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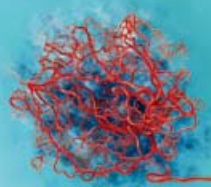
Avastin has been approved across multiple tumor types: [1-6]



First-line mCRC Superior OS (p<0.001)	30% Increase in median OS
First-line mNSCLC Superior OS (p=0.003)	19% Increase in median OS
Front-line OC Superior PFS (p<0.001)	37% Increase in median PFS
First-line mBC Superior PFS (p<0.0001)	95% Increase in median PFS
First-line mRCC Superior PFS (p=0.0001)	89% Increase in median PFS
Relapsed GBM	6-month PFS: 42.6% ORR: 28.2%

Abbreviated Prescribing Information – Avastin Roche Injection 100mg/4 ml (bevacizumab)
Indications: *Metastatic colorectal cancer (mCRC)* - in combination with fluoropyrimidine-based chemotherapy for treatment of mCRC. Metastatic breast cancer *(mBC)* - in combination with paclitaxel for 1st line treatment of mBC. *Non small cell lung cancer (NSCLC)* - in addition to platinum-based chemotherapy for 1st line treatment of unresectable, advanced, metastatic or recurrent NSCLC other than predominantly squamous cell histology. *Advanced and/or metastatic renal cell carcinoma (mRCC)* - in combination with interferon alfa-2a for the treatment of mRCC. Glioblastoma - for the treatment of glioblastoma with progressive disease following prior therapy as a single agent. Epithelial ovarian, fallopian tube or primary peritoneal cancer - in combination with carboplatin and paclitaxel for front-line treatment of advanced (FIGO stage III B, III C & IV) epithelial ovarian, fallopian tube or primary peritoneal cancer.
Dosage & Administration: Physicians experienced in antineoplastic medicines should supervise Avastin Roche administration. Continue treatment until progression of underlying disease or unacceptable toxicity (except for Glioblastoma). *mCRC* - 5mg/kg or 10mg/kg every 2 weeks; or 7.5mg/kg or 15mg/kg once every 3 weeks. *mBC* - 10mg/kg every 2 weeks; or 15mg/kg every 3 weeks. *NSCLC* - 7.5mg/kg or 15mg/kg every 3 weeks in addition to platinum-based chemotherapy for up to 6 cycles, then as monotherapy. *mRCC/Glioblastoma* - 10mg/kg once every 2 weeks. *Epithelial ovarian/Fallopian tube/Primary peritoneal cancer* - 15mg/kg once every 3 weeks in addition to carboplatin and paclitaxel for up to 6 cycles, then as monotherapy. **Method of administration:** *initial dose:* IV infusion over 90 minutes; if initial dose well tolerated, *second dose:* IV infusion over 60 minute; if second dose well tolerated, *subsequent doses:* IV infusion over 30 minutes. Do not administer as IV push or bolus or mix with glucose. Dose reduction for adverse events not recommended. If indicated, discontinue or temporarily suspend therapy. No recommendations for use in children or adolescents. No dose adjustment in the elderly.
Contraindications: Hypersensitivity to bevacizumab or any of the excipients, Chinese hamster ovary cell products and other recombinant human or humanised antibodies. Pregnancy.
Warnings & Precautions: *Gastrointestinal (GI) perforation:* increased risk for development of GI perforation; intra-abdominal inflammatory process may be a risk factor for GI perforations in patients with metastatic carcinoma of the colon or rectum thus caution is needed; discontinue therapy permanently in patients who develop GI perforation. *Fistulae:* increased risk for development of fistulae; permanently discontinue in tracheoesophageal or any Grade 4 fistula, consider discontinuation in non-GI fistula. *Wound healing:* do not initiate for at least 28 days following major surgery or until surgical wound is fully healed; withhold for elective surgery. *Hypertension:* control pre-existing hypertension prior to initiation. Monitor blood pressure during therapy and control hypertension with standard antihypertensive therapy; the use of diuretics to manage hypertension is not advised in patients on cisplatin-based chemotherapy. Permanently discontinue if medically significant hypertension remains uncontrolled or for hypertensive crisis/encephalopathy. *Reversible Posterior Leukoencephalopathy Syndrome (RPLS):* should RPLS develops, confirm by brain imaging, treat symptoms and discontinue Avastin Roche. RPLS signs include: seizures, headache, altered mental status, visual disturbance or cortical blindness with/without associated hypertension. *Proteinuria:* Patients with a history of hypertension may be at increased risk for the development of proteinuria; monitoring of proteinuria by dipstick urinalysis is recommended prior to starting and during therapy. Therapy should be permanently discontinued if Grade 4 proteinuria is developed. *Arterial thromboembolism:* including cerebrovascular accidents, transient ischaemic attacks and myocardial infarctions, especially if prior history or elderly. Permanently discontinue if arterial thromboembolic events develops. *Venous thromboembolism:* including pulmonary embolism; discontinue in Grade 4 pulmonary embolism and closely monitor where ≤Grade 3. *Haemorrhage,* especially tumour-associated haemorrhage: discontinue permanently if Grade 3/4. Risk of CNS haemorrhage in patients with untreated CNS metastases has not been prospectively evaluated in clinical studies. Patients should be monitored for signs and symptoms of CNS bleeding and discontinue Avastin Roche in cases of intracranial bleeding. Caution in patients with congenital bleeding diathesis, acquired coagulopathy or during anticoagulant therapy. Serious/fatal *pulmonary haemorrhage/haemoptysis* in non-small cell lung cancer: do not use where recent significant pulmonary haemorrhage/haemoptysis (>1/2 teaspoon of red blood). *Congestive Heart failure (CHF):* caution in patients with clinically significant cardiovascular disease or pre-existing CHF; most of the patients who experienced CHF had metastatic breast cancer and had received previous treatment with anthracyclines, prior radiotherapy to the left chest wall or other risk factors for CHF, such as pre-existing coronary heart disease or concomitant cardiotoxic therapy. *Neutropenia and infections:* fatal infection with or without severe neutropenia in combination with myelotoxic chemotherapy, mainly seen in combination with platinum- or taxane-based therapies in the treatment of NSCLC and mBC. *Hypersensitivity:* Close observation during and following the administration. Infusion should be discontinued and appropriate medical therapies should be administered if a reaction occurs. *Osteonecrosis of the jaw/(ONJ):* concomitant treatment with i.v. bisphosphonates and invasive dental procedures are identified risk factors to ONJ; patients who have previously received or are receiving i.v. bisphosphonates should avoid invasive dental procedures, if possible. Eye disorders including endophthalmitis, intraocular inflammation such as sterile endophthalmitis, uveitis and vitritis, retinal detachment, retinal pigment epithelial tear, intraocular pressure increased, intraocular haemorrhage such as vitreous haemorrhage or retinal haemorrhage and conjunctival haemorrhage have been reported following compounding for unapproved intravitreal use, some appeared as serious adverse reactions. *Ovarian Failure / Fertility:* Fertility preservation strategies should be discussed with women of child-bearing potential prior treatment.
Drug Interactions: No clinically relevant pharmacokinetic interaction between co-administered chemotherapy and Avastin Roche. Safety and efficacy with concomitant radiotherapy has not been established. Microangiopathic haemolytic anaemia has been reported when Avastin Roche was used with sunitinib malate; hypertension, elevated creatinine and neurological symptoms were also observed. Increased rates of severe neutropenia, febrile neutropenia, or infection with or without severe neutropenia have been observed in patients on platinum- or taxane-based therapies in the treatment of NSCLC and mBC. **Use in Pregnancy & Lactation:** Avastin Roche should not be used during pregnancy because no adequate & well-controlled data in pregnant women. Inhibition of foetal angiogenesis is anticipated. Avastin Roche may have temporary adverse effect on female fertility and cause ovarian failure. Women with childbearing potential must use effective contraception during and for up to 6 months after treatment. Discontinue breast-feeding during treatment and for at least 6 months after last dose.
Undesirable Effects: For full listings please refer to the Avastin Roche package insert. *Most serious reactions:* GI perforation; haemorrhage including pulmonary haemorrhage/haemoptysis; and arterial thromboembolism. *Serious reactions, very common:* Febrile neutropenia, leucopenia, thrombocytopenia, neutropenia, peripheral sensory neuropathy, hypertension, diarrhoea, nausea, vomiting, asthenia and fatigue. *Serious reactions, common:* Sepsis, abscess, infection, anaemia, dehydration, cerebrovascular accident, syncope, somnolence, headache, congestive cardiac failure, supraventricular tachycardia, arterial thromboembolism, deep vein thrombosis, haemorrhage, pulmonary embolism, dyspnoea, hypoxia, epistaxis, intestinal perforation and obstruction, ileus, abdominal pain, GI disorder, stomatitis, palmar-plantar erythrodysaesthesia syndrome, muscular weakness, myalgia, arthralgia, proteinuria, urinary tract infection pain, lethargy and mucosal inflammation. *All grades, very common:* Anorexia, dysgeusia, headache, dysarthria, eye disorder, lacrimation increased, hypertension, dyspnoea, epistaxis, rhinitis. constipation, stomatitis, rectal haemorrhage, diarrhoea, ovarian failure, exfoliative dermatitis, dry skin, skin discolouration, arthralgia, proteinuria, pyrexia, asthenia, pain and mucosal inflammation. *Other reactions:* Hypertensive encephalopathy. RPLS (rare). Renal thrombotic Microangiopathy manifested as proteinuria. Nasal septum perforation. Pulmonary hypertension. Dysphonia. GI ulcer. Hypersensitivity. ONJ. Laboratory abnormalities and Post Marketing – refer to package insert.
Date of preparation: September 2012
Full prescribing information should be viewed prior to prescribing.

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The Cover Shot

The Cannonball Tree 砲彈樹 (Couroupita guianensis 玉蕊科), named after its brown cannon ball fruits, originated from South America, but is commonly found in India at least for about 3000 years. It can grow up to a height of 25 metres.

These Cannonball Trees, outside their natural environment, have been planted in India, Thailand and other Buddhist countries very often and sometimes exclusively planted on temple grounds for religious reasons.

Its flowers are very large, distinctively orange, scarlet and pink in colour and highly fragrant, and form large bunches measuring up to 3m in length. They produce large spherical and woody fruits ranging from 15 to 24 cm in diameter, containing up to 200 or 300 seeds per fruit.

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Editorial

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It is well recognised that the incidences of malignancy are on the rise world wide. In Hong Kong there were 26,390 new cancer cases and 19,076 cancer deaths accounting for more than 30 % of mortality in the year 2010. Now about one in three individuals may suffer from some malignancies in their lifetime. There has been little progress in the systemic treatment since the introduction of platinol compound in the 70's and taxanes in the 80's. Similarly for radiotherapy treatment, the invention of linear accelerator and use of after-loading brachytherapy were the only advances in the last century. Fortunately, the treatment of malignancies has advanced tremendously in the last decade. The development of biological science and the ever-revolving computer technology have made modern cancer treatment no longer a "weapon of Mass Destruction" but rather like a "magic bullet" targeting against the tumour.

For systemic treatment, the development of various targeted drugs and molecular tests for predicting response have revolutionised the management of various cancers. Notable examples include the use of oral Tyrosine Kinase inhibitors in EGFR mutated Non Small Cell Lung Cancer, anti-HER2 agents in HER2 positive breast cancer and Rituximab in B-cell Non-Hodgkin Lymphoma. Some less common cancers like Gastrointestinal Stromal Tumour (GIST) and renal cell carcinoma, which are well known to be chemo- and radioresistant, can now be successfully treated with targeted drugs too.

Radiotherapy has long been accused of causing excessive side effects due to its indiscriminate damage to adjacent organs. But with the current precision high-tech radiotherapy machines such as RapidArc, Tomotherapy and Cyberknife, many of the once toxic treatments become feasible even in elderly patients. In fact more and more patients with oligo-metastasis are treated aggressively with radiotherapy, leading to a change in the treatment philosophy.

The better results of treatment make patients more willing to participate in clinical trials and therefore new drugs are released much faster than it has been. There are vast amounts of material to be covered in the area of oncology and we have the pleasure to have well trained oncology specialists who are working in the community to cover these important subjects. In this issue, lung cancer, breast cancer and lymphoma will be discussed. Other malignancies will be covered in a later issue. We trust after reading these articles, readers can have a deeper understanding in the management of these diseases.

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1st line treatment in EGFR mutation positive advanced NSCLC[1]

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EGFR = Epidermal Growth Factor Receptor
M+ = Mutation-positive
NSCLC = Non-Small Cell Lung Cancer

Reference
1. IRESSA HK Prescribing Information, Jun 2011

Abbreviated Prescribing Information
Presentation: Gefitinib film-coated tablet. **Indications:** 1) First line treatment of locally advanced or metastatic NSCLC who have activating mutations of the EGFR TK. 2) Treatment of locally advanced or metastatic NSCLC after failure of cytotoxic chemotherapy. Previous therapy should have included a platinum and a taxane. **Dosage:** 250mg once daily. Tablet can be dispersed in half a glass of drinking water (non-carbonated) without crushing it, stir until the tablet is dispersed and drink immediately. The liquid can also be administered through a naso-gastric tube. **Contraindications:** Severe hypersensitivity to any ingredients of this product; Pregnancy & lactation. **Precautions:** EGFR mutation assessment is recommended for first line treatment; Interstitial lung disease; Worsening of respiratory symptoms; Asymptomatic increase in liver transaminases. **Interactions:** CYP3A4 inhibitors e.g. itraconazole, ketoconazole, clotrimazole & ritonavir; CYP3A4 inducers e.g. rifampicin, phenytoin, carbamazepine, barbiturates & St John's wort; Drugs that increase gastric pH; Warfarin; Metoprolol. **Undesirable effects:** Diarrhoea, nausea, vomiting, stomatitis, elevations in alanine aminotransferase, anorexia, rash, asthenia. **Full local prescribing information is available upon request. APLHK.IRE.0611**

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Management of Early and Locally Advanced Lung Cancer

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I. Introduction

Lung cancer is the most common cancer in Hong Kong. In 2009, there were 4,365 new lung cancers (16.8% of all cancers) and 3,692 lung cancer deaths (28.8% of all cancers). The high mortality rate is partly attributed to the late presentation with about 45% of patients being diagnosed as stage IV metastatic incurable disease. Approximately 15-20% of lung cancers present with early or localised disease (Stage I/II) and surgical resection is the standard treatment with five-year survival rates of approximately 60-70%. However, the recurrence rate is 30-70%. Adjuvant radiotherapy is not recommended as it has a deleterious effect on survival at least in stage I and II disease with clear margins and low nodal disease, as shown in meta-analysis. About 25 to 30% of patients presented with stage III locally advanced disease. Concurrent chemotherapy combined and radiotherapy is the mainstay of treatment with surgery in selected patients.

II. Non surgical management of early lung cancer

A) Adjuvant chemotherapy after surgery in early lung cancer

Early lung cancer refers to stage I and II disease (Table 1). Surgery is the primary treatment. Adjuvant chemotherapy has been shown in a previous meta-analysis published in 1995 which suggested an overall survival benefit of 5% in 5 years after use of cisplatin-based chemotherapy[1]. This was confirmed in later studies as in the LACE study published in 2008 showing a 5.4% improvement in overall survival at 5 years for stage II (HR 0.83) and IIIA disease (HR 0.83) favouring cisplatinum and vinorelbine combination but there was no benefit in stage IA and IB disease[2].

Another study[3] has demonstrated a small benefit of adjuvant chemotherapy in stage IB disease with tumour size >4cm with overall survival of 99 months vs 77 months (P=0.43).

B) Stereotactic radiotherapy in early lung cancer

In the old days, patients who were unable to tolerate surgery due to old age, chronic lung diseases, heart diseases and other medical problems would be treated with conventional radiotherapy but the five year survival rates ranged from only 10-30% due to large volume of radiation with suboptimal dose of radiation.

With the introduction of various new radiotherapy techniques, higher doses of radiation can be given to early lung cancers with a smaller volume. Stereotactic body radiotherapy (SBRT) refers to the use of a high dose and highly conformal hypofractionated radiotherapy to treat small tumours. This technique is facilitated by accurate set up using imaged guided radiotherapy (IGRT) that is, taking images by the radiotherapy machines to confirm setup position. In addition, this technique can incorporate the use of breathing control during radiotherapy. Active breathing control (ABC) is a promising method for decreasing breathing motion during a course of radiotherapy. It involves the controlled temporary suspension of breathing in a reproducible phase of the breathing cycle. This device continues to monitor the patient's air flow and uses a computer-controlled valve to close the flow of air to the patient in a predetermined point of the breathing cycle, causing a controlled breath hold. The radiotherapy treatment machine is then turned on and the patient is irradiated only during the period when breathing is temporarily suspended in the same position in each treatment. The ABC device allows decreasing the treatment margin from 2-3cm under normal respiration to 5mm (Figure 1). This decreases the treatment volume for lung tumours that move with breathing, allows dose escalation and decreases treatment toxicities. Data suggested more than 80% 5 year local control can be achieved which is comparable to the standard treatment with surgery[4].

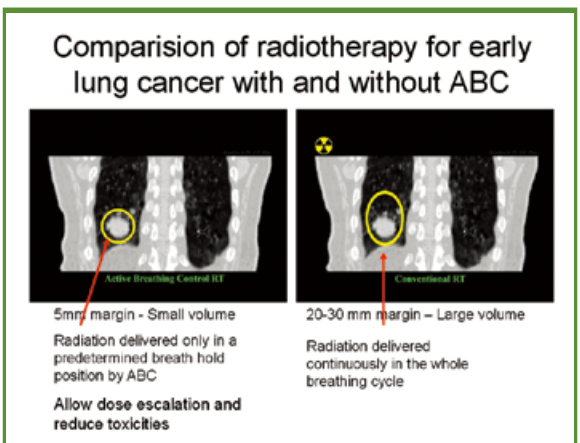

Figure 1. Comparision of radiotherapy for early lung cancer with and without Active breathing control (ABC)

Table 1. Lung cancer staging (ISALC 7th edition)

ISALC 7th edition	N0	N1 (ipsilateral peribronchial/ hilar/ intrapulmonary)	N2 (ipsilateral mediastinal and/or subcarinal	N3 (Contralateral mediastinal, scalene or SCF
T1a (≤2cm)	IA	IIA	IIIA	IIIB
T1b (>2-3cm)				
T2a (≤5cm)	IB			
T2b (>5-7cm)	IIA	IIB		
T3 (>7cm, invades chest wall, main bronchus 2cm distal to carina, separate tumour nodule in same lobe)	IIB	IIIA		
T4 (invades surrounding structures, separate tumour nodule in different ipsilateral lobe)	IIIA		IIIB	
M1a (Contralateral lung, pleural nodules/effusion)	IV			
M1b (distant)				

III. Treatment of locally advanced lung cancer

This refers to stage IIIA (T1-3N2, T3N1, T4N0, T4N1) and stage IIIB (T4N2, T1-4N3) disease. PET-CT scan is required for accurate documentation of disease extent and staging. MRI brain should be considered for patients with symptoms suggestive of brain metastasis. This group of disease presents a management challenge for clinicians. It can be attributed to the heterogeneity of locally advanced stage III disease (Table 1). Patient may have stage IIIA disease clinically with a small tumour suspicious of involvement of the pleura or a small suspicious mediastinal node that curative surgery can be offered followed by adjuvant therapy. On the other hand, patients may have T4 disease with a bulky tumour invading mediastinum and bilateral bulky N3 supraclavicular lymph nodes with poor medical condition for which only palliative treatment can be considered. Therefore this group of disease should be assessed by a multidisciplinary team with diversify treatment options.

Treatment options include:

- Surgery followed by post-op chemotherapy +/- radiotherapy (microscopic N2 disease)
- Definitive chemoradiation +/- induction chemotherapy +/- consolidation chemotherapy
- Pre-op chemoradiation followed by surgery
- Palliative treatment with radiotherapy, chemotherapy, target therapy or their combinations.

A) Definitive chemoradiation

Clinical and patient factors may influence choice of concurrent chemoradiation. These include age older than 75, weight loss, poor performance status, poor pulmonary function and comorbidities.

Definitive chemoradiation is the standard treatment modality for inoperable stage III lung cancer. Chemotherapy can be given concurrently with radiotherapy (concurrent chemoradiation) or given sequentially with radiotherapy (sequential chemoradiation). A Cochrane meta-analysis demonstrated a significant 14% reduction in the risk of deaths with concurrent chemoradiation compared with sequential treatment.

Another meta-analysis[5] published by the NSCLC Collaborative Group in 2010 comparing concurrent chemoradiation with sequential chemoradiation consisted of 6 randomised controlled trials including 1205 patients with median follow up of 6 years showed overall survival benefit of 5.7% at 3 years; 4.5% at 5 years (HR 0.84, p=0.004) favouring concurrent chemoradiation. However, concurrent chemoradiation has increased acute grade 3/4 oesophageal toxicity from 4% to 18% (RR 4.9, p<0.001). The most commonly used chemotherapy regimen in concurrent chemoradiation is cisplatinum combined with either one of etoposide, vinorelbine and paclitaxel. Radiotherapy usually consists of 60Gy to 63Gy given in 30 to 35fractions over 6-7 weeks.

B) Induction chemotherapy followed by chemoradiation

Induction chemotherapy was used before definitive chemoradiotherapy for both improving systemic control and shrinking down the tumour before radiotherapy. However, this was proved to have no survival benefits over chemoradiation alone in a randomised controlled comparison by Vokes et al[6]. The median overall survival was 12 months (induction chemotherapy followed by chemoradiation) vs 14 months (concurrent chemoradiation). There was no significant differences in nonhaematological toxicity between the treatment groups. The incidence of grade 3/4 oesophagitis was very high (about 30%) in both arms. Patient selection may have influenced the median survival in this trial. Approximately 25% of the patients enrolled had weight loss in excess of 5%, which has been shown to be a poor prognostic factor.

C) Consolidation chemotherapy after chemoradiation

A three-arm study[7] compared sequential chemotherapy and radiotherapy, induction chemotherapy followed by concurrent chemoradiation, and concurrent chemoradiation followed by consolidation chemotherapy was published in 2005. In the sequential and induction arms, paclitaxel and carboplatin were administered for two cycles prior to radiation therapy. The median survival was 16.3 months in the consolidation arm, 12.7 months in the induction arm, and 13.0 months in the sequential arm. The induction and consolidation arms were associated with greater toxicity. The incidences of grade 3/4 oesophagitis and pulmonary toxicity were highest in the consolidation arm (28% and 16%, respectively). Although the study was not powered for direct comparison of the three treatment arms, the prolonged median survival for concurrent treatment followed by consolidation chemotherapy adds support to the argument that providing the definitive treatment upfront followed by systemically active doses of chemotherapy is the preferred therapeutic approach in stage III NSCLC.

The Southwest Oncology Group (SWOG) study 95045 also supported the use of consolidation chemotherpay after definitive chemoradiation in patients with stage IIIB NSCLC. In this trial, consolidation with 3 cycles of docetaxel following concurrent cisplatin-etoposide and radiotherapy extended median overall survival from 15 months to 26 months.

However, not all studies showed similar benefits of consolidation chemotherapy. In the Hoosier Oncology Group (HOG) LUN 01-24 study[9], consolidation with docetaxel after cisplatin-etoposide and concurrent radiation did not have any survival advantage over cisplatin-etoposide and concurrent radiation alone in patients with stage III inoperable NSCLC. The median survival time was 21.2 months for the docetaxel arm compared with 23.2 months for the observation arm (P = .883). The consolidation arm was associated with increased toxicities. Grade 3 to 5 toxicities during docetaxel included febrile neutropenia (10.9%) and pneumonitis (9.6%); 28.8% of patients were hospitalised during docetaxel (v 8.1% in observation arm), and 5.5% died as a result of docetaxel.

D) Pre-op chemoradiation followed by surgery

The RTOG/Intergroup group conducted a study comparing pre-op concurrent chemoRT (45Gy) followed by lobectomy/pneumonectomy vs concurrent chemoRT (61Gy). A lower dose of radiation was used in the preop chemoRT arm is to minimise toxicities. There was suggestion of improvement in progression free survival with the pre-op chemoRT arm (12.8 months) vs the chemoRT arm (10.5 months). There was no significant difference in overall survival, 23.6 months in the pre-op RT arm vs 22.2 months in the concurrent chemoRT arm[10].

IV) Conclusion

Surgery is the standard treatment for early stage I and II non small cell lung cancers. Adjuvant chemotherapy will be considered in stage II disease and may be considered in stage IB disease with large tumour (>4cm). For patients refusing surgery or not suitable for surgery because of medical comorbidities, stereotactic radiotherapy will be a good option for those with smaller tumours. Long term results are pending confirming its efficacy comparing with surgery.

Concurrent chemotherapy and radiotherapy is the standard treatment method for locally advanced stage III disease. In selected cases, induction chemotherapy and/or consolidation chemotherapy can be considered.

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Treatment for Stage IIIB and IV Non-small Cell Lung Carcinoma

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Dip. Epidemiology & Applied Statistics (CUHK), MD (HK)
Specialist in Clinical Oncology

Dr. Sin-ming CHOW

Introduction

Carcinoma of the lung remains the most common cancer in Hong Kong. It is the leading cancer sites in Hong Kong in both genders: 21% in males and 12.5% in females (Hong Kong Cancer Registry 2010). The combinations of poor prognostic factors such as diagnosis at advanced stages (80-90% stage IIIB – IV), old age with medical co-morbidities, poor response to conventional chemotherapy and suboptimal radiation therapy technique result in its notorious name of a lethal disease.

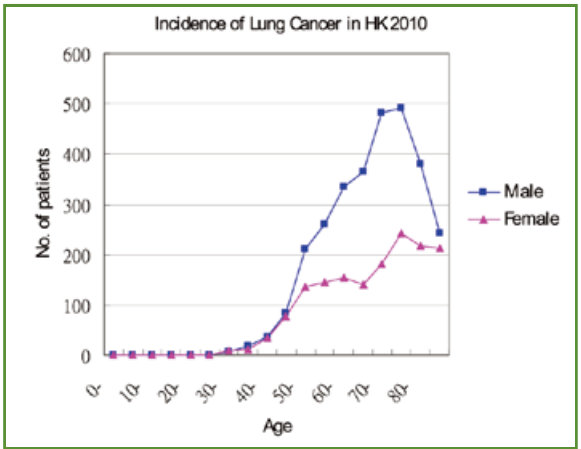

Figure 1. The incidence of male and female lung cancers in Hong Kong.

In Asia, the lung cancer incidence ranks number one in males and number three in females according to the World Health Organization[1]. East Asians have a higher proportion of never-smokers and a better overall survival compared with Caucasians. The female gender, in a meta-analysis, is an independent prognostic factor for better survival.

In recent years, rapid development in molecular biology, radiotherapy delivery and chemotherapy opened possibilities of individual treatment of non-small cell lung cancer (NSCLC). The commonest type of NSCLC is adenocarcinoma (about 70-80%). For stage IIIB and IV disease (any T4 or N3 or M1 disease), they are commonly grouped together to guide treatment.

Importance of pathology and tumour directed treatment

The simple classification of carcinomas of the lung into small cell and non-small cell carcinomas no longer fits the up-to-date management of lung cancer. Adequate biopsy with molecular studies serves to guide further treatment. Subtyping of NSCLCs and mutation analysis of specific receptors guides the choice of targeted therapy[2,3]. The advances in CT scan screening with guided biopsies, endobronchial ultrasonography (EBUS) and staging by new imaging technique such as PET-CT scan made possible earlier diagnosis and prompt treatment. Studies for low dose CT screening prove that the disease can be highly curable by surgery. However, lung cancer is often diagnosed at an advanced stage in underdeveloped countries.

Molecular genetics is advancing at a high speed. The discovery of association of genetic changes in tumours in response to targeted treatment facilitates specific treatment selection.

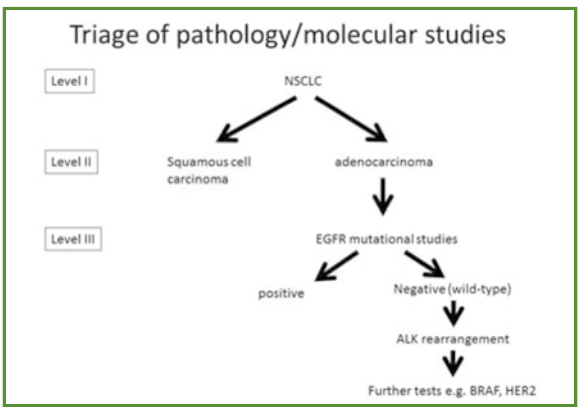

Figure 2. Triage of pathology/molecular studies in NSCLC

Chemotherapy

In the past, chemotherapy and radiotherapy was the mainstay of treatment. Chemotherapy using a doublet of platinum agents with other drugs is most effective with tolerable side-effects. In the past decade, new drugs such as paclitaxel, docetaxel, gemcitabine and pemetrexed are used with success in non-small cell lung cancers.

'Watch and wait' approach versus 'maintenance' approach

As a result of cumulative toxicity of chemotherapy, patients can only receive a limited number of cycles of

chemotherapy. Some specific drugs will not cause severe suppression of bone marrow and can be administered easily in outpatient settings. Therefore, elderly patients are able to receive chemotherapy with good tolerance. With the same virtue, the concept of maintenance is able to be implemented.

Now, various maintenance approaches can be adopted in specific scenarios. For example, continuation of less toxic chemotherapy (pemetrexed) [4]or switching to targeted agents as maintenance (e.g. bevacizumab, cetuximab) can be considered in selected cases.

Targeted treatment

EGFR mutation

Mutations in the tyrosine kinase domain of Epidermal Growth Factor Receptor (EGFR) were found to be correlated with good responses to tyrosine kinase inhibitors (TKI). EGFR mutations are more common in non-smokers with adenocarcinoma. In the Chinese population, about 50% of NSCLCs are EGFR mutation-positive. Older age and acinar predominant subtype of adenocarcinomas are independent predictors of EGFR mutations in a Chinese study [3].

Studies confirmed that TKI is superior to chemotherapy in terms of progression free survival (PFS). Quality of life studies confirmed a global improvement after TKI treatment. Gefitinib and erlotinib are currently the available TKIs[5,6]. New irreversible erbB family blockers showed promising results. First line afatinib in LUX-Lung 3 trial improved the PFS compared with chemotherapy. The side-effects of TKIs are generally mild e.g. rash, paronychia, and diarrhoea. Interstitial lung disease (ILD) was reported to be around 1 – 5%. ILD causing mortality varies from about 1 to 3%.

The approximate median time to progression in EGFR mutation positive patients is 9 to 12 months. To circumvent this acquired resistance, various approaches are being explored. Case studies and small reports revealed that afatinib and cetuximab led to regression in some TKI-resistant tumours.

EML4-ALK translocation

EGFR mutation negative (Wild type) tumours can be submitted for ALK rearrangement testing. The patients have younger age and are usually non-smokers or light-smokers. Crizotinib was proven to have better PFS and overall response rate compared with single agent chemotherapy[7].

HER2 mutation

In a Japanese study, 3% of patients had HER2 mutations. Recently, HER2 gene amplification was recognised as one of the mechanisms for acquired resistance to EGFR-TKI in EGFR mutated patients. Initial case reports demonstrated a good clinical response to HER2 inhibitors.

Anti-angiogenesis

Tumours having a high microvascular density and expression of vascular endothelial growth factors are associated with poorer prognosis. Exploration to target on antiangiogensis are being undertaken. A meta-analysis confirms that platinum based chemotherapy, when combined with bevacizumab, an anti-angiogenetic agent, increases the PFS and overall survival (OS)[8]. The effect of bevacizumab was higher in adenocarcinoma and patients with less weight loss (≤5%).

Radiotherapy

The use of radiotherapy (RT) in local tumours can produce eradication of the tumour and cause symptom relief. RT to bone and brain metastases is effective. For patients with oligometastases, local RT to the central nervous system or limited systemic disease can prolong disease control by TKIs in EGFR mutants or ALK gene rearrangement positive NSCLCs [9].

Supportive treatment

It cannot be ignored that certain surgical or medical supportive measures can improve quality of life and prolong overall survival. Zoledronic acid can decrease skeletal related events for patients with bone metastases. Recently, denosumab (a human anti-RANKL monoclonal antibody) was also found to be effective and can prolong overall survival in patients with metastatic lung cancer [10].

Conclusion

NSCLC treatment is advancing at a great speed in recent years. The survival and quality of life are improved. Various new drugs are currently under investigation. New approaches and new thoughts on this disease would be awaited.

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Surgical Treatment for Early Breast Cancer

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Surgical treatment for early breast cancer

Surgery is the mainstay of treatment for early breast cancers for decades. The conventional Halsted's radical mastectomy had effectively achieved a good local control of the breast cancer and even achieved a cure for some of the early & localised disease. However in patients with occult micrometastasis, systemic recurrence could still occur after radical mastectomy. It was hypothesised by Bernard Fisher[1] that breast cancer was primarily a systemic disease and surgical treatment had little impact on the survival of breast cancer patients. Today we know "local control cannot cure all patients, but no patients are cured without it". Therefore effective local treatment should be complementary with the systemic treatments.

Surgery for early breast cancer

Stage 0, I & II breast cancer disease are considered as early breast cancers and possible treatment options will include either breast conserving therapy (BCT) or modified radical mastectomy (MRM) with or without breast reconstruction.

Since the late 19th century, radical mastectomy and the subsequent MRM were the most effective surgical treatment for breast cancers with significant reduction of the local recurrence rate to as low as 6%. It involved removal of the breast, underlying pectoral muscle (in radical mastectomy) and also lymph nodes up to level 3 of the axilla. During the period of 1970-80s, a series of large scale studies were undertaken to evaluate the effectiveness and safety of BCT versus MRM. BCT includes complete removal of the tumour with a rim of unaffected tissue (margin) followed by local breast irradiation. When compared with MRM, BCT achieved the same survival rate and almost similar local control rate but it spared the patients from morbidity of mastectomy. The first study was reported by Veronesi U. in 1981[2]. The subsequent studies also demonstrated similar findings. Therefore BCT is now the first choice of breast cancer surgery and is feasible in about two-thirds of patients in USA.

Patient selection for breast conserving therapy

During the whole regime of BCT, our aim is to minimise the chance of local or ipsilateral breast tumour recurrence (IBTR). The prognostic significance of IBTR has received recent focus with evidence linking local recurrence with an increased risk of distant metastasis and mortality [3]. The risk of distant metastasis was 3.41 times greater in patients who experienced IBTR. The adjuvant radiotherapyhad reduced the risk of IBTR to about 0.5–2% per year and the higher risk was demonstrated in the first few years[4] and a median time to IBTR of 36 months[5]. The individual patient's risks can vary widely depending on the patient, pathological and treatment characteristics. Young age (< 30-35 year old), lymphovascular invasion, negative oestrogen receptor status, skin involvement, nodal stage, multifocality, positive margins and omission of RT are factors that have been demonstrated to be associated with increased risk of IBTR. Therefore patient selection is important. Unfortunately some tumour characteristics cannot be obtained until the first attempt of operation had been undertaken, a number of patients might need second operations for the re-excision for a further margin or even mastectomy.

There are two absolute contraindications to BCT: either a clear margin cannot be achieved or inability to conduct a complete radiotherapy to the breast. Therefore, patients requiring radiotherapy in their first or second trimester of pregnancy, patients with wide spread multifocal disease or local recurrence of breast cancer after their previous BCT (irradiated breast) will not be suitable candidates. Patients with collagen, vascular or autoimmune diseases such as scleroderma, may have overwhelming skin reactions to radiotherapy and cannot tolerate and finish the required regimen. They should be considered for mastectomy. Cosmetic outcome is a relative concern. It is not sensible to conserve a markedly disfigured breast after removal of a relatively large tumour from a relatively small breast. This is the most common indication for mastectomy. However, with a better oncoplastic surgical technique or the conduction of a neoadjuvant chemotherapy (chemotherapy before operation) aiming to shrink down the tumour, a quality BCT with a good margin in parallel with a good cosmetic result can be achieved in patients with large tumours. Oncoplastic surgery defines the appropriate adequate surgery to extirpate a cancer in the breast combined with partial or total reconstruction as well as immediate or delayed reconstruction with access to a full range of techniques to correct excision defects.

Patients indicated for mastectomy

When local control cannot be achieved with BCT (even after the neoadjuvant chemotherapy), patients will need mastectomy. Although the modified radical mastectomy has similar survival benefits compared with BCT in breast cancer patients, important differences in other outcome parameters have been spotted.[6] It include a lower body image and a significant change in lifestyle related to clothing choice for patients with mastectomy. Therefore reconstruction should be offered to women who have undergone mastectomy and this may help to improve their postoperative psychosocial outcomes. In general, a higher body image is observed in women who have had some reconstructive procedures than women who haven't. Options for reconstructive techniques following mastectomy vary with the surgeons' preferences and the availability of expertise. It is mainly classified into: immediate vs. delayed, autologous tissue vs. implants. Immediate reconstruction does not increase the incidence of surgical complications, or influence the administration of postoperative chemotherapy[7]. Autologous tissue reconstruction tends to achieve a significantly better cosmetic and long term result when compared with implants for post-mastectomy reconstruction.[8] There are many types of autologous tissue reconstructions. e.g. pedicled transverse rectus abdominis myocutaneous [TRAM] flap, free TRAM flap, latissimus dorsi flap. A skin-sparing mastectomy is particularly well suited for immediate TRAM reconstruction and has been increasingly utilised without adverse impact on oncologic outcomes.[9] Breast reconstruction can have an impact on the psychosocial well-being of mastectomy patients. Careful individualisation in the preoperative setting allows selection of the appropriate reconstructive technique to optimise surgical, cosmetic and psychosocial outcomes. (fig 1 and 2)

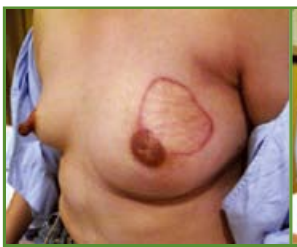

Fig 1: Extensive multicentric DCIS at upper outer quadrant of left breast with skin & partial areolar sparing mastectomy and pedicle TRAM reconstruction.

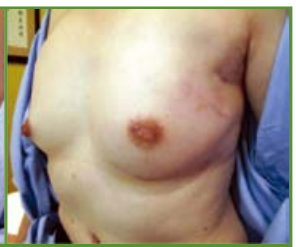

Fig 2: History of L breast DCIS with BCT in 2006. Ipsilateral breast tumour recurrence with DCIS detected in 2012 and was further treated with skin & areolar sparing mastectomy and pedicle TRAM reconstruction

Management of the Axilla

There has been a significant change in the approach of axillary management in women with clinically node-negative breast cancers. It was a routine to have radical or, later, the modified radical mastectomy as an essential part of breast surgical treatment for breast cancer. They included axillary clearance of lymph nodes from level I to level III. They aimed for the staging of the disease and for a better locoregional control in case of metastatic involvement of lymph nodes. Although the NSABP B04 trial had demonstrated that, in women treated with mastectomy alone, axillary dissection did not contribute to survival[10], we still continue to adopt this for staging and local control. It ended up that all node negative patients would have an unnecessary operation and be exposed to the potential risks of related morbidities in the axilla. This is even more important in the current trend of earlier diagnosis of breast cancers which have a lower risk of axillary node involvement because more patients attend the breast screening programme and are aware of breast cancers. Nowadays the sentinel node biopsy (SNB) has effectively assisted us to obtain the important information about their axilla nodal status. The sentinel node is a reproducibly identifiable node (or nodes) that drains the breast and predicts the status of the remaining axillary nodes. It was first studied and reported by Giuliano et al.[11] Its clinical application and accuracy were further confirmed with a few large scale studies & reviews[12] and today SNB is widely accepted as a reliable minimally invasive technique for staging of the axilla in women with T1–T3, clinically node-negative breast cancers. Contraindications to the procedure are uncommon and include pregnancy and lactation, and inflammatory and other T4 breast cancers.

Although most of the patients with confirmed axillary lymph node metastasis after SNB will have axillary dissection, its further treatment benefits and perhaps survival, especially with multimodality therapy, are now being questioned and studied. With result of the ACOSOG Z11 trial is a randomised controlled trial[13] in women with limited SN involvement (≤2 involved nodes), removal of the SNs followed with the subsequent systemic therapy and the loco-regional radiation therapy which is part of BCT, is recommended as a similarly effective method of maintaining local control because the further axillary dissection in this subgroup did not demonstrate any benefit in survival but just increase the morbidity of treatment. For women with greater numbers of involved lymph nodes and those who have undergone mastectomy, the safety of this approach is uncertain, and axillary dissection remains the standard of care. [14]

Conclusion

Recent advancements in the locoregional surgical treatment of early breast cancers has achieved a better outcome in terms of the survival and lessening of the morbidity of previous compulsory mutilating procedures. The new methods such as oncoplastic techniques in breast conserving therapy, reconstruction after mastectomy and sentinel lymph node biopsy have been well studied and confirmed to improve quality of life and cosmetic outcome of the patients.

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Dermatological Quiz

Dermatological Quiz

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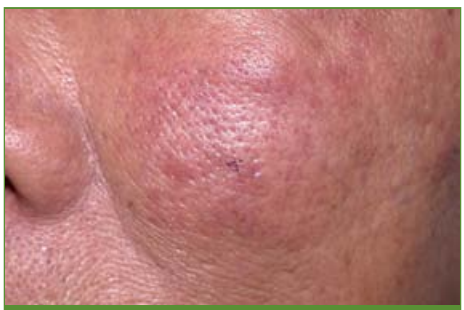

Fig. 1a: Erythematous plaques over left cheek

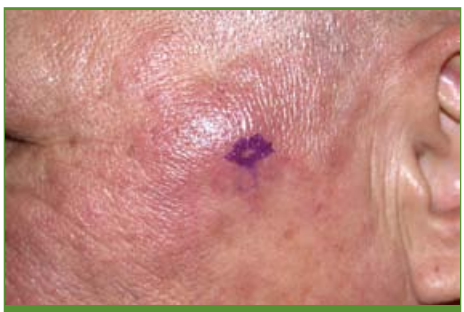

Fig. 1b: Close-up of the ill-defined plaque

This 76-year-old man presented with pruritic, slow growing, erythematous, indurated and ill-defined plaques over his left cheek (Fig. 1a & 1b) and left temporal area for three years. Past health: he had history of bilateral lacrimal swellings one year ago (with biopsy done but the diagnosis was unknown). He also had multiple medical diseases including chronic obstructive pulmonary disease, hypertension, hyperlipidaemia, ischaemic heart disease, minor stroke and gout. His skin lesions had been treated with topical steroids but without response. Skin biopsy showed confluent perivascular and periadnexal lymphoid infiltrates. The infiltrates comprised of small lymphocytes, plasma cells, histiocytes, and a few eosinophils. The lymphoplasmacytic infiltrate was accompanied by deposition of sclerotic collagen in the dermis. Blood tests showed an elevated serum IgG level: 2340 mg/dL (Normal range: 700 to 1600mg/dL). Further analysis showed elevated serum IgG4 level: 1060 mg/dL (Normal range: 0 to 135mg/dL).

Questions:

1.What are your clinical differential diagnoses before the skin biopsy?
2.What are your histopathological diagnoses after the skin biopsy?
3.What further investigations should be done to establish the diagnosis?

(See P.33 for answers)

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Adjuvant Treatment for Early Breast Cancer

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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 May 2013.

Adjuvant treatment aims to kill off the residual microscopic tumour cells (after surgery) that may have been left in loco-regional areas or disseminated to other body parts. The role of adjuvant treatment in reducing the risk of recurrence and cancer-specific mortality of breast cancers has long been established[1]. After breast cancer surgery, there are two main questions that need to be answered: who needs adjuvant treatment and what kind of adjuvant treatment is necessary? To answer these questions, we need prognostic tools to evaluate the recurrence risks and predictive factors to individualise systemic treatment.

Prognostic Factors

Whilst the AJCC/UICC anatomical TNM staging system is widely used for clinical statistics and studies, the primary tumour size and nodal information alone are often inadequate for prognostic purposes (Table 1). Clinical tools like Adjuvant Online have also been developed to facilitate decision of systemic adjuvant therapy by integrating these clinico-pathological factors. Expensive multigene assays (e.g. Oncotype Dx) may sometimes be needed to evaluate the benefit of additional chemotherapy in ER-positive node-negative breast cancer patients who are already adequately treated with adjuvant hormonal therapy alone.

Table 1. Important prognostic factors for breast cancers

1.	primary tumour size
2.	nodal involvement status
3.	histological type and grade
4.	resection margins
5.	presence of lymophovascular invasion (LVI)
6.	hormonal receptors (Oestrogen Receptor [OR] and Progestogen Receptor [PgR]) status
7.	HER2 (Human Epidermal Receptor 2) receptor status
8.	proliferation markers such as the Ki67 labelling index
9.	multigene assay (e.g. Oncotype DX)

Predictive factors for Systemic therapy and Personalised Treatment

Breast cancer is no longer considered as a single disease. Increasing numbers of subtypes with different natural histories and responses to treatment are continuously recognised[2]. These subtypes can be defined by complex genetic array tests, but, in practice clinicians will use approximations to this classification basing on the commonly available immunohistochemical receptor tests.

The common clinical subtypes with their own implications on systemic adjuvant treatment are shown in Fig 1. This approach is the basis of modern personalised treatment. The use of proliferation markers (Ki67) can further help to identify endocrine-responsive tumours which are slow growing and not responding well to chemotherapy.

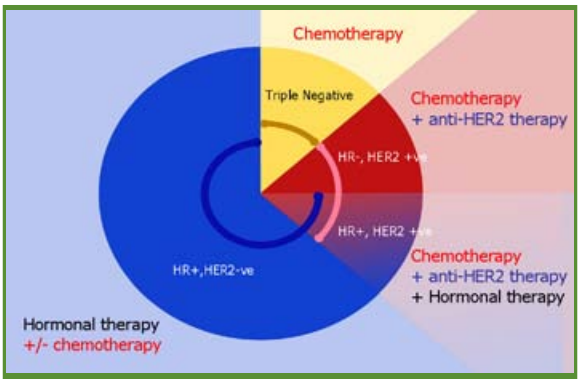

Fig 1. With the commonly available hormonal receptor (HR) and HER2 receptor status, various subtypes with different implications on systemic treatment can be identified. Some tumours will respond to both hormonal therapy and anti-HER2 targeted therapy (shown as the overlapped part of the blue and red sections). Fifteen percent of tumours are negative to all three receptor tests and are hence called Triple Negative breast cancers. This is a particularly aggressive subtype.

Before recommending an adjuvant treatment plan, other clinical and social factors like age, medical co-morbidities, patient preference and family planning etc also need to be considered. A multidisciplinary meeting may facilitate the decision process too.

Systemic Adjuvant Therapy

Systemic adjuvant therapy is needed if there is a substantial risk of distant recurrences and mortality. The choice of therapy will depend on the clinical subtypes as described in Table 1.

A. Adjuvant Hormonal Therapy

Since the early 1980s, adjuvant therapy with tamoxifen has been the standard approach to reduce the risk of recurrences in hormonal receptor positive breast cancers. Long-term data have demonstrated that the use of tamoxifen can reduce recurrence and mortality by more than 30% [1]. In premenopausal patients, tamoxifen (20 mg daily for 5 years) remains the standard therapy. However, recently presented randomised study suggests that 10 years treatment may be needed for high risk patients[3]. Tamoxifen is usually well tolerated but there are two rare potentially life-threatening complications-endometrial cancer and thromboembolism. Annual gynaecological examinations are therefore advised for these patients. Another important precaution is to avoid the use of drugs with strong CYP2D6 inhibition, such as some selective serotonin reuptake inhibitors (SSRIs). This is because tamoxifen needs to be metabolised via CYP2D6 enzyme into endoxifen, its primary active metabolite. Drugs inhibiting CYP2D6 may adversely affect the function of tamoxifen.

Aromatase inhibitor (AI) is a new class of oral hormonal drug which only works in postmenopausal women. There are only minor differences between the three available AIs, namely, Anastrozole, Letrozole and Exemestane. After menopause, most of the body's oestrogen is produced in peripheral tissues through the enzyme aromatase. AI blocks the action of aromatase, hence further lowers oestrogen levels in the body. AIs have been proven to be superior to tamoxifen and they can be either used upfront for 5 years or sequentially after 2–3 years of tamoxifen. Whether a longer duration of AIs over 5 years will give better clinical benefit remains to be explored. Although AI will not increase the risk of endometrial cancer and thromboembolism, it may cause mild joint pain and increase the risk of bone loss. Regular weight bearing exercises, vitamin D and calcium supplement will help to prevent bone loss. Monitoring with DEXA (dual energy X-ray absorption) scan is also recommended to allow early treatment of osteoporosis. Bisphosphonates (e.g. zoledronic acid) and Denosumab, a new generation monoclonal antibody that binds to a protein involved in the function of osteoclasts, may also be considered in high risk patients to prevent further bone loss.

B.Adjuvant Chemotherapy

Adjuvant chemotherapy is recommended in patients with endocrine non-responsive tumours and high risk endocrine-responsive tumours in which hormonal therapy alone is inadequate. There are a large number of acceptable chemotherapy regimens and the choice depends on the predicted risk, treatment efficacy, toxicities, cost, convenience, patient's age, co-morbidities and oncologist's own preference. Anthracyclines remain the backbone of many regimens, though anthracycline-free regimens with similar efficacy have been developed. The more potent third-generation regimens usually include both taxanes and anthracyclines, in either concurrent or sequential fashion.

For relatively low risk node-negative patients, 4 cycles of chemotherapy may be adequate; for node-positive or high risk node-negative patients, 6 to 8 cycles are usually needed. Prophylactic granulocyte colony-stimulating factor (G-CSF) may be necessary for regimens with high risk of neutropenia or dose-dense regimens (given in biweekly fashion). Apart from neutropenic fever, other important side effects may include premature menopause, infertility, taxane-related neuropathy, cardiotoxicity and a very small risk of leukaemia.

C. Adjuvant Anti-HER2 Targeted Therapy

HER2 (Human Epidermal Receptor 2) is a receptor protein found on the surface of cells. When the human epidermal growth factor, which occurs naturally in the body, attaches itself to HER2 receptors on breast cancer cells, it can stimulate the growth of cells. Around 20% of breast cancers have over-expression of these HER2 receptors and HER2 positivity is associated with aggressive disease, high risk of relapse and poor survival.

The development of anti-HER2 targeted therapy signifies a major breakthrough in breast cancer management[4]. Trastuzumab is a monoclonal antibody that binds to the HER2 receptor, interfering with its function and hence inhibiting cell growth. When used in combination with chemotherapy, adjuvant trastuzumab lowers both the hazard of recurrence and the hazard of death by around 40%. The optimum duration of adjuvant trastuzumab is 1 year, being given in 3-weekly intervals. Though trastuzumab can be started after completion of chemotherapy, it may be more effective if used concurrently with chemotherapy. This strategy also helps to shorten the whole treatment course. The extra side effects of trastuzumab are limited but cardiac monitoring during therapy is needed because of its potential cardiotoxicity which, however, is usually mild and reversible.

Adjuvant Radiotherapy

Radiotherapy can generally reduce the risk of local recurrence by about two-thirds. Long term follow-up has also shown that one death is prevented for every four recurrences and these benefits are not substantially reduced by side effects[5].

Patients undergoing breast conserving surgery are recommended whole breast radiotherapy (usually with boost to the tumour bed) and long term studies have shown equivalent survival with patients undergoing mastectomy. Accelerated partial breast irradiation (APBI) by various techniques is an attractive approach to shorten the overall treatment time and has yielded promising early results. However, this approach is only suitable for selected low risk patients and is not popular in Hong Kong at present.

Adjuvant radiotherapy is also recommended for high risk post-mastectomy patients, including those having four or more positive axillary nodes, 1–3 positive axillary nodes with additional risk factors or very close resection margins. Regional irradiation of supraclavicular lymph nodes is often added in patients with axillary node involvement. However, since relapses in the axillary or internal mammary region are uncommon, additional coverage of these sites would only be considered if residual tumour is suspected.

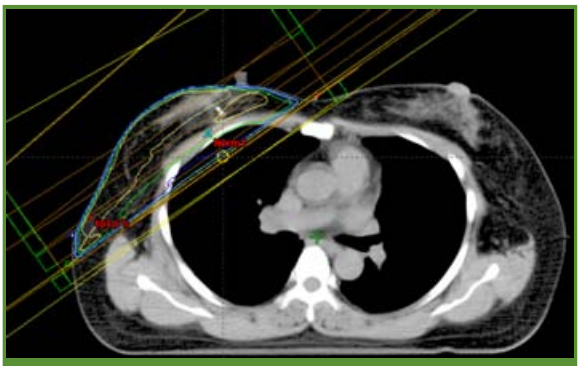

Fig 2. Tangential opposing beams are used to spare underlying lung tissues during adjuvant radiotherapy for breast cancer. Further customised shielding is often added to protect the heart for left-sided treatment.

Sequencing of Adjuvant Treatment

For patients requiring different modalities of adjuvant therapies, chemotherapy with or without anti-HER2 agent, is usually started upfront, to be followed by radiotherapy and hormonal therapy if necessary. Whilst concurrent use of chemotherapy with either radiotherapy or hormonal drugs is not recommended, anti-HER2 targeted therapy can be continued safely during radiotherapy or hormonal therapy.

Our prior discussion focuses on post-operative adjuvant therapy but neoadjuvant (pre-operative) chemotherapy or hormonal treatment with or without Trastuzumab is increasingly used to downsize tumours before surgery. This approach is especially useful for locally advanced tumours or tumours with borderline size for breast conserving surgery.

Conclusion

Adjuvant systemic therapy and radiotherapy are integral parts of modern breast cancer management. A careful risk assessment and personalised approach to individualise treatment help to improve the clinical outcome and minimise treatment toxicity.

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MCHK CME Programme Self-assessment Questions

Please read the article entitled "Adjuvant Treatment for Early Breast Cancer" by Dr. Tsz-kok YAU 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 May 2013. 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. Different subtypes of breast cancer require different approaches in adjuvant therapy.
2. Multigene assay (e.g. Oncotype DX test) is needed in all breast cancer patients to guide adjuvant treatment.
3. Tamoxifen may slightly increase the risk of endometrial cancer and thromboembolism.
4. Aromatase inhibitor, a newer class of oral hormonal drug for breast cancer, works in both premenopausal and postmenopausal patients.
5. Aromatase inhibitor may increase the risk of osteoporosis.
6. Adjuvant chemotherapy is only needed in patients with endocrine non-responsive tumours.
7. Prophylactic granulocyte colony-stimulating factor (G-CSF) may be necessary for chemotherapy regimens with high risk of neutropenia.
8. HER2(Human Epidermal Receptor 2) positive breast cancers are more aggressive and have a higher risk of relapse.
9. Cardiac monitoring is needed for patients receiving anti-HER2 targeted agents (Trastuzumab).
10. All post-mastectomy patients should require post-operative radiotherapy to reduce the risk of local recurrence.

ANSWER SHEET FOR MAY 2013

Please return the completed answer sheet to the Federation Secretariat on or before 31 May 2013 for documentation. 1 CME point will be awarded for answering the MCHK CME programme (for non-specialists) self-assessment questions.

Adjuvant Treatment for Early Breast Cancer

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Answers to April 2013 Issue

Angioplasty and Stenting for Intracranial Atherosclerotic Stenosis: Position Statement of the Hong Kong Society of Interventional and Therapeutic Neuroradiology

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

Metastatic Breast Cancer – The Extended Marathon

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Introduction

Breast cancer is the most common cancer in women worldwide. An estimate of 1.64 million new cases and nearly 425,000 breast cancer deaths were noted across the world in 2010. In Hong Kong, breast cancer ranks first in terms of female cancer incidence (3,014 new cases) and ranks third for female cancer mortality (561 breast cancer deaths) in 2010. About 5-10% of breast cancers are metastatic at diagnosis. For patients with early breast cancers who have been previously treated with curative intent, about 15% to 20% of node-negative disease and 20% to 40% of node-positive disease will relapse. In the 1970s, only 10% to those who were diagnosed to have metastatic breast cancer were alive at 5 years. Today, the median survival of metastatic patients is around 2 to 3.5 years, and up to 25-35% can survive for 5 years[1].

Metastatic breast cancer can occur months or years after definitive treatment for earlier stage disease. The most common metastatic sites are bone (60-80%), liver (50%), lung (60-70%) and brain (10-20%). Metastases can be found either through routine follow-up tests or when symptoms occur, e.g. bone pain, shortness of breath, cough, abdominal pain, and fatigue. Although there are an increasing number of treatment options available, the vast majority of metastatic breast cancers is incurable. Nevertheless, it is amenable to treatment. The goal of treatment is to slow down or stop the growth of the tumour, thus relieving the cancer-associated symptoms and improving the quality of life, and hopefully to prolong survival in some patients. Contemporary treatment approach to metastatic breast cancer is to treat it as a chronic condition and keep it under control for as long as possible.

Assessment and Re-staging

Most women with metastatic breast cancer present with progressive symptoms over weeks or months. These symptoms may be non-specific and difficult to distinguish from less sinister problems. Initial assessment should include a complete history and physical examination, haematology and biochemistry tests, serum tumour markers (e.g. CA 15.3, CEA) and imaging of the bone, chest, abdomen and brain. Since the biology of the metastatic disease may be different from the primary tumour, biopsy of the metastatic lesion is recommended, whenever technically feasible. Special immunohistochemical staining will be performed on the biopsy specimen to evaluate the hormonal receptor (oestrogen receptor ER, progesterone receptor PR) and HER2 status of the current metastatic disease, as this will guide the use of hormonal therapy and anti-HER2 therapy. If re-biopsy from the metastatic lesion is not possible, the hormonal receptor and HER2 status of the original primary breast tumour will be used to guide treatment selection. Realistic treatment goals should be discussed with the patient's preference taken into account. Numerous factors should be considered before coming up to a personalised therapy (Table 1).

Table 1. Factors to consider in deciding treatment options for metastatic breast cancer

Disease-related factors	Patient-related factors
Previous therapies and response	Menopausal status
Disease-free interval	Biological age
Biological factors (Hormonal receptors ER/ PR, HER2)	Co-morbidities
	Performance status
Tumour burden (number and site of metastasis)	Patient's preference
	Psychological factors
Need for rapid disease or symptom control	

Principles in Management

Systemic treatment options for metastatic breast cancer include endocrine therapy, chemotherapy, targeted biological therapy and bone-targeted agents. The choice between these treatment options takes into account of the biological behaviour of the tumour (hormonal receptor and HER2 status), whether there is a need for a rapid response, a balance of treatment toxicities and benefits, and impact on the quality of life. A number of clinical factors can predict the likelihood of response to treatment and long-term outcome. Patients who have a longer disease-free interval from the initial diagnosis, fewer symptoms, better performance status, soft tissue or bone metastasis, less prior therapy, and hormone receptor positive disease are more likely to experience longer survival than those who are heavily pre-treated with short disease-free interval, more symptoms and extensive visceral metastases.

In patients with significant symptomatic disease who need a rapid treatment response, e.g. shortness of breath due to lung metastasis, significant impairment of liver function due to high tumour burden, chemotherapy is the preferred option. In patients with hormone receptor positive disease, endocrine therapy is preferred unless the disease is aggressive which requires a quicker response. In patients with HER2 positive disease, targeted anti-HER2 agents, used either as monotherapy or in combination with chemotherapy or endocrine therapy, is recommended.

Chemotherapy

Breast cancer is a chemosensitive disease. Cytotoxic chemotherapy is recommended for those with hormonal receptor negative disease, hormone refractory disease, or those with rapidly progressive visceral disease where a fast treatment response is required. Commonly used agents/regimens are listed in Table 2.

Chemotherapy can be used as sequential single agents or in combinations. Response rates for single agents range from 20% to 60%, with response duration of 6 to 12 months. Combination chemotherapy yields a higher response rate and improved time to progression but at the expenses of a higher toxicity, and is usually reserved for selected, fit patients with rapidly progressing disease[2,3]. In general, sequential single agent chemotherapy is preferred as it has the advantage of giving each drug at its maximum tolerated dose without overlapping toxicities that can occur with combination chemotherapy. Furthermore, randomised trials that have planned crossover treatment (combination AB vs A followed by B) have demonstrated little survival benefits[4] .

Common side effects of chemotherapy include fatigue, alopecia, myelosuppression (neutropenia, thrombocytopenia, anaemia), gastrointestinal upset (nausea, vomiting, epigastric discomfort, diarrhoea), neuropathy (taxanes regimen), cardiotoxicity (anthracycline regimen). Advances in the use of supporting drugs during chemotherapy decrease the side effects, thus improving the quality of life during chemotherapy. The use of filgrastim (a granulocyte colony stimulating factors) can help to boost the production of neutrophils during the period of neutropenia induced by chemotherapy, thus reducing the chance of neutropenic fever. Chemotherapy-induced nausea and vomiting can be prevented in up to 80% of patients with the improvement in anti-emetic therapy, such as serotonin (5HT3) antagonists (e.g. ondansetron, tropisetron, granisetron, palonosetron), neurokinin 1 (NK1) antagonists (e.g. aprepitant), steroid (e.g. dexamethasone).

Table 2. Commonly used chemotherapy agents in metastatic breast cancer

Single Agents	Combinations
Anthracycline Doxorubicin Epirubicin Pegylated liposomal doxorubicin	FAC (5 Fluorouracil, Doxorubicin, Cyclophosphamide)
Taxanes Paclitaxel Docetaxel Albumin-bound paclitaxel	FEC (5 Fluorouracil, Epirubicin, Cyclophosphamide)
Anti-metabolites Capecitabine (Oral) Gemcitabine	AC (Doxorubicin, Cyclophosphamide)
Microtubule inhibitors Vinorelbine (Oral or IV) Eribulin	EC (Epirubicin, Cyclophosphamide)
Others Cyclophosphamide (Oral or IV) Platinum agents	AT (Doxorubicin/Docetaxel; Doxorubicin/Paclitaxel)
	CMF (Cyclophosphamide, Methotrexate, 5 Fluorouracil)
	GT (Gemcitabine, Paclitaxel)
	XT (Docetaxel, Capecitabine)

Endocrine Therapy

About two-thirds of breast cancers are hormone-receptor positive. Endocrine therapy is the preferred option in patients with hormone-receptor positive disease, unless in clinically aggressive disease which needs a rapid response with chemotherapy or if there are doubts about the endocrine responsiveness of the tumour. Commonly used endocrine agents are listed in Table 3. The most commonly used agents are tamoxifen and aromatase inhibitors. The choice of endocrine agents is based on menopausal status and prior agents used in adjuvant setting. About two-thirds of patients respond to endocrine therapy with a median duration of tumour control of 8 to 12 months in first-line setting. Some patients may have longer duration of control. Response to one form of endocrine therapy usually indicates sensitivity to subsequent second- and third-line endocrine therapies, although with shorter duration of response than initial therapy. Endocrine therapy tends to have a slow onset of action and evaluation of response after 3-4 months of treatment is recommended.

Premenopausal patients

Ovaries are the main source of oestrogen in premenopausal women. Treatment options to suppress the action of oestrogen include ovarian ablation (by surgical oophorectomy, ovarian irradiation or injection of LHRH analogues), tamoxifen, or a combination of tamoxifen with ovarian ablation. Meta-analysis comparing the combination of tamoxifen and LHRH analogue to LHRH analogue alone showed more favourable results for the combination arm in terms of response rate, progression-free survival and overall survival[5].

Postmenopausal patients

In postmenopausal women, oestrogen comes from the conversion of adrenal androgen by an enzyme called aromatase (aromatase is found in the muscle and fat cells throughout the body). Aromatase inhibitors (AI) work by blocking the enzyme aromatase. Third generation aromatase inhibitors (anastrozole, letrozole, exemestane) are more potent, more selective and better tolerated than first generation aromatase inhibitors (aminoglutethimide). They are preferred over tamoxifen as first-line hormonal therapy in post-menopausal women as they have consistently shown superioir response rate and prolonged time to treatment progression[6,7].

Treatment options after progression of AI includes another AI (from a nonsteriodal AI to a steroidal AI and vice versa), tamoxifen or fulvestrant.

Anti-HER2 Therapy

HER2 (also known as c-erbB2), a growth factor receptor, is over-expressed in 20% to 25% of breast cancer patients and is associated with a more aggressive disease. Trastuzumab is a monoclonal antibody that works by binding to the extra-cellular domain of the HER2 receptors of the breast cancer cells, thus blocking the downstream HER2 signalling to inhibit cell proliferation. It is effective in patients whose tumours demonstrate intense staining on immunofluorescence for HER2 protein (c-erbB2 IHC score 3), or have HER2 gene amplification as demonstrated by fluorescence in-situ hybridisation (FISH) testing. It was approved

in 1998 as the first targeted therapy for HER2 positive metastatic breast cancer and has led to significant improvements in the outcome of this cohort of patients. It is given by intravenous infusion every week or every three weeks. The clinical benefits had been demonstrated as monotherapy, in combination with various chemotherapy regimens, and endocrine therapy. Table 4 shows some of the landmark studies of trastuzumab in metastatic breast cancer. Trastuzumab monotherapy has response rates of 15% to 20%. When added to first-line chemotherapy for HER2 positive disease, trastuzumab near doubled the response rates from 30% to ~ 60%, with a 60% increase in the time to disease progression (7.2 months vs 4.5 months) and a 24% increase in median survival (25.1 months vs 20.3 months)[8]. Side effects of trastuzumab include flu-like symptoms and myalgia. Hypersensitivity reactions can be minimised by prophylactic premedications. Cardiac dysfunction, usually reversible, occurs in about 5-10% of metastatic breast cancer patients receiving trastuzumab (varies depending on patients' age, co-morbidities, prior use of chemotherapy which are cardiotoxic, prior left sided chest wall irradiation). Serial monitoring of left ventricular ejection fraction every 3 to 4 months is recommended.

When disease progresses while on first-line trastuzumab-containing regimen, available data suggest that it is beneficial to continue anti-HER2 therapy (continue trastuzumab or change to another anti-HER2 agent), while changing the chemotherapy or endocrine therapy to another chemotherapy / endocrine therapy. However, the optimal duration of anti-HER2 therapy is currently unknown and may be continued for as long as possible.

Lapatinib is an oral tyrosine kinase inhibitor that targets both the HER1 and HER2 receptors. It is a small molecule that works intracellularly and can be effective when trastuzumab fails. Unlike trastuzumab, lapatinib can cross the blood-brain barrier, thus improving the outcome of CNS disease. Lapatinib is approved for HER2 positive metastatic breast cancer in combination with capecitabine (failed prior therapy with anthracycline, taxane and trastuzumab) or letrozole (post-menopausal women with hormone receptor positive disease for whom hormonal therapy is indicated). It is an oral drug that is taken once daily without treatment break. Side effects of lapatinib include diarrhoea, skin rashes, nausea and fatigue. Lapatinib is less cardiotoxic with a reported incidence of symptomatic heart failure of <1%.

Recently there are newly approved anti-HER2 agents, e.g. pertuzumab, trastuzumab emtansine (T-DM1), both show promising results and provide more treatment options for patients.

Other Biological Agents

Bevacizumab is a monoclonal antibody that directs against the vascular endothelial growth factor (VEGF), which plays an important role in tumour angiogenesis. Bevacizumab combined with chemotherapy for first line treatment improves response rate, with ~30% improvement in progression free survival, but not overall survival[9]. There are no validated predictive biomarkers to select patients who are most likely to derive significant benefit from anti-angiogenic therapy. Therefore, it may only be considered in carefully selected patients. It is given by intravenous infusion every 2-3 weeks in combination with chemotherapy. Toxicities include proteinuria, hypertension, cardiovascular and haemorrhagic events.

Everolimus is an oral drug that inhibits the mTOR pathway, which plays an important role in regulating cancer cell division and blood vessel growth. It was approved in 2012 for use in combination with exemestane to treat postmenoapausal women with advanced hormone-receptor positive, HER2 negative breast cancer, whose disease has failed after a non-steroidal aromatase inhibitor (e.g. arimidex or letrozole).

Special Problems

Bone metastasis

The majority of metastatic breast cancer patients have bone metastasis. It causes pain and some will lead to pathological fracture or spinal cord compression. Apart from systemic treatment, bone-directed therapy with biosphosphonates (e.g. zoledronic acid, pamidronate) or RANK-ligand inhibitor (e.g. denosumab) is recommended to reduce pain and prevent decrease skeletal-related events. Radiotherapy to painful bony metastatic sites can achieve symptomatic relief in up to 80% of patients. Prompt initiation of radiotherapy can improve the neurological outcome of patients with spinal cord compression. Surgical intervention may be considered to prevent or stabilise pathological fractures or relieve nerve compression leading to neurological deficits.

Brain metastasis

Improvements in systemic therapy have paradoxically led to an increase in the prevalence of brain metastases, especially in patients with HER2 positive tumours. Common symptoms include focal limb weakness, headache, nausea, vomiting, confusion and convulsion. Dexamethasone is effective in relieving cerebral oedema and provide temporary symptomatic relief. For patients with a single or a few small metastatic foci, good performance status and well-controlled extracranial disease, surgical resection or radiosurgery followed by whole brain radiotherapy improves local control and disease-free survival. For patients with extensive brain metastases, whole brain radiotherapy is required.

Oligometastatic Disease

For a distinctive subset of patients with "oligometastatic" disease, which is characterised by solitary or a few metastatic lesions limited to a single organ, systemic treatment together with "aggressive" local treatment (e.g. surgical resection, targeted radiation) treatment may offer favourable outcomes with very long periods of remission and tumour control.

Conclusions

Metastatic breast cancer is a heterogeneous disease. The optimal management is complex and challenging. Physicians must take into account of multiple disease-

related factors, both clinical and biological, as well as patient-related factors to formulate a personalised treatment plan. New targeted therapies add to the wide choices of standard chemotherapies and endocrine therapies already available, hoping to offer a better efficacy with less toxicity. Apart from objective measures in terms of response rate, progression-free and overall survival, subjective improvement in the quality of life and palliation of symptoms are also important treatment goals in the "extended marathon" of life with metastatic breast cancer.

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Table 3. Endocrine therapy in metastatic breast cancer

Class of agent	Mechanism of Action	Drug	Suitability	Common side effects
Selective oestrogen receptor modulators	Blocks the binding of oestrogen to oestrogen receptors	Tamoxifen (20mg daily PO)	Pre- and post-menopausal	Hot flushes Night sweating Fatigue Vaginal discharge Thromboembolism (rare) Endometrial abnormalities
Oestrogen receptor down-regulator	- Blocks the binding of oestrogen to oestrogen receptors - Change the shape of oestrogen receptors so that oestrogen cannot bind onto them - Decrease the number of oestrogen receptors	Fulvestrant (250mg or 500mg IMI once every month)	Post-menopausal	Hot flushes Pain at injection site Headache Joint pain
Luteinising hormone-releasing hormone (LHRH) analogue	Disrupt the production of luteinising hormone in pituitary gland which subsequently suppresses the ovarian production of oestrogen	Goserelin (3.6mg SC once every month)	Pre-menopausal	Hot flushes Vaginal dryness Headache Joint pain
Aromatase inhibitors Non-steroidal Steroidal	Block the production of oestrogen from non-ovarian source	Anastrozole (1mg daily PO) Letrozole (2.5mg daily PO) Exemestane (25mg daily PO)	Post-menopausal	Joint pain Fatigue Hot flushes Osteoporosis

Table 4. Landmark studies of trastuzumab in metastatic breast cancer

Study	N	Treatment Arms	Efficacy Outcome
Trastuzumab Monotherapy			
Cobleigh et al (1999)	222	Trastuzumab 4mg/kg loading then 2mg/kg weekly	RR 15% TTP 9.1m OS 13m
Vogel et al (2002)	104	Trastuzumab (4mg/kg loading then 2mg/kg weekly vs 8mg/kg loading then 4mg/kg weekly	RR 26% TTP 18.8m (in responding patients) OS 24.4m
Trastuzumab plus chemotherapy			
Slamon et al (2001)	469	Chemotherapy (AC or EC in anthracycline-naive, Paclitaxel in anthracycline-pretreated) +/- Trastuzumab	RR 50% vs 32% (p<0.001) TTP 7.4m vs 4.6m (p<0.001) OS 25.1m vs 20.3m (p<0.001)
Marty et al (2005)	186	Chemotherapy (Docetaxel) +/- Trastuzumab	RR 61% vs 34% (p<0.001) TTP 11.7m vs 6.1m (p<0.001) OS 31.2m vs 22.7m (p=0.033)
Gasparini et al (2007)	124	Chemotherapy (Paclitaxel) +/- Trastuzumab	RR 75% vs 57% (p=0.038) TTP 10m vs 6.8m (p=0.076) OS not reached
Trastuzumab plus endocrine therapy			
Kaufman et al (2009)	207	Anastrozole +/- Trastuzumab	RR 20% vs 7% (p=0.018) PFS 4.8m vs 2.4m (p=0.002) OS 28.5m vs 23.9m (p=0.325)
Huober et al (2011)	57	Letrozole +/- Trastuzumab	RR 27% vs 13% (p=0.31) TTP 14.1m vs 3.3m (p=0.23) OS not reported

N, patient number; A, Adriamycin; C, Cyclophosphamide; E, Epirubicin; RR, response rate; TTP, time to progression; PFS, progression-free survival; OS, overall survival

Brief Review and Update on Non-Hodgkin Lymphoma (B and T-cell Lymphoma)

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Epidemiology and Classification

The Non-Hodgkin Lymphomas (NHLs) are a diverse group of lymphoproliferative disorders in which the cell of origin is a B or T lymphocyte in the majority of cases and, more rarely, a natural killer cell.

Classification

The National Comprehensive Cancer Network (NCCN,USA) guidelines categorise NHL according to the following scheme(1) :

- B-cell lymphomas
  - Indolent lymphomas
    - Chronic lymphocytic leukaemia/small lymphocytic lymphoma
    - Follicular lymphoma
    - Marginal zone lymphoma (MZL)
      - MALT (mucosa-associated lymphoid tissue) lymphoma
      - Splenic MZL
      - Nodal MZL
  - Aggressive lymphomas
    - Diffuse large B-cell lymphoma
    - Mantle cell lymphoma
  - Highly aggressive lymphomas
    - Burkitt's lymphoma
    - Lymphoblastic lymphoma
    - AIDS-related B-cell lymphoma
- T-cell lymphomas:
  - Peripheral T-cell lymphoma(include anaplastic large cell lymphoma, ALCL)
  - Mycosis fungoides/Sézary syndrome

Diagnosis

The initial presentation of a patient with Non-Hodgkin Lymphoma (NHL) can be varied. Painless lymphadenopathy may be the most common presentation, Constitutional symptoms, including fatigue and malaise in addition to the classic B-symptoms of fever, drenching sweats, and weight loss, increase the likelihood of an NHL diagnosis. It is important to elicit a history of predisposing factors, such as autoimmune disorders including Sjögren's syndrome, systemic lupus erythematosus, coeliac disease, and rheumatoid arthritis, as well as exposures to immunosuppressive agents, chemotherapy, radiation, and other occupational exposures including herbicides, pesticides, and hair dye. Travel and high-risk behaviours may be important, since a number of infectious pathogens have been associated with NHL, including hepatitis B and C, HIV, human herpes virus 8, Epstein-Barr virus, & Helicobacter pylori,.

On physical examination, features of NHL may include lymphadenopathy, hepatomegaly and splenomegaly. Laboratory features include an elevated lactate dehydrogenase level as well as leukopenia, anaemia, or thrombocytopenia in the setting of significant bone marrow involvement, hypersplenism, or autoimmune complications.

The diagnosis is made by haematopathologic review of an excisional lymph node biopsy or, at the very least, an adequate core needle biopsy. Fine-needle aspiration is largely unhelpful as a diagnostic tool in NHL. Immunophenotypic analysis is essential, and at times, molecular and genetic testing may assist in making a diagnosis.

Staging and Additional Workup

In addition to a complete history and physical examination, more studies are needed for adequate assessment of the extent of disease and to determine prognosis and plan a treatment course. Laboratory studies should include a complete blood count, evaluation of renal and hepatic functions, and lactate dehydrogenase (LDH), albumin, calcium, electrolytes, and uric acid levels. In certain patients, HIV testing, hepatitis B and C serology, & serum protein electrophoresis are needed. Analysis of spinal fluid for lymphomatous involvement is needed in patients with highly aggressive NHL subtypes, in patients determined to be at high risk for central nervous system dissemination, or in patients with neurologic signs or symptoms.

Imaging studies, including computed tomography (CT) studies of the chest, abdomen, and pelvis, are indicated in most patients. Bone marrow aspirate and biopsy are essential, and analysis of cardiac function is needed for patients who will receive anthracyclines(e. g. Doxorubicin) as part of their treatment course. Upper endoscopy is used to assess gastric lymphoma, and colonoscopy may be useful in the setting of mantle cell lymphomas. Cranial or spinal imaging may be indicated in patients with neurologic deficits. NHL is staged by the Ann Arbor staging system, originally developed for Hodgkin lymphoma, to identify patients with limited disease who might be benefited from radiation therapy (Table 1).

Table 1. Ann Arbor Staging System for NHL

Stage	Area of Involvement	Modifiers	Description
I	Single LN group	X	Bulky disease (> 10 cm)
II	Multiple LN groups, same side of diaphragm	E	Extranodal extension or single site of extranodal involvement
III	Multiple LN groups, both sides of diaphragm	A	Lack of B symptoms
IV	Multiple extranodal sites or LNs plus extranodal involvement	B	Presence of B symptoms (> 10% weight loss, fever, drenching night sweats)

LN, lymph node

Positron emission tomography (PET) scanning using fluorodeoxyglucose is frequently used as part of initial staging for certain NHL subtypes. It is most useful for the aggressive histologies, with variable sensitivities for the indolent types of NHL. A meta-analysis of PET in the initial staging and restaging of lymphomas demonstrated a median sensitivity of 87.5%, a specificity of 93.8% and a false-positive rate of 11.4 % in NHL patients. However, the routine use of PET has been debated, since only approximately 10% of patients will be upstaged by PET. Integration of PET and CT images appears to be more accurate for the initial staging of NHL than with either modality alone. PET scanning can be recommended for diffuse large B-cell lymphoma. Evidence is insufficient for its use in other NHL subtypes.

Prognosis and Survival

The NHLs can be divided into two prognostic groups: the indolent lymphomas and the aggressive lymphomas.

Indolent NHL types have a relatively good prognosis with a median survival of as long as 10 to 20 years, but they are usually not curable in advanced clinical stages. Early-stage (stage I and stage II) indolent NHLs can be effectively treated with radiation therapy alone. Most of the indolent types are nodular (or follicular) in morphology.

The aggressive type of NHLs has a shorter natural history, but a significant number of these patients can be cured with intensive combination chemotherapy regimens.

In general, with modern treatment of patients with NHL, the overall survival at 5 years is over 60%. Of patients with aggressive NHL, more than 50% can be cured. The vast majority of relapses occur in the first 2 years after therapy. While indolent NHL is responsive to immunotherapy, radiation therapy, and chemotherapy, a continuous rate of relapse is usually seen in advanced stages. Patients, however, can often be re-treated with considerable success as long as the disease histology remains low grade. Patients who present with or convert to aggressive forms of NHL may have sustained complete remissions with combination chemotherapy regimens or consolidation with marrow or stem cell support.

General Treatment Considerations

Treatment options in Non-Hodgkin Lymphoma (NHL) greatly depend on the stage and aggressiveness of the disease.

For low-risk, asymptomatic indolent NHLs, watchful waiting (surveillance) until disease progression can be an appropriate treatment option as it does not alter survival rates when compared with more aggressive treatment.[1] For patients requiring therapy, no consensus exists on a preferred regimen. First-line therapy should include rituximab alone or with cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP); cyclophosphamide, vincristine, and prednisone (CVP); bendamustine; or fludarabine-based cytotoxic chemotherapy. Following up-front single-agent rituximab or combination immunochemotherapy, rituximab administered in a maintenance fashion should be considered. Radiolabelled anti-CD20 monoclonal antibody (e.g.Zevalin) is another option, alone or following induction chemotherapy in select patients. In addition to these regimens, high-dose chemotherapy with autologous stem cell transplantation are important treatment options for patients with relapsed or refractory disease.

Stage I localised follicular NHL presents the best opportunity for a cure with radiotherapy, although the relapse rate is approximately 50%, most occurring within 5 years. Adjuvant chemotherapy has not been shown to extend overall survival but does improve relapse-free survival.

For aggressive types of NHL (e.g. Diffuse Large B-cell lymphoma), standard chemotherapy regimens (e.g, cyclophosphamide /doxorubicin /vincristine/prednisone [CHOP]) alone or in combination with radiotherapy have been the mainstays of treatment.

The approval of rituximab (a CD20 monoclonal antibody) has substantially changed the landscape of NHL treatment. The addition of rituximab to standard cytotoxic chemotherapy agents has improved response rates, progression (relapse)-free survival, and overall survival in most B-cell lymphomas which express CD20 antigen(including diffuse large B-cell and follicular lymphomas).[3] Rituximab is typically administered in 8 cycles via intravenous infusion and is generally well tolerated, but some patients may experience severe infusion reactions. To reduce the additional cost and time burden on patients and infusion centres, the US Food and Drug Administration recently approved a 90-minute infusion for rituximab starting at cycle 2 for patients with NHL who did not experience a grade 3/4 infusion-related adverse reaction during cycle 1.

Mantle cell lymphoma constitutes about 5% of lymphomas. The clinical course is usually aggressive, frequently involving bone marrow, spleen and the gastrointestinal tract. Intensive chemotherapy is recommended, followed by haematopoietic stem cell transplant in young patients with stage III/IV disease or relapsed disease. In older patients who have relapsed, novel agents such as lenalidomide or bortezomib may be useful.

Table 2. Standard Treatment Options for NHL(Summary)

Stage	Standard Treatment Options
CNS = central nervous system; CHOP = cyclophosphamide plus doxorubicin plus vincristine plus prednisone; IF-XRT = involved-field radiation therapy; NHL = non-Hodgkin lymphoma; R-CHOP = rituximab, an anti-CD20 monoclonal antibody, plus cyclophosphamide plus doxorubicin plus vincristine plus prednisone.	
Indolent, Stage I and Contiguous Stage II Adult NHL	Radiation therapy
	Rituximab with or without chemotherapy
Indolent, Noncontiguous Stage II/III/IV Adult NHL	Watchful waiting for asymptomatic patients
	Rituximab
	Purine nucleoside analogues
	Alkylating agents (with or without steroids)
	Combination chemotherapy
	(radiolabelled anti-CD20 monoclonal antibodies-e.g.Yttrium-90 labelled ibritumomab tiuxetan (Zevalin)
	Maintenance rituximab
Indolent, Recurrent Adult NHL	Chemotherapy (single agent or combination with Rituximab)
	Rituximab
	Lenalidomide or Bortezomib(Velcade)
	Radiolabelled anti-CD20 monoclonal antibodies
	Palliative radiation therapy
Aggressive, Stage I and Contiguous Stage II Adult NHL	R-CHOP with or without IF-XRT
Aggressive, Noncontiguous Stage II/III/IV Adult NHL	R-CHOP
	Other combination chemotherapy
Adult Lymphoblastic Lymphoma	Intensive therapy
	Radiation therapy
Burkitt Lymphoma	Aggressive multidrug regimens
	Central nervous system (CNS) prophylaxis
Aggressive, Recurrent Adult NHL	Bone marrow or stem cell transplantation
	Re-treatment with standard agents
	Palliative radiation therapy

Treatment for T-cell lymphoma

Therapy for peripheral T-cell lymphoma (PTCL) subtypes is largely based on aggressive B-cell lymphoma regimens. However, outcomes are generally worse in PTCL compared with diffuse large B-cell lymphoma when treated with similar regimens. Dose-intensive regimens did not appear to have a benefit whereas the use of autologous stem cell transplantation (ASCT) in first remission appeared to improve outcomes. A complete response rate of 74% was reported when Anaplastic large-cell lymphoma (ALCL) was treated with anthracycline-based chemotherapy regimens.[4] 5-year overall survival rates were found to be markedly different whether ALCLs express ALK (anaplastic lymphoma kinase) or not. (79% and 46% for ALK-positive and ALK-negative groups, respectively).

Because ALCLs express CD30, a new anti-CD30 antibody- Brentuximab veodtin demonstrated significant activity in patients with relapsed/refractory ALCL.[5] with an overall response rate of 86%, a complete response rate of 53%, and a median duration of response not reached.

When patients with angioimmunoblastic lymphoma were treated with anthracycline-based combination chemotherapy, complete response rates of 60% to 70% were unfortunately associated with short disease-free intervals and a subsequent median survival of 1.5-3 years. Immunosuppressive therapy with glucocorticoids or cyclosporine has elicited significant, but not durable, responses. Retrospective analyses suggest that high-dose chemotherapy/ASCT in first remission may improve these poor outcomes.

ALK+ anaplastic large-cell lymphoma patients achieving complete responses may have durable remissions, not requiring consolidative therapy. For all other PTCL subcategories, high-dose chemotherapy/ASCT can be considered, because of the otherwise poor outcomes. Salvage treatment can be considered for patients with inferior responses or relapses after initial therapy. Agents such as pralatrexate, gemcitabine, denileukin diftitox, and alemtuzumab have demonstrated activity in this population.

Romidepsin was recently approved(2011) by US FDA for the treatment of patients with PTCL who have received at least 1 previous therapy. Patients with sensitive disease can be considered for an autologous stem cell transplant as salvage therapy. Further, given the demonstration of a graft-vs-lymphoma effect in patients progressing after several regimens, allogenic stem cell transplantation may also be an option.

Natural Killer/T cell-lymphoma

Primary nasal lymphomas, although rare, show predilection for Asians (including those of Hong Kong). A local retrospective large series reported the commonest subtype is Natural killer (NK) / T-cell lymphoma with cell surface CD56 expression[6]. The typical tumour presents with aggressive mid-facial angiocentric tumour often with tissue necrosis – "the Midline Granuloma".

Traditional anthracycline-containing chemotherapy like CHOP has not been effective in controlling the disease. Early Radiotherapy, especially in the elderly patients, has remained the mainstay therapy until recent years when a special chemotherapy regimen SMILE (Steroid, Methotrexate, Ifosfomide, L-asparaginase, Etoposide) has been found to be effective. The phase II study conducted by the Asia Lymphoma Study Group showed an overall response rate of 80% for newly-diagnosed as well as refractory/ relapsed patients[7]. SMILE is now first line therapy for this disease, often with radiotherapy "sandwiched" between 3 cycles of the chemotherapy regimen.

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Emirates Wolgan Valley Resort & Spa New South Wales 新南威爾斯

酒店位於著名的藍山世界遺產保護區，往返悉尼約3小時車程，建於兩座國家公園之間及高聳的懸崖之下，是世界首間零碳排放渡假村。旅客可於這裡親近無拘無束的野生動物、觀賞令人驚歎的自然美景以及感受舒適愜意的輕鬆自在。渡假村提供各種活動，包括四驅駕駛、導賞行、野生動物觀賞行以及騎馬。體驗環保型奢華旅遊新時代。[Emirates Wolgan Valley Resort & Spa 四日兩夜國泰套票由 $20,900起 (經濟倉) / $45,300起 (商務倉)] *

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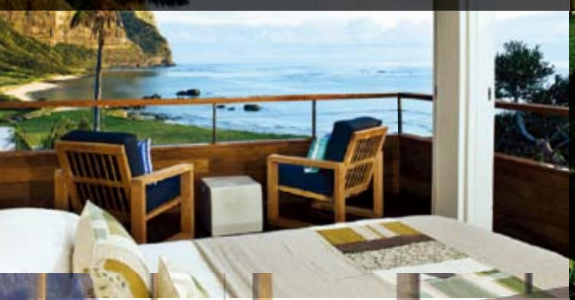

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Announcement

The Federation of Medical Societies of Hong Kong is calling for interested health care providers to offer discounted health and body check programmes to members of our member societies and their family members.
For those who are interested, please contact our secretariat with information of proposed packages and quotations.
Thank you for your kind attention!

Seminar on Ear & Hearing

In the evening of 27 March, 2013, the HKFMS Foundation organised a seminar on 'Ear & Hearing', at the Lecture Hall of the Federation. This seminar aimed at promoting the awareness on the hearing disorders, the communication difficulties due to these disorders and the advanced technology in the treatment and rehabilitation. It was a pleasure to co-organise this event with the Hear Talk Foundation, which is a non-profitable organisation calling for different expertise in fighting against hearing disorders.

It was our privilege to have invited Professor Michael TONG Chi-fai, Professor and Head of Academic Divisions, Department of Otorhinolaryngology, Head & Neck Surgery, and the Institute of Human Communicative Research in the Chinese University of Hong Kong, to deliver his talk on the different aspects of hearing loss. Another speaker, Ms. Iris NG Hoi-yee, Professional Consultant of the same Department, gave an informative speech on the role of audiologists. Various perspectives of hearing were covered in this seminar, including anatomy & physiology, assessment, impairment & disability, non-invasive rehabilitation devices and the latest advancement in the surgery and implantation solutions against hearing loss. The audience was able to update themselves with a lot of useful knowledge and insights on the topic from the seminar.

The CEO of the sponsor, Earlogic, came all the way from USA to support this seminar. We would like to take this pportunity to show our heart-felt gratitude for his invaluable support.

Public Talk on Dental Implant

A public talk for dental implants was held on 7 April, 2013 at the Lecture Hall of the Federation. It was our privilege to have invited Dr. Alfred LAU Sze-lok & Dr. Raymond Lop-keung CHOW to conduct this public talk. Both Dr. Lau & Dr. Chow are specialists of dental surgery in oral & maxillofacial surgery, as well as clinical lecturers in the University of Hong Kong. They introduced the most updated technology, and explained the risks & complications that might occur with dental implants. The talk was well-received, and the audience actively participated in the question and answer session. The talk was a fruitful and informative event. A video clipping of this public talk will be available on the website of the FMSHK soon.

Last but not least, we would like to express our most sincere appreciation to our sponsor, Nobel Biocare Asia Limited, for the full support of this event.

POSITION STATEMENT
BY THE FEDERATION OF MEDICIAL SOCIETIES OF HONG KONG

March 11, 2013

Re : Consultation on "Hong Kong Code of Marketing and Quality of Formula Milk and Related Products, and Food Products for Infants and Young Children"

The World Heath Organization published the International Code of Marketing of Breast Milk Substitutes in 1981 which has been widely adopted internationally. The Federation is fully in support of the ideas and practices of the Code.

Breast milk is the ideal food for newborns and infants. It gives infants all the nutrients they need for healthy development. It is safe and contains antibodies that help protect infants from common childhood illnesses - such as diarrhoea and pneumonia, the two primary causes of child mortality worldwide.[1] Breast milk is readily available and affordable, which helps to ensure that infants get adequate sustenance. Breast feeding reduces the risk of Sudden Infant Death Syndrome. [2]

Beyond the immediate benefits for children, breastfeeding contributes to a lifetime of good health. Adults who have been breastfed as babies often have lower blood pressure and lower cholesterol, as well as lower rates of overweight, obesity and type-2 diabetes. There is evidence that people who have been breastfed perform better in intelligence tests. [3]

Breastfeeding also benefits mothers. The practice when done exclusively is associated with a natural (though not fail-safe) method of birth control (98% of protection in the first 6 months after birth). It reduces risks of breast and ovarian cancer later in life, helps women return to their pre-pregnancy weight faster, and lowers rates of obesity. [4]
Breastfeeding not only benefits the babies and mothers individually. Researches have confirmed this is also extremely good for mother-child, paternal and familial bonding and mental health development of all. [5]

Support for mothers is essential. Breastfeeding has to be learned and many women encounter difficulties at the beginning. Nipple pain, and fear that there is not enough milk to sustain the baby are common. Health facilities that support breastfeeding - by making trained breastfeeding counsellors available to new mothers - encourage higher rates of the practice. To provide this support and improve care for mothers and newborns, there are now more than 20,000 "baby-friendly" facilities in 152 countries thanks to a WHO-UNICEF initiative.

Many mothers who return to work abandon breastfeeding partially or completely because they do not have sufficient time, or a place to breastfeed, express and store their milk. Mothers need a safe, clean and private place in or near their work to continue breastfeeding. Enabling conditions at work can help, such as paid maternity leave, part-time work arrangements, on-site crèches, facilities for expressing and storing breast milk, and breastfeeding breaks.

The Federation believes the government can lead by example. Government work places should contain designated rooms for breast milk extraction and storage. Government owned public places should have infant feeding rooms. Other venues like MTR stations, shopping centres should be encouraged to follow suit. Labour ordinances may have to be looked at for possible amendments and improvements in this area as well.

Infant formulas do not contain the antibodies found in breast milk. When infant formulas are not properly prepared, there are risks arising from the use of unsafe water and unsterilised equipment or the potential presence of bacteria in powdered formulas. Malnutrition can result from over-diluting formulas to "stretch" supplies. Further, frequent feedings maintain the breast milk supply. If a formula is used but becomes unavailable later, a return to breastfeeding may not be an option due to diminished breast milk production. Marketed baby formulas have varied sugar contents where some can be as high as 13.5g per serving, which is equivalent to three and a half teaspoons of sugar per 5 ounces. Baby bottle syndrome is the rapid tooth decay of baby teeth in exposure to liquids containing sugars for long periods of time. Formula feeding increases the chance of children getting cavities. [6]

While there are in fact few medical contraindications to breastfeeding, there are mothers who are unable to do so due to medical or personal reasons. In these situations evidence-based information on breast milk substitutes should be allowed to let mothers make informed choices for their babies. Misleading information in commercial advertisements should be closely scrutinised and discouraged.

On the other hand the government is also responsible for making a safe and steady supply of milk formulas a priority for our local children.

The Federation is in full support of the consultation document. However as it is voluntary in nature, we are concerned that there might not be enough motivation for the manufacturers or retailers to comply with the code. The Federation will continue to promote breast feeding. We will be one of the platforms to advocate this natural, safe and healthy method of infant feeding. Through the contact of the professionals of our member societies and the public we will continue to educate the public about the science and facts of breastfeeding and correct any misleading or utterly

incorrect information available in the public domain. We shall continue to do our best to protect the health and well-being of mothers and children and the public at large.

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APPENDIX

The statement is issued by the Executive Committee of the Federation of Medical Societies of Hong Kong and with the feedback and response from the following member societies duly acknowledged and incorporated.

1 Hong Kong Dietitians Association Ltd
2 Hong Kong Nutrition Association Limited
3 Hong Kong Society of Paediatric Dentistry
4 The Hong Kong Paediatric Society
5 The Hong Kong Society of Community Medicine
6 The Hong Kong Society of Diagnostic Radiologists

Society News

The Hong Kong Psychogeriatric Association (HKPGA)

The Hong Kong Psychogeriatric Association (HKPGA) was founded in 1998 by a group of mental health professionals working in the field of old age psychiatry in Hong Kong. Our objectives are: to promote, through a multidisciplinary approach, the study and advancement of the science and practice of psychiatry of the elderly as well as the ancillary sciences and branches of medicine and health care; to further public education; to contribute to the improvement of mental health care for Hong Kong senior citizens; and to collaborate with the relevant local and overseas organisations to achieve the above.

Current office bearers of the HKPGA are: Prof. Helen Chiu (President); Ms. Anita Wong and Dr. Joshua Tsoh (Vice-Presidents), Dr. CL Lam (Honorary Secretary), Ms. Elsie Wong (Honorary Treasurer) and Dr. SW Li (Immediate Past President). HKPGA is a member of the Federation and is an affiliate organisation of the International Psychogeriatric Association. We hold annual Chinese Tripartite Psychogeriatric Meetings with the Psychogeriatric Interest Group of the Chinese Society of Psychiatry and the Taiwanese Society of Geriatric Psychiatry.

At present, we have around 250 members, including psychiatrists, geriatricians, general practitioners, nurses, psychologists, physiotherapists, occupational therapists, social workers, and other professionals working in the field. Our members are enthusiastic in joining regular HKPGA activities, namely the HKPGA Mid-year Scientific Symposia, HKPGA Annual General Meetings cum Annual Scientific Meetings and different thematic workshops. For example, we have organised workshops on testamentary capacity and problem-solving psychotherapy in the past few years.

HKPGA promotes local mental health research by giving the HKPGA Young Scientist Awards to our outstanding members and nominating them to join the exchange programme with the Japanese Society of Psychogeriatrics (JSPG). Besides, we have been sponsoring our members to attend local and overseas conferences. In the recent decade, HKPGA has been involved in advocacy for better elderly care through participation in the following events: co-organising the dementia policy forum, renaming movement of the Chinese name of dementia and submitting proposals related to elderly care to the Legislative Council. For more information about HKPGA, please visit www.hkpga.org

Association for Integrative Aesthetic Medicine, Hong Kong (AIAM)

Association for Integrative Aesthetic Medicine, Hong Kong (AIAM) has been established since 2008. It was set up by a group of specialists in both Western and Chinese Medicine, having ideals in putting the proficiency and expertise knowledge of the members in both Western and Chinese Medicine into the development of Aesthetic Medicine. Our objectives are: (1) Advancement of academic activities be put in the first priority; (2) Promotion of useful medical areas from the integration of Western and Chinese Medicine; and (3) Contribution to Aesthetic Medicine in medical science, technology and skills.

Connection with the UMINE (Union Internationale de Médecine Esthétique) and CAAM (China Academy of Aesthetic Medicine) has been close. There have been frequent academic and professional exchanges through participation in national and international conferences.

Our Association is active in organising academic forums, talks and seminars on subjects related to aesthetic medicine and dermatology. Medical professionals with Western and Chinese medicine expertise are invited as speakers to stimulate wider integrative perspectives. The most recent seminar on "Dietary Manipulation in Skin Disorders" was successfully held on Mar 14, 2013 and warmly appraised by plenty of participants for elevating scientific understanding.

All medical professionals and personnel are welcome to apply for membership. Admission fee for ordinary members is HK$500 while the annual membership fee is currently HK$200.

Hong Kong Society for Quality of Life

The Hong Kong Society for Quality of Life (HKSoQOL, http://www.hksoqol.org) was inaugurated in 2004 as a non-profit professional organisation, made up of clinicians, nurses, allied health personnel and academics. We are committed in the promotion of informed knowledge of Quality of Life for enhancing services and policy development in public health, medical, rehabilitation and the social service sectors.

In 2012, we have continued our commitment hosting the 2012 Asian Chinese Quality of Life Conference in Guangzhou, P.R. China, together with the First Affiliated Hospital of the Guangzhou University of Traditional Chinese Medicine. We welcomed about 300 delegates from the United States, Singapore, European countries, the China Mainland and Hong Kong.

We have proudly developed a Certificate Course on Quality of Life in Research and Clinical Practice in 2012, with the Federation of Medical Societies. It was the first course of its kind in Hong Kong which attracted around 30 participants, including clinicians, nurses and allied health professionals. To a great success, a similar course will be conducted in 2013.

Looking forward, we shall very soon have our key annual event of an Annual General Meeting on June 15, 2013. The meeting will focus on two vibrating topics on how Chinese medicine may help in improving quality of life, and what we can do to improve quality of life in patients suffering from Head and Neck cancers. In addition, we will have our next international conference on quality of life in 2014, which will be excitedly held in Hong Kong. We welcome anyone to participate or be engaged in all our activities.

Of course, we could not achieve all this work without the support and guidance of our council members. Through the continued passion and dedication of our members, we are confident that we will achieve all we have committed to enhance good quality of life in all of us.

Sunday	Monday	Tuesday	Wednesday	Thursday	Friday	Saturday
			1	2	* Joint Surgical Symposium - Cardiothoracic Surgery * HKMA Shatin Doctors Network - Role of Primary Care Physicians in BPH Screening and Management 3	4
5	* A Lady with Acute Ureteric Obstruction 6	* HKMA Tai Po Community Network- Disease Burden & Treatment to "Community Acquired Pneumonia" * FMSHK Officers' Meeting * HKMA Council Meeting 7	* Hong Kong Neurosurgical Society Monthly Academic Meeting –Cervical Spinal Trauma * HKMA Shatin Doctors Network - Practical Workshop in Ophthalmology 8	* HKMA Hong Kong East Community Network - Personalized T2DM Treatment Approach * HKMA Kowloon East Community Network - Treatment of Resistant Depression * Hong Kong Medical Association; Hong Kong Sanatorium & Hospital - HKMA Structured CME Programme with HKS&H Session 4: An Update of Prenatal Diagnosis in Hong Kong 9	* Hong Kong Medical Association - Beyond LDL-C Lowering with Hybrid Therapy 10	* Refresher Course for Health Care Providers 2012/2013 - Ophthalmology advances for primary care providers 11
12	13	* HKMA Tai Po Community Network- Update on Pneumococcal Vaccines: Evolution of Pneumococcal Disease Prevention 14	15	* Certificate Course for GPs 2013 - Update on the management of mood disorders 16	17	* HKMA Cooking Class 18
19	20	21	22	* HKMA Kowloon East Community Network – Long Duration and Real Effectiveness of the Quadrivalent HPV Vaccine * HKMA Hong Kong East Community Network - Common Orthopedic Foot & Ankle Problems * FMSHK Executive Committee & Council Meeting * 14th Regional Osteoporosis Conference 2013 and Osteoporosis: Essentials of Densitometry, Diagnosis and Management - An International Course of the ISCD and IOF 23	* HKMA Shatin Doctors Network - Common Pitfalls in Management of Breast Disease 24	* Career Talk 25
* HKMA Squash Tournament 2013 26	27	28	29	* HKMA CME - Update on Premature Ejaculation * HKMA New Territories West Community Network - Management of Insomnia and Mood Disorder * MPS Workshop - Masterign Adverse Outcomes 30	31	

Date / Time	Function	Enquiry / Remarks
3 FRI 8:00 am	**Joint Surgical Symposium - Cardiothoracic Surgery** Organiser: Department of Surgery, The University of Hong Kong & Hong Kong Sanatorium & Hospital, Chairman: Prof. Stephen CHENG, Speakers: Dr. CHIU Shui-wah & Dr. CHAN Tai-leung Daniel, Venue: Hong Kong Sanatorium & Hospital	Department of Surgery, Hong Kong Sanatorium & Hospital Tel: 2835 8698 1 CME point
1:00 pm	**HKMA Shatin Doctors Network - Role of Primary Care Physicians in BPH Screening and Management** Organiser: HKMA Shatin Doctors Network, Chairman: Dr. MAK Wing Kin, Speaker: Dr. NG Man Tat, Venue: Jasmine Room, Level 2, Royal Park Hotel, 8 Pak Hok Ting Street, Shatin	Ms. Ivy LEUNG Tel: 3189 8782
6 MON 7:30 pm	**A Lady with Acute Ureteric Obstruction** Organiser: Hong Kong Urological Association, Chairman: Dr. LAM Yiu Chung, Thomas, Speaker: Dr. IP Chi Ho, Venue: Multi-disciplinary Simulation and Skills Centre, 4/F, Block F, QEH	Ms. Tammy HUNG Tel: 9609 6064 1 CME point
7 TUE 1:00 pm	**HKMA Tai Po Community Network- Disease Burden & Treatment to "Community Acquired Pneumonia"** Organiser: HKMA Tai Po Community Network, Speaker: Dr. SO Man Kit, Thomas, Venue: Chiu Chow Garden, Shop 001-003, 1/F, Uptown Plaza, Tai Po, NT	Ms. Sylvia HO Tel: 2963 5536 1 CME point
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
8:00 pm	**HKMA Council Meeting** Organiser: The Hong Kong Medical Association, Chairman: Dr. TSE Hung Hing, Venue: HKMA Head Office (5/F., Duke of Windsor Social Service Building, 15 Hennessy Road, Hong Kong)	Ms. Christine WONG Tel: 2527 8285
8 WED 7:30 am	**Hong Kong Neurosurgical Society Monthly Academic Meeting –Cervical Spinal Trauma** Organiser: Hong Kong Neurosurgical Society, Chairman: Dr. HUNG Wai Man, Speaker: Dr. LI Ka Kin, Venue: Seminar Room, Ground Floor, Block A, Queen Elizabeth Hospital	Dr. Gilberto LEUNG Tel: 2255 3368 1.5 CME points
1:00 pm	**HKMA Shatin Doctors Network - Practical Workshop in Ophthalmology** Organiser: HKMA Shatin Doctors Network, Chairman: Dr. MAK Wing Kin, Speaker: Dr. Derek YU, Venue: Room 1206-1211, 238 Nathan Road, Jordan	Ms. Kidman TAM Tel: 2388 1813 1 CME point
9 THU 1:00 pm	**HKMA Hong Kong East Community Network - Personalized T2DM Treatment Approach** Organiser: HKMA Hong Kong East Community Network, Chairman: Dr. LAM See Yui, Joseph, Speaker: Prof. Annie KUNG, Venue: HKMA Head Office (5/F., Duke of Windsor Social Service Building, 15 Hennessy Road, Hong Kong)	Ms. Candice TONG Tel: 2527 8285 1 CME point
1:00 pm	**HKMA Kowloon East Community Network - Treatment of Resistant Depression** Organiser: HKMA Kowloon East Community Network, Chairman: Dr. AU Ka Kui, Gary, Speaker: Dr. WONG Chung Hin, Willy, Venue: Lei Garden Restaurant, Shop no. L5-8, apm, Kwun Tong, No. 418 Kwun Tong Road, Kowloon	Ms. Hana YEUNG Tel: 2527 8285 1 CME point
1:15 pm	**Hong Kong Medical Association; Hong Kong Sanatorium & Hospital - HKMA Structured CME Programme with HKS&H Session 4: An Update of Prenatal Diagnosis in Hong Kong** Organiser: Hong Kong Medical Association Hong Kong Sanatorium & Hospital, Speaker: Dr. Leung Tse Ngong, Danny, Venue: Function Room A, HKMA Dr. Li Shu Pui Professional Education Centre, 2/F, Chinese Club Building, 21-22 Connaught Road Central, Hong Kong	HKMA CME Dept. Tel: 2527 8452 1 CME point
10 FRI 1:00 pm	**Hong Kong Medical Association - Beyond LDL-C Lowering with Hybrid Therapy** Organiser: Hong Kong Medical Association, Speaker: Prof. Terje PEDERSEN, Venue: Diamond Ballroom 1, Basement 1, Eaton Hotel, Jordan, Kowloon	HKMA CME Dept. Tel: 2527 8452 1 CME point
11 SAT 2:30 pm	**Refresher Course for Health Care Providers 2012/2013 - Ophthalmology advances for primary care providers** Organisers: Hong Kong Medical Association, HK College of Family Physicians, HA-Our Lady of Maryknoll Hospital, Speaker: Dr. Yick Wai Fong, Doris, Venue: Training Room II, 1/F, OPD Block, Our Lady of Maryknoll Hospital, 118 Shatin Pass Road, Wong Tai Sin, Kowloon	Ms. Clara Tsang Tel: 2354 2440 2 CME points
14 TUE 1:00 pm	**HKMA Tai Po Community Network- Update on Pneumococcal Vaccines: Evolution of Pneumococcal Disease Prevention** Organiser: HKMA Tai Po Community Network, Chairman: Dr. CHIU Sik Ho, Speaker: Dr. SO Man Kit, Thomas, Venue: Chiu Chow Garden Restaurant, Tai Po	Ms. Sylvia HO Tel: 2963 5536 1 CME point
16 THU 1:00 pm	**Certificate Course for GPs 2013 - Update on the management of mood disorders** Organiser: HA-United Christian Hospital, HK College of Family Physicians, HKMA-KLN East Community Network, Chairman: Dr. Danny MA, Speaker: Dr. Wong Mei Cheung, Venue: East Ocean Restaurant, Metro City Plaza 3, Tseung Kwan O, Kowloon	Ms. Marina Pun Tel: 3513 4888 1 CME point
18 SAT 2:30 pm	**HKMA Cooking Class** Organiser: The Hong Kong Medical Association, Chairman: Dr. PONG Chiu Fai, Dr. SIN Pui Yee, Venue: Superlife culture club, Time Square store	Ms. Phoebe WONG Tel: 2527 8285
23 THU 1:00 pm	**HKMA Kowloon East Community Network – Long Duration and Real Effectiveness of the Quadrivalent HPV Vaccine** Organiser: HKMA Kowloon East Community Network, Chairman: Dr. MA Ping Kwan, Danny, Speaker: Dr. CHEN Siu Wai, Ivo, Venue: East Ocean Seafood Restaurant, Tseung Kwan O	Ms. Hana YEUNG Tel: 2527 8285 1 CME point
1:00 pm	**HKMA Hong Kong East Community Network - Common Orthopedic Foot & Ankle Problems** Organiser: HKMA Hong Kong East Community Network, Chairman: Dr. GOH Kim Yeow, Speaker: Dr. NGAI Yiu Hing, William, Venue: HKMA Wanchai Premises, 5/F, Duke of Windsor Social Service Building, 15 Hennessy Road, Wanchai, HK	Ms. Candice TONG Tel: 2527 8285 1 CME point

Date / Time	Function	Enquiry / Remarks
23 THU 7:00 pm	**FMSHK Executive Committee & Council Meeting** Organiser: The Federation of Medical Societies of Hong Kong, Venue: Council Chamber, 4/F, Duke of Windsor Social Service Building, 15 Hennessy Road, Wanchai, Hong Kong	Ms. Nancy CHAN Tel: 2527 8898
	14th Regional Osteoporosis Conference 2013 and Osteoporosis: Essentials of Densitometry, Diagnosis and Management - An International Course of the ISCD and IOF Organisers: The Osteoporosis Society of Hong Kong & Hong Kong Society of Clinical Oncology, Venue: Hong Kong Convention & Exhibition Centre	Ms. Gigi WONG Tel: 2559 9973 http://www.oshk.org.hk/
24 FRI 1:00 pm	**HKMA Shatin Doctors Network - Common Pitfalls in Management of Breast Disease** Organiser: HKMA Shatin Doctors Network, Chairman: Dr. MAK Wing Kin, Speaker: Dr. HO Nga Sze, Venue: Jasmine Room, Level 2, Royal Park Hotel, 8 Pak Hok Ting Street, Shatin	Ms. Joyce TSUNG Tel: 2664 3808 1 CME point
25 SAT 3:00 pm	**Career Talk** Organiser: The Hong Kong Medical Association, Chairmen: Dr. PONG Chiu Fai, Dr. SIN Pui Yee, Venue: HKMA Central Premises	Ms. Phoebe WONG Tel: 2527 8285
26 SUN 2:00 pm	**HKMA Squash Tournament 2013** Organiser: The Hong Kong Medical Association, Chairman: Dr. HO Yiu Wah, Venue: Kowloon Cricket Club	Ms. Dorothy KWOK Tel: 2527 8285
30 THU 1:00 pm	**HKMA CME - Update on Premature Ejaculation** Organiser: Hong Kong Medical Association, Chairman: Dr. CHENG Chi Man, Speaker: Dr. YIP Wai Chun, Andrew, Venue: Eaton Hotel	HKMA CME Dept. Tel: 2527 8452 1 CME point
1:00 pm	**HKMA New Territories West Community Network - Management of Insomnia and Mood Disorder** Organiser: HKMA New Territories West Community Network, Chairman: Dr. CHUNG Siu Kwan, Ivan, Speaker: Dr. John SO, Venue: Plentiful Delight Banquet, Yuen Long	Ms. Hana YEUNG Tel: 2527 8285 1 CME point
6:30 pm	**MPS Workshop - Masterign Adverse Outcomes** Organiser: The Hong Kong Medical Association, Chairman: Dr. TSE Hung Hing, Speaker: Dr. LEUNG Kwok Ling, Ares, Venue: Central	HKMA CME Dept. Tel: 2527 8452 2.5 CME points

Upcoming Meeting

16/6/2013	**Hong Kong Primary Care Conference** Organiser: The Hong Kong College of Family Physicians, Venue: HKAM Jocke Club Building, Enquiry: Ms. Crystal YUNG Tel: 2861 0220
23/6/2013	**FMSHK Annual Scientific Meeting 2013 - Obesity related disorders: an emerging epidemic** Organiser: The Federation of Medical Societies of Hong Kong, Venue: Ballroom, 3/F, Sheraton Hotel, 20 Nathan Road, Kowloon, Enquiry: FMSHK Secretariat Tel: 2527 8898
10-13/7/2013	**9th Asian Dermatological Congress 2013** Organisers: Asian Dermatological Association, Hong Kong College of Dermatologists & the Hong Kong Society of Dermatology and Venereology, Chairman: Prof. Henry HL CHAN, Venue: Hong Kong Convention & Exhibition Centre, Enquiry: ADC 2013 Secretariat Tel: 3151 8900

Answers to Dermatological Quiz

Answers:

1. Cutaneous pseudolymphoma (synonyms: lymphocytoma cutis, reactive lymphoid hyperplasia), cutaneous lymphoma, lupus erythematosus tumidus, Jeissner lymphocytic infiltrate, follicular mucinosis and granulomatous rosacea

2. Cutaneous plasmacytosis, cutaneous lymphoma, Rosai-Dorfman disease, IgG4-related sclerosing disease

3. Immunohistochemical staining for IgG4 and IgG in the skin biopsy. In this patient, many IgG4+ plasma cells were present & a high proportion of IgG4+ to IgG+ cells was demonstrated. Emperipolesis (lymphophagocytosis) was absent. The final diagnosis was IgG4-related sclerosing disease.

IgG4-related sclerosing disease is a newly described syndrome, probably autoimmune in origin. Most patients are in late adulthood and with male predominance. Clinically it is characterised by mass and/or inflammatory lesions commonly involving the exocrine glands, in which autoimmune pancreatitis is the prototypic form. Other sites that have been reported include the hepatobiliary tree, lacrimal gland, salivary gland, lymph node, aorta, kidney, lung and skin, etc. This diagnosis should be suspected in any patient who has elevated serum IgG and a lymphoplasmacytic sclerosing pattern in histology. The diagnosis can only be reached by demonstration of an elevated serum IgG4, a large number of IgG4+ plasma cells together with a high proportion of IgG4+ to IgG+ cells. There is usually a favourable clinical response to systemic steroid therapy.

Dr. Lai-yin CHONG
MBBS(HK), FRCP(Lond, Edin, Glasg), FHKCP, FHKAM(Med)
Private Dermatologist

DUAL DELAYED RELEASE TECHNOLOGY
24 HOUR CONTROL*

NEW

DEXILANT
dexlansoprazole

30 MG | 60 MG DELAYED RELEASE CAPSULES

- Sets a new standard for PPI therapy, with dual releases of active drug to provide significantly extended heartburn control[1,2]
- Effective across the spectrum of GERD[3,4]
- Maintains long-term healing and therefore quality of life[5,6]
- Lifestyle-friendly PPI : once daily, taken with or without food[1,7,8]
- Acceptable safety and tolerability profiles with minimal clopidogrel interaction[1,9]

For further information, consult full prescribing information.

Reference:1. Dexilant prescribing information (DEX051-HK1.1T, HK Brandy). 2.Wittbrodt ET et al., Clin Exp Gastroenterol 2009;2:117-28. 3. Fass R et al., Ailment Pharmacol Ther 2009;29:1261-72. 4.Sharma P et al., Ailment Pharmacol Ther 2009;29:731-41. 5.Metz DC et al., Ailment Pharmacol Ther 2009;29:742-54. 6. Howden CW et al., Ailment Pharmacol Ther 2009;30:896-07. 7. Lee RD et al., Ailment Pharmacol Ther 2009;29:824-33. 8. Lee RD et al., Ailment Pharmacol Ther 2010;31:1001-11. 9. Freinger AL et al., J Am Coll Cardiol 2012;59:1304-11

*96% of patient on Dexlansoprazole 60mg achieved 24-h heartburn-free days[6]

Growing Innovation

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HK-DEX-X/26/12-2013