Potential risks: Anaemia and sexual dysfunction may occur in men with metastatic prostate cancer including those undergoing treatment with ZYTIGA. Skeletal Muscle Effects: Caution is recommended in patients concomitantly treated with drugs known to be associated with myopathy/rhabdomyolysis. **SIDE EFFECTS:** Peripheral oedema, hypokalaemia, hypertension, urinary tract infection, and alanine aminotransferase increased and/or aspartate aminotransferase increased, cardiac disorders, hepatotoxicity, fractures, and allergic alveolitis. Refer to the full prescribing information for other side effects. **PREGNANCY & LACTATION:** ZYTIGA is not for use in women. **INTERACTIONS:** ZYTIGA must not be taken with food. Avoid use of strong inducers of CYP3A4 during treatment. Caution when administer with medicinal products activated by or metabolized by CYP2D6, especially those with narrow therapeutic index. Patients should be monitored for signs of toxicity related to a CYP2C8 substrate with a narrow therapeutic index if used concomitantly. Medicinal products known to prolong the QT interval or medicinal products able to induce Torsade de pointes such as class IA or class III antiarrhythmic medicinal products, methadone, moxifloxacin, antipsychotics, etc. Not recommend to use with Spironolactone.

PLEASE REFER TO FULL PRESCRIBING INFORMATION BEFORE PRESCRIBING.
API version to be quoted on promotional material: Zytiga aPI ver.6.0

Janssen
Unit 1302-1307, Tower 1, Grand Century Place,
193 Prince Edward Road West, Mongkok, Kowloon, Hong Kong
Tel: 2736 1711 Fax: 2736 1926

CP-52573

The Current Status of Radical Cystectomy

Dr Eddie Shu-yin CHAN

MBchB, MRCS (Edin), FRCS Ed (Urol), FHKAM, MD (CUHK)

Consultant urologist, Clinical associate professor (Honorary)
Department of Surgery, Prince of Wales Hospital, The Chinese University of Hong Kong, Hong Kong

Dr Eddie Shu-yin CHAN

Radical cystectomy is the standard treatment of muscle-invasive and high risk non-muscle invasive bladder cancers. It is one of the most technically demanding operations in urology. In general, radical cystectomy comprises of three steps: (1) removal of the urinary bladder, including the prostate in males and the uterus/ovaries in females, (2) pelvic lymph node dissection and, (3) urinary diversion. Complications commonly occur in this extensive procedure, especially in patients with high surgical and anaesthetic risks. On the other hand, up to 50% of patients with muscle-invasive bladder cancers experience disease recurrence within 5 years after surgery and the majority of patients succumb eventually[1,2]. Bladder cancer management is expensive and reportedly is the most expensive malignancy to treat from diagnosis until death[3]. Herein, we present some of the latest advances and trends in the management of bladder cancer and the latest thoughts on radical cystectomy.

Role of pelvic lymph node dissection (PLND)

Bilateral pelvic lymph node dissection is an integral part of radical cystectomy, and carries both diagnostic and therapeutic values. There are studies showing that 20-40% of node-negative disease will recur after the operation, which strongly indicates the possibility of disease under-staging[1,4,5] via PLND. The number of lymph node yield is highly variable from patient to patient and hence unreliable. Handling of lymph nodes by surgeons (specimen in bulk or in packets) and pathologists will affect the lymph node number. Therefore, lymph node count may not be a good surrogate of the quality and quantity of surgery. The current approach is based on lymph node template. The extent of PLND remains controversial, though. In general, removal of lymph nodes at least up to the aortic bifurcations or crossing of ureter is necessary[6-9]. Observational studies consistently demonstrate that an extended lymph node dissection cures more patients of bladder cancer than lesser templates of lymph node dissection. Bladder cancer patients with common iliac lymph node metastases can be cured by radical cystectomy and extended lymph node dissection[10,11]. Some authors even advocate to extend the template further to level of inferior mesenteric artery[12, 13].

Enhanced Recovery after surgery

Bladder cancer patients are, in general, of advanced age, smokers with multiple co-morbidity, and of poor nutritional status and/or impaired renal function. That explains the fact that radical cystectomy is associated with high morbidity up to 60% even in high-volume centres[14,15]. More and more evidence demonstrated that introduction of "enhanced recovery after surgery" protocol (ERAS) for patients undergoing radical cystectomy has been associated with reduction in hospital stay with no increase in readmission, complications or mortality rate. The ERAS protocol should include: 1) omission of oral bowel preparation, 2) preoperative smoking cessation and nutritional support, 3) perioperative counselling and training, 4) carbohydrate loading 2-4 hours before operation, 5) avoidance of intra-operative fluid overloading, 6) avoidance of opioid analgesics, 7) early post-operative oral feeding and, 8) early mobilisation[16,17].

Fig. 1. Perioperative counselling, an important component of ERAS, plays a proven role in decreasing postoperative length of hospital stay.

Histological variant and perioperative chemotherapy

Bladder cancer is a heterogenous group of disease. It may mostly run an indolent course with multiple recurrences. About 10-20% of the bladder cancer demonstrate aggressive behaviour, either upon initially presenting muscle-invasive state or or emerging progressively during the treatment course. This divergence in cancer behaviour can be explained by various genetic mutations of bladder cancer. The understanding of tumourigenesis and better morphological description of bladder cancer, in addition to conventional staging and grading, help to

categorise the tumour according to aggressiveness and, in turn, guide optimal treatment. Urothelial cancer with micropapillary type is a new class of bladder cancer, which was first described in the 1980s. Like other histological variants, it can metastasise early, even at early non-muscle invasive stage. An aggressive treatment regimen, including radical cystectomy, is warranted for non-muscle invasive urothelial cancer with histological variant. Further investigation is needed in searching for the best management.

The overall 5-year survival rate post-cystectomy for muscle-invasive bladder cancer is merely 50%, which is such a depressing figure! The paradigm of muscle-invasive bladder cancer management has shifted from radical cystectomy alone to systemic + local therapy. Neo-adjuvant chemotherapy before radical cystectomy offers cancer-specific and overall survival benefits. Most of the patients can tolerate pre-operative chemotherapy with the use of newer chemotherapy regimen, i.e. gemcitabine + cisplatin. Despite bearing level 1 evidence[18,19], neo-adjuvant cisplatin-based chemotherapy continues to be underused in the management of MIBC, even at high-volume tertiary centres[20,21]. Chemotherapy in adjuvant settings is more controversial. Adjuvant cisplatin-based chemotherapy is supported by a recent large cohort analysis, several relatively small randomised clinical trials, and the results of a meta-analysis and composite analysis or randomised trials. However, most of the study are limited by small patient number and flawed methodology.

Robot-assisted radical cystectomy

Robot-assisted surgery in urology has experienced a remarkable growth over the last decade. In 2017, over 90% of radical prostatectomies in public hospitals were performed using surgical robots (SOMIP data, Hospital Authority). The application of robotic surgical systems on radical cystectomy remains limited to academic and high-volume centres.

The feasibility of robot-assisted radical cystectomy (RARC) has been proven. The surgical techniques have been standardised. Short-term RARC data from centres of excellence appear to show the approach to be safe and effective, with improved perioperative and functional outcomes, while maintaining comparable oncologic efficiency[22,23]. Chan et al. reported the outcome of radical cystectomies in a Hong Kong medium-volume centre after adopting RARC. Compared to open radical cystectomy, robotic approach significantly reduced median length of hospital stay from 19 to 12 days ($P < 0.0005$) after cystectomy with ileal conduit diversion. The rate of positive surgical margins was lower with RARC. There were no differences in the rate of severe complications (Clavien grades 3–5) at 30 and 90 days[24]. With the use of robot, urinary diversion and reconstruction can be performed inside abdomen, i.e. intracorporeally, without a separate laparotomy incision. Furthermore, cystectomy with minimal invasive surgery approach is also regarded as one of the components of ERAS protocol.

Fig. 2. Robot-assisted cystectomy in action.


Fig. 3. Patient after robot-assisted radical cystectomy with total intracorporeal neobladder reconstruction.

Conclusion

Primary bladder cancer is a serious worldwide health hazard, commonly affecting the elderly and smokers. Radical cystectomy is the gold standard of non-metastatic, invasive bladder cancer management. Smoking is common among patients with bladder cancer; many present with significant cardiovascular, pulmonary, and renal diseases. The combination of an extensive extirpative procedure with urinary tract reconstruction in this elderly, comorbid population leads to significant perioperative morbidity and extended recovery time following standard open surgery. The combination of improved surgical techniques, better perioperative management, optimal neo-adjuvant and adjuvant system therapy and advanced technology hold promise in improving patient outcomes, both functionally and oncologically.

References

1. Shariat SF, Karakiewicz PI, Palapattu GS et al. Outcomes of radical cystectomy for transitional cell carcinoma of the bladder: a contemporary series from the Bladder Cancer Research Consortium. J Urol 2006; 176: 2414–22.
2. Stein JP, Lieskovsky G, Cote R et al. Radical cystectomy in the treatment of invasive bladder cancer: long-term results in 1,054 patients. J Clin Oncol 2001; 19: 666–75.

3. Botteman MF, Pashos CL, Redaelli A, et al. The health economics of bladder cancer: a comprehensive review of the published literature. Pharmacoeconomics. 2003;21:1315-1330.
4. Bassi P, Ferrante GD, Piazza N et al. Prognostic factors of outcome after radical cystectomy for bladder cancer: a retrospective study of a homogeneous patient cohort. J Urol 1999; 161: 1494–7.
5. Madersbacher S, Hochreiter W, Burkhard F et al. Radical cystectomy for bladder cancer today – a homogeneous series without neoadjuvant therapy. J Clin Oncol 2003; 21: 690–6.
6. Roth B, Wissmeyer M, Zehnder P et al. A new multimodality technique accurately maps the primary lymphatic landing sites of the bladder. Eur Urol 2010; 57: 205–11.
7. Steven K, Poulsen AL. Radical cystectomy and extended pelvic lymphadenectomy: survival of patients with lymph node metastasis above the bifurcation of the common iliac vessels treated with surgery only. J Urol 2007; 178: 1218–24.
8. Stein J, Quek M, Skinner D. Lymphadenectomy for invasive bladder cancer. II. technical aspects and prognostic factors. BJU Int 2006; 97: 232–7.
9. Stein J. Lymphadenectomy in bladder cancer: how high is 'high enough'? Urol Oncol 2006; 24: 349–55.
10. Dhar NB, Klein EA, Reuther AM,et al. Outcome after radical cystectomy with limited or extended pelvic lymph node dissection. J Urol 2008; 179:873–878.
11. Zehnder P, Studer UE, Skinner EC, et al. Super extended versus extended pelvic lymph node dissection in patients undergoing radical cystectomy for bladder cancer: a comparative study. J Urol 2011; 186:1261 – 1268.
12. Abol-Enein H, Tilki D, Mosbah A, et al. Does the extent of lymphadenectomy & in radical cystectomy for bladder cancer influence disease-free survival? A prospective single-center study. Eur Urol 2011; 60:572–577.
13. Jensen JB, Ulhoi BP, Jensen KM. Extended versus limited lymph node dissection in radical cystectomy: impact on recurrence pattern and survival. Int J Urol 2012; 19:39–47.
14. Shabsigh A, Korets R, Vora KC et al: Defining early morbidity of radical cystectomy for patients with bladder cancer using a standardized reporting methodology. Eur Urol 2009; 55: 164.
15. Chang SS and Koch M: The metabolic complications of urinary diversion. Urol Oncol 2000; 5: 60.
16. Cerantola Y, Valerio M, Persson B, et al. Guidelines for perioperative care after radical cystectomy for bladder cancer: Enhanced Recovery After Surgery (ERAS) society recommendations. Clinical Nutrition 2013; 32:879-887.
17. Mukhtar S, Ayres BE, Issa R, Swinn MJ, Perry MJA. Challenging boundaries: an enhanced recovery programme for radical cystectomy. Ann R Coll Surg Engl 2013; 95: 200–206.
18. Advanced Bladder Cancer Meta-analysis Collaboration. Neoadjuvant chemotherapy in invasive bladder cancer: a systematic review and meta-analysis. Lancet 2003;361:1927–34.
19. Advanced Bladder Cancer (ABC) Meta-analysis Collaboration. Neoadjuvant chemotherapy in invasive bladder cancer: update of a systematic review and meta-analysis of individual patient data. Eur Urol 2005;48:202–6, discussion 205–6.
20. Porter MP, Kerrigan MC, Donato BM, Ramsey SD. Patterns of use of systemic chemotherapy for Medicare beneficiaries with urothelial bladder cancer. Urol Oncol 2011;29:252–8.
21. Chan ES, Yee CH, Hou SM, CF Ng. Current management practice for bladder cancer in Hong Kong: a hospital-based cross-sectional survey. Hong Kong Med J 2014;20 :229-33.
22. Orvieto MA, DeCastro GJ, Trinh Q, et al. Oncological and Functional Outcomes After Robot-assisted Radical Cystectomy: Critical Review of Current Status. Urology. 2011; 78(5):977-84.
23. Bochner BH, Dalbagni G, Sjoberg DD, et al. Comparing Open Radical Cystectomy and Robot-assisted Laparoscopic Radical Cystectomy: A Randomized Clinical Trial. Eur Urol 2015; 67: 1042–1050.
24. Chan ES, Ng CF, Yee CH, et al. Surgical robots for radical cystectomies in a medium-volume hospital. Surgical Practice (2017) 21, 136–140.

Certificate Course for Doctors, Midwives, Nurses, Radiographers &
Other Healthcare Professionals who preferably have a basic knowledge of obstetric ultrasound

Course No. C318 | CME/CNE Course

Certificate Course on

Practical Obstetric Ultrasonography

Objectives:

1) To improve and update the knowledge on obstetric ultrasonography
2) To provide tips in performing obstetric ultrasonography, and
3) to update the new algorithms in prenatal diagnosis

Jointly organised by

The Federation of Medical Societies of Hong Kong

Hong Kong Society for Ultrasound in Medicine

Date	Topics	Speakers
7 Aug	New algorithm in prenatal diagnosis	Dr. WC LEUNG Consultant Obstetrician & Chief-of-service, Department of O&G, Kwong Wah Hospital
14 Aug	Ultrasonography of early pregnancy complications including scar pregnancy	Dr. Vincent CHEUNG Clinical Associate Professor in Obstetrics& Gynaecology The University of Hong Kong
21 Aug	Ultrasonography of placenta, liquor and membranes	Dr. TY FUNG Chief of Service, Obstetrics & Gynaecology Hong Kong Baptist Hospital
28 Aug	How to integrate three- and four-dimensional ultrasonography in obstetric sonography?	Dr. KY LEUNG Consultant and Chief-of-service, Department of O&G Queen Elizabeth Hospital
4 Sep	Nomogram, fetal growth restriction and macrosomia	Dr. Meliza KONG Consultant, Department of O&G United Christian Hospital
11 Sep	Tips in performing routine mid-trimester anomaly scan	Dr. CN LEE Consultant, Department of O&G Pamela Youde Nethersole Eastern Hospital

Date : 7, 14, 21, 28 Aug, 2018 & 4, 11 Sep, 2018 (Every Tuesday)
Time : 7:00 p.m. – 8:30 p.m.
Venue : Lecture Hall, 4/F., Duke of Windsor Social Service Building, 15 Hennessy Road, Wanchai, Hong Kong
Language Media : Cantonese (Supplemented with English)
Course Fee : HK$750 (6 sessions)
Certificate : Awarded to participants with a minimum attendance of 70%
Enquiry : The Secretariat of The Federation of Medical Societies of Hong Kong
Tel.: 2527 8898 Fax: 2865 0345 Email: info@fmshk.org

CME / CNE/CPD Accreditation in application
Application form can be downloaded from website: http://www.fmshk.org

Management of Small Renal Masses

Dr Francis Chan-wing LEE

MBBS (Sydney), FRCSEd, FCSHK, FRACS, FHKAM (Surgery)
Specialist in Urology

Dr Francis Chan-wing LEE

Introduction

The epidemiology of kidney cancer has evolved in recent decades in response to the changing clinical presentation of the disease. The classic triad of haematuria, pain and a palpable mass are now exceedingly rare and present in less than 10% of renal cancers.[1] More patients are now diagnosed with asymptomatic small renal masses (SRMs) due to increased utilisation of cross-sectional imaging studies performed for unrelated reasons. Approximately 40% of renal cell carcinomas (RCC) present as incidentally detected SRMs nowadays.[2] It has been noted that despite aggressive management of renal masses, mortality rates among patients with renal cell carcinoma have remained fixed over the past decades. In this article, we will review the natural history of SRMs as well as the current management approach.

Definition of SRM, histology and natural history

The term "small" renal tumours was first used in the 1974 version of the TNM staging system to identify tumours without kidney enlargement.[3] From the 2002 version onwards, T1 tumours have been subdivided into two categories (T1a and T1b) according to the cut-off value of 4cm.[4,5] Indeed T1a tumours are the ideal candidates for nephron-sparing surgery (NSS) as recommended in the most important international guidelines. According to dimensional criteria, surgical indications and prognostic impact, SRMs are defined as solid enhancing masses ≤ 4cm in maximal diameter.[6] (Fig. 1-4)

SRMs place physicians in a difficult position, since the histology of the SRMs is not readily diagnosed by imaging. Not all SRMs are malignant. In fact 20%-30% are benign (e.g. angiomyolipoma, oncocytoma, papillary adenoma. etc.), while malignant SRMs demonstrate heterogeneous behaviour and growth potential. A significant proportion of SRMs are considered to be of low-malignant potential.[7] Among malignant tumours, clear cell RCC is the most common histological subtype, accounting for 75%, followed by papillary RCC (15%), chromophobe RCC (5%) and Bellini duct tumours (1%).[8] Tumour size is one important indicator for the malignant potential of SRMs. Benign masses were detected in 46% of tumours ≤ 1cm in size, 22% of those between 2 and 3cm and in 20% of those measuring 4cm.[9] A meta-analysis of 234 renal masses with an average tumour diameter of 2.6cm and a mean follow-up of 34 months showed the average tumour growth rate was 0.28cm/year.[10] Other observational studies demonstrated slow a mean annual tumour growth rate (0.1-0.3cm per year), with smaller neoplasms demonstrating the slowest growth.[11, 12]

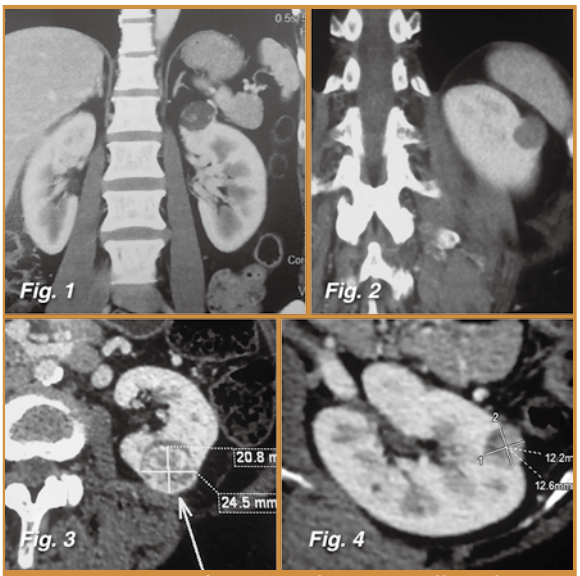


Fig. 1-4. CT images of contrast enhancing small renal masses (Source: Almassi et al. management of the small renal mass)

Individualised management

The management of small renal tumours should be based on a careful decision-making process that relies on several pre-operative parameters. The factors that influence the decision-making process include patient-related (i.e. age, co-morbidity profile, performance status and function of the contralateral kidney), tumour related factors (i.e. mode of presentation, tumour size, anatomical characteristics). The surgeon's experience is also an important factor influencing the technical feasibility of partial nephrectomy. The management approach to SRMs has been illustrated in Fig 5.

Role of percutaneous renal biopsy

The majority of SRMs are still being treated without histological diagnosis, which results in potential overtreatment. Renal tumour biopsy (RTB) has been increasingly proposed to characterise the histology of SRMs in recent years. An international consensus panel has specified how, what and when to perform RTBs for small renal tumours.[13] RTB can be indicated in patients

eligible for active surveillance or ablative treatments, those with other primary tumours, and those with multiple synchronous tumours.[13] A systemic review and meta-analysis of 57 studies on RTB showed an overall diagnostic rate of 92% with a sensitivity of 99.1% for core biopsy and 99.7% for fine-needle aspiration biopsy.[14] Furthermore, percutaneous biopsy has a low complication rate (<5%) with few major complications (<1%).[15] The risk of tumour tract seeding is extremely low, estimated at less than 0.01%.[15] These characteristics make percutaneous biopsy a useful tool in selecting appropriate candidates for focal ablation or active surveillance.

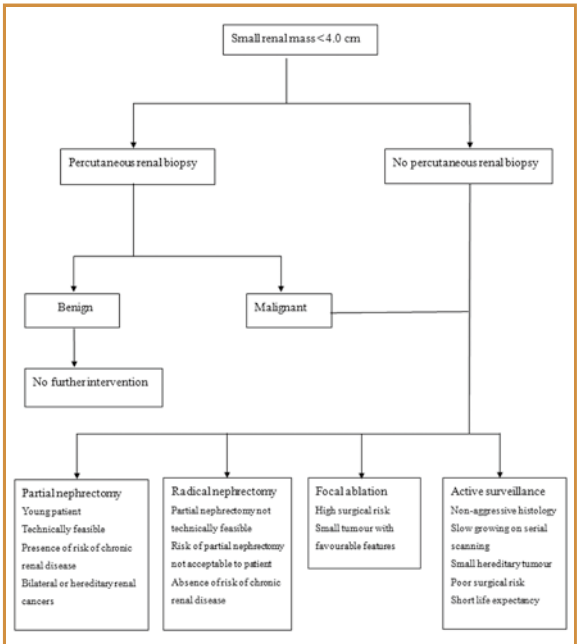


Fig. 5. Small renal mass management algorithm

Management options

a. Active surveillance (AS)

AS has emerged as an initial management option to address the potential overtreatment of localised renal masses, especially among older patients with comorbidities. The paradigm of AS is to identify patients with potentially low risk renal masses for continued surveillance or delayed intervention. The decision is based on radiographic tumour growth kinetics, and/or patient preference. The latest evidence of AS study included 457 patients managed with AS with a median tumour size of 2.1cm and median follow-up of 67 months. The five-years cancer specific mortality was 1.2%. Of 99 patients on AS without delayed intervention, one patient metastasised.[16] The study showed the rare metastasis and low cancer specific mortality rate should reassure physicians that AS is safe in appropriately selected patients in the intermediate to long term. AS in young healthy patients is typically reserved when benign pathology has been confirmed on percutaneous biopsy. Surveillance is avoided though, in non-compliant patients who are unwilling to attend regular follow-up.

b. Local ablative therapy

Over the past two decades, in situ ablation of small renal masses has been introduced as a therapeutic option. Focal ablation is a useful approach to treat elderly patients and those with multiple comorbidities, due to its ease of use, fewer complication rates and shorter convalescence.[17] Using either radiofrequency ablation or cryoablation equipment, this procedure can be performed either laparoscopically or percutaneously.[18,19] However, to date no randomised prospective trials have compared ablation to surgery. A meta-analysis based on retrospective studies found higher recurrence rates with focal ablation compared to partial nephrectomy.[20] Prospective randomised trials comparing partial nephrectomy are necessary to compare these treatment modalities and understand the long term efficacy of ablation in younger patients.

c. Surgery

Surgical extirpation via partial (PN) or radical nephrectomy (RN) remains the gold standard for T1a neoplasms. Surgery should be considered in healthy patients, where repeated ionising radiation exposures carry an inherent risk of secondary malignancy.[21] The greatest paradigm shift in treatment over the past decade has been the widespread adoption of PN for the treatment of SRMs. Since the early 2000s, multiple retrospective reports and prospective randomised trials demonstrated oncologic equivalency between PN and RN.[22-25] In addition to similar oncological outcomes, PN resulted in the preservation of kidney function and a reduction in the risk of developing chronic kidney disease.[26] By preserving renal function, PN confers lower risk of subsequent cardiovascular events and overall mortality compared to radical nephrectomy in multiple retrospective studies.[26]

However PN is more technically complex and carries a higher rate of peri-operative morbidity compared to radical nephrectomy, mostly secondary to haemorrhage and urine leakage.[25] The minimally invasive approach via laparoscopic or robotic assisted techniques has lower rates of peri-operative morbidity and blood transfusion, as well as a shorter length of stay when compared to the open approach.[27]

Conclusion

Small renal masses represent a heterogeneous group of neoplasms. There are emerging data demonstrating the safety of active surveillance. Percutaneous renal mass biopsy has emerged as a useful tool to aid in selecting candidates most appropriate for surveillance. Minimally invasive ablative therapies can be adopted when the surgical risk is high. Partial nephrectomy remains the standard of care whenever technically feasible for healthy patients with long life expectancy.

References

1. Jayson M, Sanders H. Increased incidence of serendipitously discovered renal cell carcinoma. Urology 1998;51(2):203-5.
2. Volpe A, Panzarella T, Rendon RA, et al. The natural history of incidentally detected small renal masses. Cancer 2004;100(4):738-45.
3. Sobin LH, Fleming ID. TNM Classification of Malignant Tumors, fifth edition (1997). Union Internationale Contre le Cancer and the American Joint Committee on Cancer. Cancer 1997;80(9):1803-4.
4. Ficarra V, Novara G, Galfano A, et al. Neoplasm staging and organ-confined renal cell carcinoma: a systematic review. European urology 2004;46(5):559-64.

5. Motzer RJ, Jonasch E, Agarwal N, et al. Kidney cancer, version 3.2015. Journal of the National Comprehensive Cancer Network : JNCCN 2015;13(2):151-9.
6. Jewett MA, Mattar K, Basiuk J, et al. Active surveillance of small renal masses: progression patterns of early stage kidney cancer. European urology 2011;60(1):39-44.
7. Eggener SE, Rubenstein JN, Smith ND, et al. Renal tumors in young adults. The Journal of urology 2004;171(1):106-10.
8. Frank I, Blute ML, Cheville JC, et al. Solid renal tumors: an analysis of pathological features related to tumor size. The Journal of urology 2003;170(6 Pt 1):2217-20.
9. Schlomer B, Figenshau RS, Yan Y, et al. Pathological features of renal neoplasms classified by size and symptomatology. The Journal of urology 2006;176(4 Pt 1):1317-20; discussion 20.
10. Chawla SN, Crispen PL, Hanlon AL, et al. The natural history of observed enhancing renal masses: meta-analysis and review of the world literature. The Journal of urology 2006;175(2):425-31.
11. Mason RJ, Abdolell M, Trottier G, et al. Growth kinetics of renal masses: analysis of a prospective cohort of patients undergoing active surveillance. European urology 2011;59(5):863-7.
12. Pierorazio PM, Johnson MH, Ball MW, et al. Five-year analysis of a multi-institutional prospective clinical trial of delayed intervention and surveillance for small renal masses: the DISSRM registry. European urology 2015;68(3):408-15.
13. Tsivian M, Rampersaud EN, Jr., del Pilar Laguna Pes M, et al. Small renal mass biopsy--how, what and when: report from an international consensus panel. BJU international 2014;113(6):854-63.
14. Marconi L, Dabestani S, Lam TB, et al. Systematic Review and Meta-analysis of Diagnostic Accuracy of Percutaneous Renal Tumour Biopsy. European urology 2016;69(4):660-73.
15. Lane BR, Samplaski MK, Herts BR, et al. Renal mass biopsy--a renaissance? The Journal of urology 2008;179(1):20-7.
16. McIntosh AG, Ristau BT, Ruth K, et al. Active Surveillance for Localized Renal Masses: Tumor Growth, Delayed Intervention Rates, and >5-yr Clinical Outcomes. European urology 2018.
17. Bandi G, Hedican S, Moon T, et al. Comparison of postoperative pain, convalescence, and patient satisfaction after laparoscopic and percutaneous ablation of small renal masses. Journal of endourology 2008;22(5):963-7.
18. Zlotta AR, Wildschutz T, Raviv G, et al. Radiofrequency interstitial tumor ablation (RITA) is a possible new modality for treatment of renal cancer: ex vivo and in vivo experience. Journal of endourology 1997;11(4):251-8.
19. Welch HG, Schwartz LM, Woloshin S. Are increasing 5-year survival rates evidence of success against cancer? Jama 2000;283(22):2975-8.
20. Kunkle DA, Egleston BL, Uzzo RG. Excise, ablate or observe: the small renal mass dilemma--a meta-analysis and review. The Journal of urology 2008;179(4):1227-33; discussion 33-4.
21. Volpe A, Cadeddu JA, Cestari A, et al. Contemporary management of small renal masses. European urology 2011;60(3):501-15.
22. Fergany AF, Hafez KS, Novick AC. Long-term results of nephron sparing surgery for localized renal cell carcinoma: 10-year followup. The Journal of urology 2000;163(2):442-5.
23. Lee CT, Katz J, Shi W, et al. Surgical management of renal tumors 4 cm. or less in a contemporary cohort. The Journal of urology 2000;163(3):730-6.
24. Uzzo RG, Novick AC. Nephron sparing surgery for renal tumors: indications, techniques and outcomes. The Journal of urology 2001;166(1):6-18.
25. Van Poppel H, Da Pozzo L, Albrecht W, et al. A prospective, randomised EORTC intergroup phase 3 study comparing the oncologic outcome of elective nephron-sparing surgery and radical nephrectomy for low-stage renal cell carcinoma. European urology 2011;59(4):543-52.
26. Huang WC, Elkin EB, Levey AS, et al. Partial nephrectomy versus radical nephrectomy in patients with small renal tumors--is there a difference in mortality and cardiovascular outcomes? The Journal of urology 2009;181(1):55-61; discussion 61-2.
27. Ghani KR, Sukumar S, Sammon JD, et al. Practice patterns and outcomes of open and minimally invasive partial nephrectomy since the introduction of robotic partial nephrectomy: results from the nationwide inpatient sample. The Journal of urology 2014;191(4):907-12.

Chinese Music – from Ancient to Modern

Dr Martin Kwok-tin WONG

MBBS(HK), FRCSEd, FCSHK, FRCSEd(Urol), FHKAM(Surgery)
Specialist in Urology

Dr Martin Kwok-tin WONG

Generally speaking, there are two kinds of music traditions – classical and folk. Music from the "classical tradition" refers to art music or "sophisticated" music composed by scholars and literati in China's historical past. Chinese classical music often has thematic, poetic or philosophical associations and is typically played solo, on instruments such as the qin (commonly known as guqin), 7-string zither with over 3,000 years of well-documented history, or the pipa, a lute with over 2,000 years of history. Traditional music in the classical sense is intimately linked to poetry and to various forms of lyric drama, and is more or less poetry without words. In the same manner as poetry, music sets out to express human feelings, soothe suffering and bring spiritual elevation. The instruments demand not only a mastery of technique but a high degree of sensitivity (and inner power) to evoke the subtle sonorities and deep emotional expression that rely very much on the left hand techniques (such as sliding, bending, pushing or crossing of the strings to produce typical singing effects and extreme dynamic ranges), where synchronised ensemble playing is virtually impossible without losing certain subtleties. This type of music has come down to us as an oral tradition from masters to students, although written notation documenting left and right hand techniques have been in use for nearly two thousand years. For instance, the earliest score for guqin we still have today is the "Jieshi Diao Youlan" (碣石調幽蘭), literally "Solitary Orchid in the Stone Tablet Mode". It is the name of a piece of Chinese music or melody for the guqin which was composed during the 6th or 7th century, with the earliest preserved text dating from the 7th century, and is possibly the oldest surviving piece of written music in the Far East. The manuscript is now found in Kyoto, Japan. It is believed to be a copy of an earlier manuscript and contains a lot of written 'corrections', mistakes and vagueness. Because it is damaged in some places, there has been much study into how it is played. Interestingly, such ancient guqin notation is not like our modern stave scores. The manuscript of Youlan is written in a special old form of guqin notation, known as *wenzi pu* (文字譜), literally "written character notation". The playing of a single note may involve a whole paragraph of words. (Fig.1)

In traditional China, most well-educated people and monks could play classical music as a means of self-cultivation, meditation, mind purification and spiritual elevation, union with nature, identification with the values of past sages, and communication with divine beings or with friends and lovers. They would never perform in public, or for commercial purposes, as they would never allow themselves to be called "professional musicians". This was in part to keep a distance from the entertainment industry where performing artists used to be among the lowest in social status. In fact, masters of classical music had their own profession as scholars and officers, and would consider it shameful if they had to make a living from music. They played music for themselves, or for their friends and students, and they discovered friends or even lovers through music appreciation (there are plenty of romantic stories about music in Chinese literature).

Up to the beginning of the twentieth century, classical music had always belonged to the elite society and it was not popular among ordinary people. Today it is really for everybody who enjoys it, and professional musicians playing Chinese classical music are as common as elsewhere in the world. However, it is still rare to hear classical music in concert halls due to the influence of the so-called "Cultural Revolution" (1966-1976), when all classical music was deemed to be "bourgeois" and outlawed, and the spiritual side of traditional arts was "washed out" through the "revolutionary" ideology. As well, the influence of modern pop culture since the 1980s has had a negative impact on the popularity of classical music performances.

While the classical tradition was more associated with the elite society throughout Chinese history, the resources for folk traditions are many and varied. Apart from the Han Chinese (漢族), there are many ethnic minorities living in every corner of China, each with their own traditional folk music. Unlike classical music, folk traditions are often vocal (such as love songs and story-telling etc.), or for instrumental ensembles (such as the Cantonese "Five-piece ensembles" (五架頭) (Fig.2), and music for folk dances, and regional operas). The various folk melodies have become a major source of inspiration for the growing repertoire of contemporary music. In fact, in many contemporary compositions, existing folk melodies were simply modified, enriched (creatively through advanced playing techniques and the use of harmonies), and extended. Some were transcribed so successfully that they may be regarded as an important part of the growing classical repertoire; for instance the famous "Autumn moon over the quiet lake" (平湖秋月) composed by Lu Wencheng (呂文成) for Gaohu (高胡). The repertoire is further extended by pieces composed or arranged for multi-instrument ensembles. Needless to say, most contemporary works are quite Westernizsed, particularly those for ensembles and orchestras (modelled on orchestras in the West),

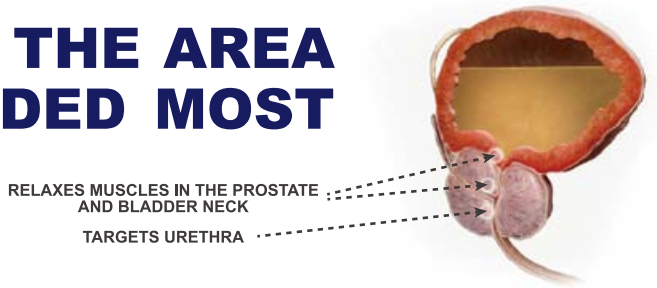
which are easily accessible to the general public, yet veer further away from the classical traditions. Quite often some of the traditional classical masterpieces are presented in commercially-packaged shows to look and sound "modern", which often gives a wrong impression to listeners who never really know the original flavour of the music, particularly the spiritual side of the classical tradition.

Fig. 1. Jieshi Diao Youlan

Fig. 2. Cantonese Five-piece ensemble

URIEF® TARGETS THE AREA WHERE IT'S NEEDED MOST

AVAILABLE NOW



- **A highly uroselective α_{1A}-adrenoceptor antagonist** [1,2,3,4]
  - High affinity for α_{1A}-adrenoreceptors (α_{1A}:α_{1B}=162:1)
  - More than 200-fold higher affinity for human prostate than for aorta
- **Rapid and sustained BPH symptom relief** [5]
  - BPH symptom relief in 3 to 4 days
  - Q_{max} increased within 2 to 6 hrs after the first dose
- **Safe and well tolerated** [6,7]
  - Low incidence of vasodilatory and orthostatic effects
  - No incidence of QTc prolongation

INDICATIONS: Bladder outlet obstruction associated with benign prostatic hyperplasia. **DOSAGE AND ADMINISTRATION:** The adult dosage for oral use is 4 mg of silodosin twice daily after breakfast and evening meal. The dosage may be reduced according to the patient's conditions.

References:
1. Laborde EE, McVary KT. Rev Urol 2009; 11(suppl 1):S19-25. **2.** Tatemichi S, Kobayashi K, Maezawa A, et al. Yakugaku Zasshi. 2006; 126:209-16. **3.** Yoshida M, Jomma Y, Kawabe K, Expert Opin. Investig. Drugs. 2007; 16:1955-65. **4.** Tatemichi S, Kobayashi KK, Maruyama I, et al. Yakugaku Zasshi. 2006; 126:217-23. **5.** Marks LS, Gittelman MC, Hill LA et al. J Urol. 2009; 181(6):2534-40. **6.** Yu H, Lin A, Yang S, et al. BJU Int. 2011. **7.** Morganroth J, Lepor H, Hill LA, et al. Clin Pharmacol Ther. 2010; 87(5):609-13.

Please contact (852) 2708-9166 for adverse drug reactions (ADR) reporting to Synmosa Biopharma (HK) Co., LTD.

SYNMOSA BIOPHARMA (HK) CO., LTD.
Flat F, 9/F, Hop Hing Industrial Building, 702-704 Castle Peak Road, Lai Chi Kok, Kowloon, Hong Kong

健喬集團 synmosa

日本 KISSEI 授權製造

URIEF® Silodosin 4mg

Medical Diary of August

Sunday	Monday	Tuesday	Wednesday	Thursday	Friday	Saturday
			1	2	3	4
5	★FMSHK Certificate Course in Obstetrics 2018 (4) 6	★FMSHK Certificate Course in Practical Obstetric ltrasonography (1) ★FMSHK Officers' Meeting ★HKMA Council Meeting 7	★The Hong Kong Neurosurgical Society Monthly Academic Meeting –Our Sonic Armamentarium ★HKMA Central, Western & Southern Community Network - Early Diagnosis & Management of Alzheimer's Disease & Mild Cognitive Impairment 8	★HKMA Hong Kong East Community Network - Lecture Series on O&G (Session 1) - Menstrual Disorders and Medical Treatment ★HKMA Kowloon East Community Network - The Management of Osteoarthritis of Knee ★HKMA New Territories West Community Network - Chronic Illness Management on DM and Dyslipidemia Patients ★HKMA-HKS&H CME Programme 2017-2018 – "Update in Medical Practice" 9	10	11
12	★FMSHK Certificate Course in Obstetrics 2018 (5) 13	★HKMA Kowloon West Community Network - Managing Non-Valvular Atrial Fibrillation Patients in Primary Care ★HKMA Yau Tsim Mong Community Network - Advance in Stroke Prevention & Treatment ★FMSHK Certificate Course in Practical Obstetric Ultrasonography (2) 14	15	16	17	18
★HKMA Dragon Boat Fun Day 2018 19	★FMSHK Certificate Course in Obstetrics 2018 (6) 20	★FMSHK Certificate Course in Practical Obstetric Ultrasonography (3) 21	★HKMA Central, Western & Southern Community Network - The Use of Probiotics 22	★HKMA Hong Kong East Community Network - Lecture Series on O&G (Session 2) - Maternal Nutrition in the First 1000 Days and Before ★HKMA Kowloon East Community Network - Update Management on Atopic Dermatitis ★HKMA New Territories West Community Network - Osteoporosis & Degeneration - From Prevention to Treatment ★FMSHK Executive Committee Meeting ★FMSHK Council Meeting 23	24	★HKMA-MPS Expert Witness Training 25
★HKMA-MPS Expert Witness Training 26	27	★HKMA Kowloon West Community Network - BPH Management In Hong Kong ★FMSHK Certificate Course in Practical Obstetric Ultrasonography (4) 28	29	30	31	

Nocdurna®
Desmopressin

Restful nights for active days

Night-time visits bring daytime consequences

In up to 88% of cases, nocturia is caused by Nocturnal Polyuria, the night-time overproduction of urine[1,2]

Regularly disturbed sleep[3,4]* impacts on quality of life[5,6]** and daily functioning.[5,6†]

NOCDURNA – low dose gender-specific desmopressin

- Targets night-time overproduction of urine – Nocturnal Polyuria
- Reduces the number of nocturnal voids and increases the time to first void (FUSP*)[3,5-8]
- Acts rapidly and with sustained effect[5-9]
- Tailored dosages: for men 50µg; for women 25µg
- Suitable for **adult patients of all ages** including over 65s[3,5-9]

As measured by: *FUSP (First Uninterrupted Sleep Period)[3,4] and PSQI,[3] **N-QoL[5,6] and †WPAI[5,6]

PSQI, Pittsburgh Sleep Quality Index; N-QOL, Nocturia Quality of Life; WPAI, Work Productivity and Activity Impairment

References

1. Weiss JP, *et al. J Urol* 2011; 186: 1358-63. 2. van Kerrebroeck, *et al. Int J Clin* Pract 2010; 64: 807-16. 3. Bliwise DL, *et al. Sleep Med* 2014; 15: 1276-8. 4. Bliwise D, *et al. J Clin Sleep Med* 2015; 11(1): 53-55. 5. Sand PK, *et al. J Urol* 2013; 190: 958-64. 6. Weiss JP, *et al. J Urol* 2013; 190: 965-72. 7. Yamaguchi O, *et al. BJU Int* 2013; 111: 474-84. 8. Weiss JP, *et al. Neurourol Urodyn* 2014; 33: S19-S24. 9. Juul KV, *et al. Neurourol Urodyn* 2013; 32: 363-70.

Abbreviated Prescribing Information of NOCDURNA 25 mcg and 50 mcg

Indication: Symptomatic treatment of nocturia due to idiopathic nocturnal polyuria in adults. **Dosage & Administration:** Women: 25 mcg daily, one hour before bedtime, administered sublingually without water. *Men:* 50 mcg daily, one hour before bedtime, administered sublingually without water. **Contraindications:** Hypersensitivity to the active substances or to any of the excipients; habitual or psychogenic polydipsia; known or suspected cardiac insufficiency or other conditions associated with fluid overload, sufficient to require treatment with diuretics, including a history of such conditions; renal insufficiency (creatinine clearance below 50 ml/min); hyponatremia and syndrome of inappropriate ADH secretion (SIADH). **Undesirable Effects:** Dry mouth, hyponatraemia, headache, dizziness, nausea, diarrhoea, weight increase, malaise, abdominal pain, muscle cramps, confusion, decreased consciousness, and in severe case, convulsions and coma. **Special Warnings:** Fluid intake must be limited to a minimum from 1 hour before until 8 hours after administration. Treatment without concomitant reduction of fluid intake may lead to prolonged fluid retention and/or hyponatremia (headache, nausea/vomiting, weight gain, and, in severe cases, convulsions). Patients 65 years and older should have their serum sodium monitored before initiating the treatment, in the first week of treatment (4-8 days) and again at one month after treatment initiation. Treatment should be discontinued if the serum sodium level falls below the lower limit of normal range (i.e.135 mmol/L). Caution is required in case of: Patients with conditions characterized fluid and/or electrolyte imbalance. Concomitant treatment with drugs, which are known to induce SIADH, e.g. tricyclic antidepressants, selective serotonin reuptake inhibitors, chlorpromazine, diuretics and carbamazepine, and some antidiabetics of the sulfonylurea group, particularly chlorpropamide. Concomitant treatment with NSAIDs, thiazide or loop diuretics. Cystic fibrosis, coronary heart disease, hypertensions, chronic renal disease and pre-eclampsia. Patients taking lithium.

For additional information, please consult the product package insert before prescribing.

FERRING PHARMACEUTICALS

Ferring Pharmaceuticals Ltd.
Suites 2604-05, 26/F, AXA Tower, Landmark East, 100 How Ming Street,
Kwun Tong, Kowloon, Hong Kong
Tel.: +852 2622 8000 Fax: +852 2622 8001 www.ferring.com

UR025/17/Oct/HK

Date / Time	Function	Enquiry / Remarks
6 MON 7:00 PM	**FMSHK Certificate Course in Obstetrics 2018 (4)** Organiser: The Federation of Medical Societies of Hong Kong; Venue: Lecture Hall, 4/F., Duke of Windsor Social Service Building, 15 Hennessy Road, Wanchai, Hong Kong	The Secretariat of FMSHK Tel: 2527 8898 Fax:2865 0345
7 TUE 7:00 PM	**FMSHK Certificate Course in Practical Obstetric Ultrasonography (1)** Organiser: The Federation of Medical Societies of Hong Kong; Venue: Lecture Hall, 4/F., Duke of Windsor Social Service Building, 15 Hennessy Road, Wanchai, Hong Kong	The Secretariat of FMSHK Tel: 2527 8898 Fax:2865 0345
8:00 PM	**FMSHK Officers' Meeting** Organiser: The Federation of Medical Societies of Hong Kong; Venue: Gallop, 2/F, Hong Kong Jockey Club Club House, Shan Kwong Road, Happy Valley, Hong Kong	Ms. Nancy CHAN Tel: 2527 8898
9:00 PM	**HKMA Council Meeting** Organiser:The Hong Kong Medical Association; Chairman: Dr. HO Chung Ping, MH, JP; Venue: HKMA Wanchai Premises, 5/F, Duke of Windsor Social Service Building, 15 Hennessy Road, HK	Ms. Christine WONG Tel: 2527 8285
8 WED 7:30 AM	**The Hong Kong Neurosurgical Society Monthly Academic Meeting –Our Sonic Armamentarium** Organizer: Hong Kong Neurosurgical Society; Chairman: Dr LAW Hing Yuen; Speaker(s): Dr HO Man Kit, Jason; Venue:Seminar Room, G/F, Block A, Queen Elizabeth Hospital	CME Accreditation College:1.5 points College of Surgeons of Hong Kong Enquiry: Dr. WONG Sui To Tel: 2595 6456 Fax. No.: 2965 4061
1:00 PM	**HKMA Central, Western & Southern Community Network - Early Diagnosis & Management of Alzheimer's Disease & Mild Cognitive Impairment** Organiser:HKMA Central, Western & Southern Community Network; Chairman: Dr. YIK Ping Yin; Speaker: Prof. WONG Ka Sing, Lawrence; Venue: HKMA Central Premises, Dr. Li Shu Pui Professional Education Centre, 2/F, Chinese Club Building, 21-22 Connaught Road Central, HK	Mr. Ian YAU Tel: 2527 8285 1 CME Point
9 THU 1:00 PM	**HKMA Hong Kong East Community Network - Lecture Series on O&G (Session 1) - Menstrual Disorders and Medical Treatment** Organiser:HKMA Hong Kong East Community Network; Chairman: Dr. LEUNG Kwan Kui, Terence; Speaker: Dr. LAI Wai Man, Sonia; Venue: HKMA Wanchai Premises, 5/F, Duke of Windsor Social Service Building, 15 Hennessy Road, HK	Ms. Candice TONG Tel: 2527 8285 1 CME Point
1:00 PM	**HKMA Kowloon East Community Network - The Management of Osteoarthritis of Knee** Organiser:HKMA KLN East Community Network; Chairman: Dr. AU Ka Kui, Gary; Speaker: Dr. WONG Tsz Cheung; Venue: Lei Garden Restaurant, Shop No. L5-8, apm, Kwun Tong, No. 418 Kwun Tong Road, Kowloon	Mr. Ian YAU Tel: 2527 8285 1 CME Point
1:00 PM	**HKMA New Territories West Community Network - Chronic Illness Management on DM and Dyslipidemia Patients** Organiser:HKMA New Territories West Community Network; Chairman: Dr. CHEUNG Kwok Wai, Alvin; Speaker: Dr. CHAN Nor, Norman; Venue: Pak Loh Chiu Chow Restaurant, Shop A316, 3/F, Yoho Mall II, 8 Long Yat Road, Yuen Long	Mr. Ian YAU Tel: 2527 8285 1 CME Point
1:00 PM	**HKMA-HKS&H CME Programme 2017-2018 –"Update in Medical Practice"** Organiser:Hong Kong Medical Association; Hong Kong Sanatorium & Hospital; Speaker: Dr. HSU Shing Jih, Axel; Venue: HKMA Central Premises, Dr. Li Shu Pui Professional Education Centre, 2/F, Chinese Club Building, 21-22 Connaught Road Central, HK	HKMA CME Dept. Tel: 2527 8285 1 CME Point
13 MON 7:00 PM	**FMSHK Certificate Course in Obstetrics 2018 (5)** Organiser: The Federation of Medical Societies of Hong Kong; Venue: Lecture Hall, 4/F., Duke of Windsor Social Service Building, 15 Hennessy Road, Wanchai, Hong Kong	The Secretariat of FMSHK Tel: 2527 8898 Fax:2865 0345
14 TUE 1:00 PM	**HKMA Kowloon West Community Network - Managing Non-Valvular Atrial Fibrillation Patients in Primary Care** Organiser:HKMA Kowloon West Community Network; Chairman: Dr. TONG Kai Sing; Speaker: Dr. LEE Kin Tong, Joe; Venue: Fulum Palace, Shop C, G/F, 85 Broadway Street, Mei Foo Sun Chun, Mei Foo	Mr. Ian YAU Tel: 2527 8285 1 CME Point
1:00 PM	**HKMA Yau Tsim Mong Community Network - Advance in Stroke Prevention & Treatment** Organiser:HKMA Yau Tsim Mong Community Network; Chairman: Dr. CHENG Kai Chi, Thomas; Speaker: Prof. WONG Ka Sing, Lawrence; Venue: Crystal Ballroom, 2/F, The Cityview Hong Kong, 23 Waterloo Road, Kowloon	Ms. Candice TONG Tel: 2527 8285 1 CME Point
7:00 PM	**FMSHK Certificate Course in Practical Obstetric Ultrasonography (2)** Organiser: The Federation of Medical Societies of Hong Kong; Venue: Lecture Hall, 4/F., Duke of Windsor Social Service Building, 15 Hennessy Road, Wanchai, Hong Kong	The Secretariat of FMSHK Tel: 2527 8898 Fax:2865 0345
19 SUN 2:00 PM	**HKMA Dragon Boat Fun Day 2018** Organiser:The Hong Kong Medical Association; Chairman: Dr. YAM Chun Yin; Dr. CHENG Po Yi, Priscilla; Venue: Sai Sha Wan, Sai Kung	Mr. Allen NG Tel: 2527 8285
20 MON 7:00 PM	**FMSHK Certificate Course in Obstetrics 2018 (6)** Organiser: The Federation of Medical Societies of Hong Kong; Venue: Lecture Hall, 4/F., Duke of Windsor Social Service Building, 15 Hennessy Road, Wanchai, Hong Kong	The Secretariat of FMSHK Tel: 2527 8898 Fax:2865 0345
21 TUE 7:00 PM	**FMSHK Certificate Course in Practical Obstetric Ultrasonography (3)** Organiser: The Federation of Medical Societies of Hong Kong; Venue: Lecture Hall, 4/F., Duke of Windsor Social Service Building, 15 Hennessy Road, Wanchai, Hong Kong	The Secretariat of FMSHK Tel: 2527 8898 Fax:2865 0345
22 WED 1:00 PM	**HKMA Central, Western & Southern Community Network - The Use of Probiotics** Organiser:HKMA Central, Western & Southern Community Network; Chairman: Dr. YIK Ping Yin; Speaker: Dr. NG Fook Hong; Venue: HKMA Central Premises, Dr. Li Shu Pui Professional Education Centre, 2/F, Chinese Club Building, 21-22 Connaught Road Central, HK	Mr. Ian YAU Tel: 2527 8285 1 CME Point
23 THU 1:00 PM	**HKMA Hong Kong East Community Network - Lecture Series on O&G (Session 2) - Maternal Nutrition in the First 1000 Days and Before** Organiser:HKMA Hong Kong East Community Network; Chairman: Dr. YIP Yik Pang, Kenneth; Speaker: Dr. YEO Lee Kung, Evelyn; Venue: HKMA Wanchai Premises, 5/F, Duke of Windsor Social Service Building, 15 Hennessy Road, HK	Ms. Candice TONG Tel: 2527 8285 1 CME Point

XGEVA®
denosumab

INDISPENSIBLE PARTNERS TO PROTECT THE BONES

Throughout the treatment journey of Prostate and Breast Cancer

XGEVA® (denosumab) Abbreviated Prescribing Information

XGEVA® (denosumab) Solution for Injection 120 mg

INDICATIONS Indicated for prevention of skeletal related events (pathological fracture, radiation to bone, spinal cord compression or surgery to bone) in adults with bone metastases from solid tumours, and treatment of adults and skeletally mature adolescents with giant cell tumour of bone that is unresectable or where surgical resection is likely to result in severe morbidity. **DOSAGE AND ADMINISTRATION** Supplementation of at least 500 mg calcium and 400 IU vitamin D daily is required in all patients, unless hypercalcaemia is present. Prevention of skeletal related events in adults with bone metastases from solid tumours: The recommended dose is 120 mg administered as a single subcutaneous injection once every 4 weeks into the thigh, abdomen or upper arm. Giant cell tumour of bone: The recommended dose of XGEVA is 120 mg administered as a single subcutaneous injection once every 4 weeks into the thigh, abdomen or upper arm with additional 120 mg doses on days 8 and 15 of treatment of the first month of therapy. Patients with renal impairment: No dose adjustment is required in patients with renal impairment. Patients with hepatic impairment: The safety and efficacy of denosumab have not been studied in patients with hepatic impairment. *Elderly patients (age ≥65)*: No dose adjustment is required in elderly patients. Paediatric population: XGEVA is not recommended in paediatric patients (age < 18) other than skeletally mature adolescents with giant cell tumour of bone. **CONTRAINDICATIONS** Contraindicated in patients with hypersensitivity to the active substance or to any of the excipients, and in patients with severe, untreated hypocalcaemia. Contraindicated in patients with unhealed lesions from dental or oral surgery. **SPECIAL WARNINGS AND PRECAUTIONS FOR USE** *Calcium and Vitamin D supplementation*: Supplementation with calcium and vitamin D is required in all patients unless hypercalcaemia is present. *Hypocalcaemia*: Pre-existing hypocalcaemia must be corrected prior to initiating therapy with XGEVA. Hypocalcaemia can occur at any time during therapy with XGEVA. *Renal impairment*: Patients with severe renal impairment (creatinine clearance < 30 ml/min) or receiving dialysis are at greater risk of developing hypocalcaemia. *Osteonecrosis of the jaw (ONJ)*: ONJ has been reported in patients receiving XGEVA. The start of treatment or of a new course of treatment should be delayed in patients with unhealed open soft tissue lesions in the mouth. A dental examination with preventive dentistry and an individual benefit-risk assessment is recommended prior to treatment with XGEVA in patients with concomitant risk factors. *Atypical fractures of the femur*: Atypical femoral fractures have been reported in patients receiving XGEVA. Atypical femoral fractures may occur with little or no trauma in the subtrochanteric and diaphyseal regions of the femur. *Patients with growing skeletons*: XGEVA is not recommended in patients with growing skeletons. Clinically significant hypercalcaemia has been reported in XGEVA-treated patients with growing skeletons weeks to months following treatment discontinuation. *Others*: Patients being treated with XGEVA should not be treated concomitantly with other denosumab containing medicinal products, or with bisphosphonates. **INTERACTIONS** No interaction studies have been performed. **PREGNANCY, LACTATION AND FERTILITY** *Pregnancy*: There are no adequate data from the use of XGEVA in pregnant women. XGEVA is not recommended for use in pregnant women and women of childbearing potential not using highly effective contraception. *Breast-feeding*: It is unknown whether denosumab is excreted in human milk. *Fertility*: No data are available on the effect of denosumab on human fertility. **UNDESIRABLE EFFECTS** Hypocalcaemia has commonly been reported following XGEVA administration, mostly within the first 2 weeks. The most common adverse reactions with XGEVA are musculoskeletal pain. The adverse reactions identified in clinical trials and from post-marketing experience: Very common (≥ 1/10) adverse reactions include: dyspnoea, diarrhoea and musculoskeletal pain. Common (≥ 1/100 to < 1/10) adverse reactions include: hypocalcaemia, hypophosphataemia, tooth extraction, hyperhidrosis and osteonecrosis of the jaw. **OVERDOSE** There is no experience with overdose in clinical studies.

Abbreviated Prescribing Information Version: HKPI20160002

Please read the full prescribing information prior to administration and full prescribing information is available on request.

XGEVA® is a registered trademark owned or licensed by Amgen Inc., its subsidiaries, or affiliates.

Prolia® (Denosumab) Abbreviated Prescribing Information

Prolia® (denosumab) Solution for Injection in Pre-filled Syringe 60 mg/mL

INDICATIONS Prolia is indicated for: i) treatment of postmenopausal women with osteoporosis at high risk for fracture, defined as a history of osteoporotic fracture, or multiple risk factors for fracture; or patients who have failed or are intolerant to other available osteoporosis therapy; ii) treatment to increase bone mass in men with osteoporosis at high risk for fracture, defined as a history of osteoporotic fracture, or multiple risk factors for fracture; or patients who have failed or are intolerant to other available osteoporosis therapy; iii) treatment to increase bone mass in men at high risk for fracture receiving androgen deprivation therapy for nonmetastatic prostate cancer. In these patients Prolia also reduced the incidence of vertebral fractures; iv) treatment to increase bone mass in women at high risk for fracture receiving adjuvant aromatase inhibitor therapy for breast cancer. **DOSAGE AND ADMINISTRATION** The recommended dose of Prolia is 60 mg administered as a single subcutaneous injection once every 6 months. Administer Prolia via subcutaneous injection in the upper arm, the upper thigh, or the abdomen. All patients should receive calcium 1000 mg daily and at least 400 IU vitamin D daily. **CONTRAINDICATIONS** Hypocalcemia and pregnancy, as well as hypersensitivity to any component of the product. **SPECIAL WARNINGS AND PRECAUTIONS FOR USE** *Hypersensitivity*: Clinically significant hypersensitivity including anaphylaxis has been reported with Prolia. Symptoms have included hypotension, dyspnea, throat tightness, facial and upper airway edema, pruritis, and urticaria. *Hypocalcemia and Mineral Metabolism*: Hypocalcemia may be exacerbated by the use of Prolia. Pre-existing hypocalcemia must be corrected prior to initiating therapy with Prolia. Hypocalcemia following Prolia administration is a significant risk in patients with severe renal impairment (creatinine clearance < 30 mL/min) or receiving dialysis. Adequately supplement all patients with calcium and vitamin D. *Osteonecrosis of the Jaw (ONJ)*: ONJ has been reported in patients receiving Prolia. The start of treatment or of a new course of treatment should be delayed in patients with unhealed open soft tissue lesions in the mouth. A dental examination with preventive dentistry and an individual benefit-risk assessment is recommended prior to treatment with Prolia in patients with concomitant risk factors. All patients should be encouraged to maintain good oral hygiene, undergo routine dental check-ups, and immediately report any oral symptoms such as dental mobility, pain or swelling, or non-healing of sores or discharge during treatment with Prolia. While on treatment, invasive dental procedures should be performed with caution and avoided in close proximity to Prolia treatment. *Atypical Subtrochanteric and Diaphyseal Femoral Fractures*: Atypical low-energy or low trauma fractures of the shaft have been reported in patients receiving Prolia. Patients should be advised to report new or unusual thigh, hip, or groin pain. *Multiple Vertebral Fractures (MVF) Following Discontinuation of Prolia Treatment*: Following discontinuation of Prolia treatment, fracture risk increases, including the risk of multiple vertebral fractures. If Prolia treatment is discontinued, consider transitioning to an alternative antiresorptive therapy. *Serious Infections*: Serious infections leading to hospitalization were reported in clinical trial. Advise patients to seek prompt medical attention if they develop signs or symptoms of severe infection, including cellulitis. *Dermatologic Adverse Reactions*: Dermatitis, eczema, and rashes. Most of these events were not specific to the injection site. Consider discontinuing Prolia if severe symptoms develop. Musculoskeletal Pain: Severe and occasionally incapacitating bone, joint, and/or muscle pain. Consider discontinuing use if severe symptoms develop. *Suppression of Bone Turnover*: In clinical trials treatment with Prolia resulted in significant suppression of bone remodeling as evidenced by markers of bone turnover and bone histomorphometry. *Osteonecrosis of the external auditory canal*: Osteonecrosis of the external auditory canal has been reported with denosumab. Possible risk factors include steroid use and chemotherapy and/or local risk factors such as infection or trauma. **INTERACTIONS** In subjects with postmenopausal osteoporosis, Prolia (60 mg subcutaneous injection) did not affect the pharmacokinetics of midazolam, which is metabolized by cytochrome P450 3A4 (CYP3A4), indicating that it should not affect the pharmacokinetics of drugs metabolized by this enzyme in this population. **PREGNANCY AND LACTATION** *Pregnancy*: Pregnancy: Category X. *Breast-feeding*: It is not known whether Prolia is excreted into human milk. **PEDIATRIC, GERIATRIC AND RENAL IMPAIRMENT** *Pediatric*: Prolia is not recommended in pediatric patients. *Geriatric*: No overall differences in safety or efficacy were observed in clinical studies between elderly patients and younger patients and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out. *Renal Impairment*: No dose adjustment is necessary in patients with renal impairment. **UNDESIRABLE EFFECTS** The most common adverse reactions reported with Prolia in patients with postmenopausal osteoporosis are back pain, pain in extremity, musculoskeletal pain, hypercholesterolemia, and cystitis. The most common adverse reactions reported with Prolia in men with osteoporosis are back pain, arthralgia, and nasopharyngitis. The most common (per patient incidence ≥ 10%) adverse reactions reported with Prolia in patients with bone loss receiving androgen deprivation therapy for prostate cancer or adjuvant aromatase inhibitor therapy for breast cancer are arthralgia and back pain. Pain in extremity and musculoskeletal pain have also been reported in clinical trials. The most common adverse reactions leading to discontinuation of Prolia in patients with postmenopausal osteoporosis are back pain and constipation. **OVERDOSE** There is no experience with overdosage with Prolia.

Abbreviated Prescribing Information Version: HKPROPI01

Please read the full prescribing information prior to administration and full prescribing information is available on request.

Prolia® is a registered trademark owned or licensed by Amgen Inc., its subsidiaries, or affiliates.

AMGEN®

Amgen Asia Holding Limited

Suites 408-12, 4/F, One Island East, 18 Westlands Road, Island East, Hong Kong.

Tel: (+852) 2808 3988 Fax: (+852) 2808 2626

HK-01285-XGA-2018-Jun

AIC_567

Date / Time	Function	Enquiry / Remarks
23 THU 1:00 PM	**HKMA Kowloon East Community Network - Update Management on Atopic Dermatitis** Organiser:HKMA KLN East Community Network; Chairman: Dr. AU Ka Kui, Gary; Speaker: Dr. HO Ka Keung; Venue: V Cuisine, 6/F., Holiday Inn Express, Hong Kong Kowloon East, 3 Tong Tak Street, Tseung Kwan O	Mr. Ian YAU Tel: 2527 8285 1 CME Point
1:00 PM	**HKMA New Territories West Community Network - Osteoporosis & Degeneration - From Prevention to Treatment** Organiser:HKMA New Territories West Community Network; Chairman: Dr. CHEUNG Kwok Wai, Alvin; Speaker: Dr. NG Fu Yuen, Charles; Venue: Atrium Function Rooms, Lobby Floor, Hong Kong Gold Coast Hotel, 1 Castle Peak Road, Gold Coast, HK	Mr. Ian YAU Tel: 2527 8285 1 CME Point
7:00 PM	**FMSHK Executive Committee Meeting** Organiser: The Federation of Medical Societies of Hong Kong; Venue: Council Chamber, 4/F, Duke of Windor Social Service Building, 15 Hennessy Road, Wanchai, Hong Kong	Ms. Nancy CHAN Tel: 2527 8898
8:00 PM	**FMSHK Council Meeting** Organiser: The Federation of Medical Societies of Hong Kong; Venue: Council Chamber, 4/F, Duke of Windor Social Service Building, 15 Hennessy Road, Wanchai, Hong Kong	Ms. Nancy CHAN Tel: 2527 8898
25 SAT 12:30 PM	**HKMA-MPS Expert Witness Training** Organiser:Hong Kong Medical Association; Medical Protection Society; Speaker: Dr. Ming Keng TEOH; Mr. Chris HOWSE; Ms. Jaime LAM; Dr. David KAN; Dr. Katie GRANT; Venue: Auditorium, 1/F, Duke of Windsor Social Service Building, 15 Hennessy Road, Wanchai, Hong Kong	HKMA CME Dept. Tel: 2527 8285 3 CME Point
26 SUN 12:30 PM	**HKMA-MPS Expert Witness Training** Organiser:Hong Kong Medical Association; Medical Protection Society; Speaker: Dr. Katie GRANT; Mr. Woody CHANG; Mr. Phyllis CHIU; Ms. Tracy CHEUNG; Prof. Albert LEE: Dr. Bernard MURPHY; DR. Ming Keong TEOH; Venue: Auditorium, 1/F, Duke of Windsor Social Service Building, 15 Hennessy Road, Wanchai, Hong Kong	HKMA CME Dept. Tel: 2527 8285 3 CME Point
28 TUE 1:00 PM	**HKMA Kowloon West Community Network - BPH Management In Hong Kong** Organiser:HKMA Kowloon West Community Network; Chairman: Dr. TONG Kai Sing; Speaker: Dr. WONG Chun Wing, Simon; Venue: Fulum Palace, Shop C, G/F, 85 Broadway Street, Mei Foo Sun Chun, Mei Foo	Mr. Ian YAU Tel: 2527 8285 1 CME Point
7:00 PM	**FMSHK Certificate Course in Practical Obstetric Ultrasonography (4)** Organiser: The Federation of Medical Societies of Hong Kong; Venue: Lecture Hall, 4/F., Duke of Windsor Social Service Building, 15 Hennessy Road, Wanchai, Hong Kong	The Secretariat of FMSHK Tel: 2527 8898 Fax:2865 0345

Upcoming Event

1 Sept 2018 14:00-22:00PM	**Annual Conference 2018 – Creativity for Care (創意醫療 關顧無價)** Organiser: Hong Kong College of Health Service Executives; Chairman: Dr LIU Shao-haei, President & Ms Macky TUNG, Chairlady; Speaker(s): Dr Neale FONG & Mr Bernard Charnwut CHAN GBS, JP; Venue: Cordis Hotel Hong Kong, Mongkok	Ms Rachel YAU T: 2527 8898 Email: rachel.yau@fmshk.org
9 Sept 2018, Sunday 08:50 to 17:00	**Li Shu Pui Symposium 2018 – MANAGEMENT OF URGENT CLINICAL CONDITIONS** Organiser:Hong Kong Sanatorium & Hospital; Venue: Ballroom, JW Marriott Hotel Hong Kong, Pacific Place, 88 Queensway, Hong Kong	Tel: 2835 8800 Website: www.hksh.com/lsp2018
29-30 Sept 2018	**The 10th Hong Kong Allergy Convention – Personalised Medicine in Allergy** Organiser: Hong Kong Institute of Allergy; Chairman: Dr Marco HO; Venue: Hong Kong Convention and Exhibition Centre	HKAC 2018 Secretariat T: 2559 9973 F: 2547 9528 CME Point: To be applied

Presentation: Docetaxel concentrate and solvent for solution for infusion. **Indications and dosage:** *Breast Cancer:* In combination with doxorubicin and cyclophosphamide for adjuvant treatment of operable node-positive and node-negative breast cancer (docetaxel 75 mg/m² 1-hour after doxorubicin 50 mg/m² and cyclophosphamide 500 mg/m² every 3 weeks for 6 cycles); in combination with doxorubicin for treatment of locally advanced or metastatic breast cancer who have not previously received cytotoxic therapy (docetaxel 75 mg/m² and doxorubicin 50 mg/m² every three weeks); monotherapy for the treatment of locally advanced or metastatic breast cancer after failure of cytotoxic therapy containing an anthracycline or an alkylating agent (docetaxel 100 mg/m² every three weeks); in combination with trastuzumab for treatment of metastatic breast cancer whose tumors overexpress HER2 and who previously have not received chemotherapy for metastatic disease (docetaxel 100 mg/m² every three weeks with trastuzumab administered weekly); in combination with capecitabine for the treatment of locally advanced/ metastatic breast cancer after failure of cytotoxic chemotherapy containing an anthracycline (docetaxel 75 mg/m² every three weeks combined with capecitabine at 1250 mg/m² twice daily (within 30 minutes after a meal) for 2 weeks followed by 1-week rest period). *Non-small cell lung cancer, NSCLC:* Treatment of locally advanced/ metastatic NSCLC after failure of prior platinum-based chemotherapy (docetaxel 75 mg/m² as a single agent); in combination with cisplatin for the treatment of patients with unresectable, locally advanced or metastatic NSCLC and in patients who have not previously received chemotherapy for this condition (docetaxel 75 mg/m² immediately followed by cisplatin 75 mg/ m² over 30-60 minutes every three weeks). *Prostate cancer:* In combination with prednisone or prednisolone for treatment of hormone refractory metastatic prostate cancer (docetaxel 75mg/m² every three weeks and prednisone or prednisolone 5mg orally twice daily is administered continuously). *Ovarian Cancer:* Treatment of metastatic carcinoma of the ovary after failure of first-line or subsequent chemotherapy (docetaxel 100mg/ m² as 1-hour infusion every three weeks). *Head and Neck cancer:* Monotherapy in treatment of recurrent and/or metastatic squamous cell carcinoma of the head and neck after failure of a previous chemotherapy regimen (docetaxel 100mg/m² as 1-hour infusion every three weeks). Induction treatment of locally advanced squamous cell carcinoma of the head and neck (followed by radiotherapy: docetaxel 75mg/m² as a 1 hour infusion, followed by cisplatin 75mg/m², as a 1 hour infusion (both on day 1 only), followed by 5-fluorouracil 750mg/m² per day given as a continuous infusion for 5 days, repeated every 3 weeks for 4 cycles) (Followed by chemoradiotherapy: docetaxel 75mg/m² as a 1 hour infusion on day 1, followed by cisplatin 100mg/m², as a 30-minute to 3 hour infusion, followed by 5-fluorouracil 1000mg/m² per day given as a continuous infusion from day 1 to day 4, repeated every 3 weeks for 3 cycles). *Gastric Adenocarcinoma:* Treatment of metastatic gastric adenocarcinoma, including adenocarcinoma of the gastroesophageal junction, who have not received prior chemotherapy for metastatic disease (docetaxel 75mg/m² as a 1 hour infusion, followed by cisplatin 75mg/m², as a 1 to 3 hour infusion (both on day 1 only), followed by 5-fluorouracil 750mg/m² per day given as a 24-hour continuous infusion for 5 days, starting at the end of the cisplatin infusion, repeated every 3 weeks). **Further Dosage Information:** Docetaxel is administered as a 1-hour infusion every three weeks, (*Breast, non-small cell lung, ovarian & head and neck cancers*) Premedication consisting of an oral corticosteroid, such as dexamethasone 16 mg per day (e.g. 8 mg BID) for 3 days starting 1 day prior to docetaxel administration, unless contraindicated, can be used. Prophylactic G-CSF may be used to mitigate the risk of hematological toxicities. (*Prostate cancer*) Given the concurrent use of prednisone or prednisolone the recommended premedication regimen is oral dexamethasone 8 mg, 12 hours, 3 hours and 1 hour before the docetaxel infusion. For dosage adjustments during treatment, please refer to detailed prescribing information. **Contraindications:** Hypersensitivity to docetaxel or any excipients, patients with baseline neutrophil count of <1,500 cells/mm³, pregnancy and lactation, severe liver impairment. **Precautions:** Premedication consisting of an oral corticosteroid is needed. Frequent monitoring of complete blood counts (retreat with docetaxel if ANC ≥1,500 cells/mm³ before next cycle, and dose reduction recommended if severe neutropenia, i.e. <500 cells/mm³ for seven days or more). Patients treated with docetaxel in combination with cisplatin and 5-fluorouracil should receive prophylactic G-CSF to mitigate the risk of complicated neutropenia (febrile neutropenia, prolonged neutropenia or neutropenic infection) and should be closely monitored. Observe closely for hypersensitivity reactions especially during the first and second infusions. Hypersensitivity reactions may occur within a few minutes following the initiation of the infusion of docetaxel, thus facilities for the treatment of hypotension and bronchospasm should be available. Severe reactions, such as severe hypotension, bronchospasm or generalised rash/erythema require immediate discontinuation of docetaxel and appropriate therapy and should not be re-challenged. Monitor closely for severe fluid retention. If new or worsening pulmonary symptoms develop, patients should be closely monitored, promptly investigated, and appropriately treated. For patients with elevated liver function test (LFTs), recommend dose is 75 mg/m² and LFTs should be measured at baseline and before each cycle. For patients with serum bilirubin levels >ULN and/or ALT and AST >3.5 times the ULN concurrent with serum alkaline phosphatase levels >6 times the ULN, docetaxel should not be used unless strictly indicated. The development of severe peripheral neurotoxicity requires a reduction of dose. When patients are candidates for treatment with docetaxel in combination with trastuzumab, they should undergo baseline cardiac assessment and further monitored during treatment (e.g. every three months). Patients with impaired vision should undergo a prompt and complete ophthalmologic examination. In case cystoid macular oedema is diagnosed, docetaxel treatment should be discontinued and appropriate treatment initiated. Contraceptive measures must be taken during and for at least three months after cessation of therapy. The concomitant use of docetaxel with strong CYP3A4 inhibitors should be avoided. **Additional precautions in adjuvant treatment of breast cancer:** G-CSF and dose reduction should be considered in complicated neutropenia. Evaluate and treat promptly on symptoms such as abdominal pain and tenderness, fever, diarrhea, with or without neutropenia. Monitor for symptoms of congestive heart failure during therapy and during the follow up period. **Interactions:** Metabolism of docetaxel may be modified by the concomitant administration of compounds which induce, inhibit or are metabolised by cytochrome P450-3A. Docetaxel may increase the clearance of carboplatin, CYP3A4 inhibitors. **Undesirable effects:** Neutropenia, anaemia, alopecia, nausea, vomiting, stomatitis, diarrhoea, asthenia, hypersensitivity reactions (flushing, rash with or without pruritis, chest tightness, back pain, dyspnoea, fever or chills etc.), Paresthesia, dysesthesia, pain, infusion site reactions, infections, thrombocytopenia, anorexia, peripheral sensory neuropathy, peripheral motor neuropathy, arrhythmia, hypertension, haemorrhage, nail disorders, myalgia, arthralgia, fluid retention, increase in blood bilirubin, alkaline phosphatase, AST, ALT. *For uncommon, rare and very rare undesirable effects, please refer to the full prescribing information.* Preparations: 20mg x 1 vial, 80mg x 1 vial. ***Full prescribing information is available upon request.*** APHHK-DOC-14.12

AXOTERE® (docetaxel)

Time Life Confidence

SAHK.DOC, 18.07.0265

Presentation: Cabazitaxel concentrate and solvent for solution for infusion. **Indications:** In combination with prednisone or prednisolone for the treatment of metastatic castration resistant prostate cancer previously treated with a docetaxel containing regimen. **Dosage:** 25 mg/m² administered as a 1-hour intravenous infusion every 3 weeks in combination with oral prednisone or prednisolone 10 mg administered daily throughout treatment. The recommended premedication regimen should be given at least 30 minutes prior to each administration of cabazitaxel. Dose modifications should be made if patients experience prolonged Grade ≥3 neutropenia, febrile neutropenia or neutropenic infection, Grade ≥3 diarrhoea, or Grade ≥2 peripheral neuropathy. If patients continue to experience any of these reactions at 20 mg/m2, further dose reduction to 15 mg/m² or discontinuation may be considered. **Contraindications:** Hypersensitivity to cabazitaxel or polysorbate 80 or excipients, or taxanes; neutrophil counts less than 1,500/mm3, severe hepatic impairment (bilirubin ≥ 3 x ULN), concomitant vaccination with yellow fever vaccine. **Precautions:** Premedication is recommended prior to the initiation of cabazitaxel infusion. Prophylactic G-CSF should be considered to reduce the risk or manage neutropenia complications, especially in patients with high risk clinical features (age ≥65 years, poor performance status, previous episodes of febrile neutropenia, extensive prior radiation ports, poor nutritional status, or other serious comorbidities). Bone marrow suppression manifested as neutropenia, anaemia, thrombocytopenia, or pancytopenia may occur. Caution advised in patients at risk of developing gastrointestinal complications: neutropenia, elderly, concomitant use with NSAIDs, anti-platelet therapy or anticoagulants, history of pelvic radiotherapy or gastrointestinal disease. Caution is recommended in patients with haemoglobin <10 g/dl and appropriate measures should be taken as clinically indicated. Treatment should be discontinued in case of any degradation of renal function to renal failure eCTCAE 4.0 Grade 3. Caution in patients with moderate and severe renal impairment. Elderly patients (≥65 years of age). Patients with haemoglobin <10 g/dl. Administration of live or live attenuated vaccines should be avoided. Haemoglobin and haematocrit should be checked before treatment with cabazitaxel and if patients exhibit signs or symptoms of anaemia or blood loss. If new or worsening pulmonary symptoms develop, patients should be closely monitored, promptly investigated, and appropriately treated. **Interactions:** Strong CYP3A inhibitors and inducers. St. John's Wort. Organic Anion Transport Polypeptides (OATP1B1) substrates. Live or live attenuated vaccines. **Undesirable effects:** *Very common: anaemia, leukopenia, neutropenia,* febrile neutropenia, thrombocytopenia, diarrhoea, anorexia, dysgeusia, dyspnoea, cough, nausea, vomiting, constipation, abdominal pain, alopecia, back pain, arthralgia, haematuria, fatigue, pyrexia, asthenia. *For common, uncommon, rare and very rare undesirable effects, please refer to the full prescribing information.* **Preparation:** 60mg x 1 vial. **Legal Classification:** Part 1, First & Third Schedules Poison ***Full prescribing information is available upon request.*** APHHK-CAB-18.01

mHRPC: Metastatic hormone refractory prostate cancer

JEVTANA® (cabazitaxel)

SAHK.CAB, 18.07.0266

SANOFI

Answers to Radiology Quiz

Answer:

1. This frontal supine abdominal radiograph demonstrates presence of ectopic gas densities outlining the right kidney, in keeping with retroperitoneal gas. Mottled gas densities are also seen within the right kidney, suggesting emphysematous change. Free gas is seen outlining the lateral aspect of the right hepatic lobe. Corresponding selected images from the contrast-enhanced CT confirm the findings discerned on the abdominal radiograph. There is gross evidence of bubbly irregular gas densities within the oedematous right renal parenchyma as well as the right collecting system, extending from the renal pelvis to the urinary bladder. No evidence of fluid collection is seen within the right kidney or at the perinephric region.

2. Right emphysematous pyelonephritis and cystitis.

3. There are 2 main types of emphysematous pyelonephritis. In type I, more than 1/3 of the parenchyma is destroyed, with intra-renal or extra-renal fluid collections characteristically absent. In type II disease, less than 1/3 of the parenchyma is destroyed, with presence of renal / extra-renal collections seen. Our patient has type I emphysematous pyelonephritis.

4. Emphysematous pyelonephritis has a female predisposition, and a high proportion of these patients having concomitant uncontrolled diabetes. Other predisposing factors include: urinary tract obstruction from urolithiasis and immunocompromised states. The most common implicated microbes include: Escherichia coli (most common), Klebsiella pneumoniae and Proteus mirabilis. In mild cases, conservative treatment with intravenous antibiotics could be considered. Drainage of retroperitoneal or perinephric collections could be performed via percutaneous image-guided modalities. However, where fulminant infection exists, such as the case presented above, nephrectomy and an aggressive course of intravenous antibiotics are warranted to manage this disease associated with a high mortality rate.

Dr Victor Siang-hua CHAN
FRCR
Department of Radiology, Queen Mary Hospital

H ZENTRE

THE CENTRE OF ZEN & LIFESTYLE

15 MIDDLE ROAD, TSIM SHA TSUI

SUPERB LOCATION · PURPOSE-BUILT FOR WELLNESS

INTERNATIONAL ACCOLADES FOR ENERGY EFFICIENCY & USE

INTELLIGENT CARPARK WITH AMPLE PARKING SPACES

REMARKABLE HEADROOM · RELIABLE POWER SUPPLY

LEASING HOTLINE: 2908 8625

HENDERSON LEASING AGENCY LIMITED

OAB: overactive bladder

Abbreviated prescribing information of Betmiga® prolonged-release tablets

Version: 003 PI version: Apr 2016. **Composition:** Mirabegron **Indication:** Symptomatic treatment of urgency, increased micturition frequency and/or urgency incontinence as may occur in adult patients with overactive bladder (OAB) syndrome. **Dosage:** Adult including elderly 50 mg once daily with or without food. **Administration:** Swallow whole with liquids. Do not chew/divide/crush. **Contraindications:** Mirabegron is contraindicated in patients with **-** Hypersensitivity to the active substance or to any of the excipients. **-** Severe uncontrolled hypertension defined as systolic blood pressure ≥ 180 mm Hg and/or diastolic blood pressure ≥ 110 mm Hg. **Special warnings and precautions for use:** Renal impairment: Betmiga has not been studied in patients with end stage renal disease (GFR < 15 mL/min/1.73 m2 or patients requiring haemodialysis) and, therefore, it is not recommended for use in this patient population. Data are limited in patients with severe renal impairment (GFR 15 to 29 mL/min/1.73 m2); based on a pharmacokinetic study a dose reduction to 25 mg is recommended in this population. Betmiga is not recommended for use in patients with severe renal impairment (GFR 15 to 29 mL/min/1.73 m2) concomitantly receiving strong CYP3A inhibitors. Hepatic impairment: Betmiga has not been studied in patients with severe hepatic impairment (Child-Pugh Class C) and, therefore, it is not recommended for use in this patient population. Betmiga is not recommended for use in patients with moderate hepatic impairment (Child-Pugh B) concomitantly receiving strong CYP3A inhibitors. Hypertension: Mirabegron can increase blood pressure. Blood pressure should be measured at baseline and periodically during treatment with Betmiga, especially in hypertensive patients. Data are limited in patients with stage 2 hypertension (systolic blood pressure ≥ 160 mm Hg or diastolic blood pressure ≥ 100 mm Hg). Patients with congenital or acquired QT prolongation: Betmiga, at therapeutic doses, has not demonstrated clinically relevant QT prolongation in clinical studies. However, since patients with a known history of QT prolongation or patients who are taking medicinal products known to prolong the QT interval were not included in these studies, the effects of mirabegron in these patients is unknown. Caution should be exercised when administering mirabegron in these patients. Patients with bladder outlet obstruction and patients taking antimuscarinics medications for OAB: Urinary retention in patients with bladder outlet obstruction (BOO) and in patients taking antimuscarinic medications for the treatment of OAB has been reported in postmarketing experience in patients taking mirabegron. A controlled clinical safety study in patients with BOO did not demonstrate increased urinary retention in patients treated with Betmiga; however, Betmiga should be administered with caution to patients with clinically significant BOO. Betmiga should also be administered with caution to patients taking antimuscarinic medications for the treatment of OAB. **Undesirable effects:** Summary of the safety profile: The safety of Betmiga was evaluated in 8,433 patients with OAB, of which 5,648 received at least one dose of mirabegron in the phase 2/3 clinical program, and 622 patients received Betmiga for at least 1 year (365 days). In the three 12-week phase 3 double blind, placebo controlled studies, 88% of the patients completed treatment with Betmiga, and 4% of the patients discontinued due to adverse events. Most adverse reactions were mild to moderate in severity. The most common adverse reactions reported for patients treated with Betmiga 50 mg during the three 12-week phase 3 double blind, placebo controlled studies are tachycardia and urinary tract infections. The frequency of tachycardia was 1.2% in patients receiving Betmiga 50 mg. Tachycardia led to discontinuation in 0.1% patients receiving Betmiga 50 mg. The frequency of urinary tract infections was 2.9% in patients receiving Betmiga 50 mg. Urinary tract infections led to discontinuation in none of the patients receiving Betmiga 50 mg. Serious adverse reactions included atrial fibrillation (0.2%). Adverse reactions observed during the 1-year (long term) active controlled (muscarinic antagonist) study were similar in type and severity to those observed in the three 12-week phase 3 double blind, placebo controlled studies. List of adverse reactions: The table below reflects the adverse reactions observed with mirabegron in the three 12-week phase 3 double blind, placebo controlled studies. The frequency of adverse reactions is defined as follows: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness. Infections and infestations: Common: Urinary tract infection. Uncommon: Vaginal infection, Cystitis. Psychiatric disorders: Not known (cannot be estimated from the available data): Insomnia*. Eye disorders: Rare: Eyelid oedema. Cardiac disorders: Common: Tachycardia. Uncommon: Palpitation, Atrial fibrillation. Vascular disorders: Very rare: Hypertensive crisis*. Gastrointestinal disorders: Common: Nausea*, Constipation*, Diarrhoea*. Uncommon: Dyspepsia, Gastritis. Rare: Lip oedema. Skin and subcutaneous tissue disorders: Uncommon: Urticaria, Rash, Rash macular, Rash popular, Pruritus. Rare: Leukocytoclastic vasculitis, Purpura, Angioedema*. Musculoskeletal and connective tissue disorders: Uncommon: Joint swelling. Reproductive system and breast disorders: Uncommon: Vulvovaginal pruritus. Investigations: Uncommon: Blood pressure increased, GGT increased, AST increased, ALT increased. Renal and urinary disorders: Rare: Urinary retention*. Nervous system disorders: Common: Headache*, Dizziness*. *observed during post-marketing experience. **Full prescribing information is available upon request.**

Reference: **1.** Chapple C.R. et al. Neurourol Urodynam 2014 Jan:33 (1):17-30 **2.** Hong Kong package insert of Betmiga® Apr 2016

Betmiga®
mirabegron

Astellas Pharma Hong Kong Co., Ltd.
Unit 1103-08, 11/F, Tower 1, Grand Century Place, 193 Prince Edward Rd. West, Mongkok, Kln, H.K.
Tel: (852) 2377 9801 Fax: (852) 2856 1440

astellas

BET-MAD-160318-0001