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Editorial

- The Advent of Adjuvant Systemic Treatment — *Dr. William Foo*

Medical Bulletin

- '.....Which Makes Life Even Better' — *Dr. William Foo*
- Systemic Treatment for Colorectal Cancer — *Dr. Wai-man Sze*
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- Cancer Incidence in Hong Kong — *Dr. Chun-key Law, Mr. Oscar Mang*
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- Chemoradiation - an overview and examples
  (adapted from issues of JOC Bulletin, Joint Oncology Conference)

Dermatological Quiz

- Dermatological Quiz — *Dr. Ka-ho Lau*

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Date	: 25 August 2007
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Nutrition for Elderly - 長者健康飲食 (Course No.: C120)

Objective	: Enhance the importance of healthy eating and exercise knowledge for the elderly.
Speaker	: Ms Liza Chan Chuen Yin, Dietitian 陳荃賢營養師
Date	: 25 August 2007
Time	: 11:30 am - 1:00 pm
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Course Fee	: HK$250
Language	: Cantonese (Supplemented with English)

Weight Loss Diets and Principles 體重控制飲食療法 (Course No.: C121)

Objective	: Introduce basic concepts and principles of weight control. Topics will include assessment, factors regulating energy balance, popular diets and practices.
Speaker	: Ms Mimi Sham, Dietitian 岑楊毓湄營養師
Date	: 25 August 2007
Time	: 2:00 pm - 3:30 pm
Venue	: Lecture Hall, 4/F, Duke of Windsor Social Service Building, 15 Hennessy Road, Wanchai, Hong Kong
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The Advent of Adjuvant Systemic Treatment

Dr. William Foo

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Specialist in Clinical Oncology, Hong Kong Baptist Hospital
Editor

Dr. William Foo

Dr CK Law, Director of the Hong Kong Cancer Registry, gave a detailed account of common cancer incidence in Hong Kong. It is clear that the pattern of cancers in Hong Kong is approaching those in developed countries. We are leaving behind cancers of the stomach, oesophagus, larynx, bladder... ... and embracing the affluent cancers of the breast, colon, prostate and endometrium.

In this same issue of the HKMD, various authors have contributed synopses of systemic treatment of these modern cancers. Adjuvant chemotherapy and endocrine therapy of cancers came a long way, starting from about 40 years ago. Step by step the treatment results improved. With each turn of a decade, adjuvant treatment of major cancers improved the survival rate by increments of a few percent. The best examples are in the adjuvant treatment of breast cancer and colon cancer. The cumulative improvement through the years resulted in marked reduction of cancer deaths compared to no adjuvant treatment.

Non-small cell carcinoma of lung is beginning to catch up. There are a few trials which all showed survival benefits in resectable stage I and II non-small cell lung cancer. At least a proof of the concept was shown. The best combinations / options remain to be determined.

With the targeted therapies starting to play important roles in the treatment of metastatic cancer, their roles as adjuvant treatment is gaining momentum. Trastuzumab in breast cancer is the most current and advanced example. One might speculate that bevacizumab and cetuximab would join the army in adjuvant treatment of colon and lung cancers.

Supportive treatment in cancer is also important. In this issue, new ways of dealing with toxicity of cancer treatments were described. Cancer treatment has never been better.

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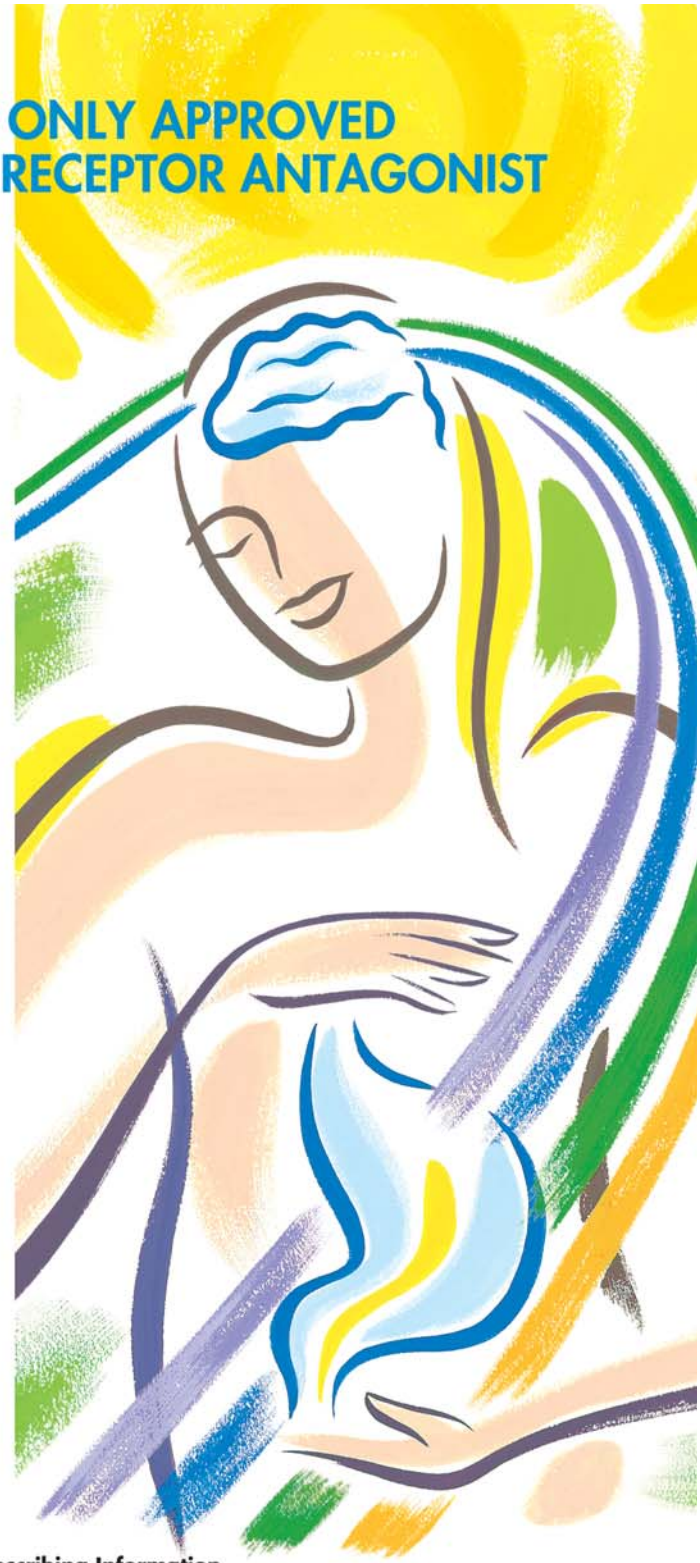

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References: 1. Hong Kong Physician Circular. **2.** Kris MG, Hesketh PJ, Somerfield PF, et al. American Society of Clinical Oncology guideline for antiemetics in oncology: update 2006. *J Clin Oncol.* 2006;24:2932-2947.

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'.....Which Makes Life Even Better'

Dr. William Foo

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Dr. William Foo

Antiemesis

Post-chemotherapy vomiting used to be the major obstacle for patient acceptance of chemotherapy. This is one of the most feared toxicity, from the patient's point of view. Cytotoxic drugs can be classified according to their emetic potential. Highly emetogenic drugs include cisplatin, paraplatin, darcarbazine and anthracyclines. Psychological factors also contribute to the onset and severity of post-chemotherapy vomiting. One tends to associate chemotherapy with vomiting. Once it has started anticipatory vomiting is significant.

Before 1990 the available antiemetic agents were: promethazine, chlorpromazine, metoclopramide, diphenhydramine, aided by lormetazapam and dexamethasone. These were only minimally effective, especially against highly emetogenic drugs.

The H3-antagonists appeared after 1990[1]. Ondansetron, Tropisetron and Graniesetron became available. Together with dexamethasone these H3-antagonists reduced acute emesis i.e. vomiting on the day of chemotherapy significantly. They have little effect on delayed vomiting i.e. vomiting after the first day of chemotherapy. They are also effective against radiation-induced vomiting.

The latest in antiemesis involved the drug aprepitant, a selective, high-affinity antagonist at substance P/neurokinin 1 (NK_1) receptors. The drug crosses the blood-brain barrier and occupies NK_1 receptors in the brain. Aprepitant acts in the CNS to inhibit emesis induced by cytotoxic chemotherapy, including both the acute and delayed emesis.

Efficacy of aprepitant in patients receiving highly emetogenic chemotherapy was established in 2 controlled clinical studies[2,3] comparing a regimen containing aprepitant in combination with a $5\text{-}HT_3$ antagonist (ondansetron) and a corticosteroid (dexamethasone) with a standard regimen containing ondansetron and dexamethasone alone. In these studies, 63-73% of those receiving the regimen with oral aprepitant or 43-52% of those receiving the standard regimen experienced a complete response (i.e., no emetic episodes and no use of rescue therapy) from 0-120 hours after treatment with cisplatin. In the acute phase (0-24 hours) after cisplatin treatment, 83-89% of patients receiving the aprepitant regimen or 68-78% of those receiving the standard regimen experienced a complete response. In the delayed phase (25-120 hours) after cisplatin treatment, 68-75% of patients receiving the aprepitant regimen or 47-56% of those receiving the standard regimen experienced complete response.

The first dose is given orally at least one hour before the start of chemotherapy. The timing is important to allow the NK_1 receptors in the chemotherapy trigger zone (ctz) in the brain stem to be occupied by the drug. Both acute and delayed vomiting are now reduced significantly. So much so that now cisplatin can be used with relative ease. Chemotherapy induced vomiting is no longer feared by the patient, and the physician.

Osteoporosis and endocrine therapy

Osteoporosis is frequently associated with hypogonadal states, in women deprived of oestrogen and men androgen. Osteoporosis is associated with morbidities such as hip fractures, spine fractures, bone pain and kyphoscoliosis.

Known remedies in such situations include increasing dietary intake of calcium (+/- supplements of vitamin D), weight bearing exercise and oral bisphosphonates.

Anti-oestrogens play an important role in the treatment of endocrine-receptor positive breast cancer, in both early and metastatic breast cancers. Known anti-oestrogens include tamoxifen and the aromatase inhibitors anastrozole, letrozole and exemestane. Aromatase inhibitors, which inhibit oestrogen synthesis in postmenopausal patients, are used more and more often, especially in the adjuvant setting. Aromatase inhibitors increase the risk of osteoporosis, which in any case is already more prevalent in postmenopausal patients.

Recently clinical trials have demonstrated that using the parenteral bisphosphonate zoledronic acid can help prevent bone loss and even increase bone density during adjuvant therapy with aromatase inhibitors in early breast cancer.

The 'Zometa-Femara Adjuvant Synergy Trial'[4] (Z-FAST) tested the efficacy in postmenopausal patients. Patients receiving adjuvant letrozole were randomly assigned to receive either upfront or delayed-start zoledronic acid (4 mg intravenously every 6 months). The delayed group received zoledronic acid when lumbar spine (LS) or total hip (TH) T score decreased to less than -2.0 or when a nontraumatic fracture occurred. The upfront and delayed groups each included 301 patients. At month 12, LS BMD was 4.4% higher in the

upfront group than in the delayed group (95% CI, 3.7% to 5.0%; P < .0001), and TH BMD was 3.3% higher (95% CI, 2.8% to 3.8%; P < .0001). In the upfront group, mean serum N-telopeptide and bone-specific alkaline phosphatase concentrations decreased by 15.1% (P < .0001) and 8.8% (P = .0006), respectively, at month 12, whereas concentrations increased significantly in the delayed group by 19.9% (P = .013) and 24.3% (P < .0001), respectively. With 1 year of follow-up, results of the primary end point of the Zometa-Femara Adjuvant Synergy Trial (Z-FAST) indicate that upfront zoledronic acid therapy prevents bone loss in the LS in postmenopausal women receiving adjuvant letrozole for early-stage breast cancer.

A similar conclusion can be drawn in premenopausal breast cancer patients receiving endocrine treatment. In a randomised trial[5], endocrine treatment without zoledronic acid led to significant (P < .001) overall bone loss after 3 years of treatment (BMD, -14.4% after 36 months; mean T score reduction, -1.4). Overall bone loss was significantly more severe in patients receiving anastrozole/goserelin (BMD, -17.3%; mean T score reduction, -2.6) compared with patients receiving tamoxifen/goserelin (BMD, -11.6%; mean T score reduction, -1.1). In contrast, BMD remained stable in zoledronic acid-treated patients.

Gonadotropin-releasing hormone (GnRH) agonists decrease bone mineral density and increase fracture risk in men with prostate cancer. GnRH agonists are now commonly used for androgen ablation for men with prostate cancer, both metastatic and non-metastatic.

In a 12-month study[6], 40 men with nonmetastatic prostate cancer who were receiving a GnRH agonist and had T scores more than -2.5 were randomly assigned to zoledronic acid (4 mg intravenously on day 1 only) or placebo. BMD of the total hip decreased by 1.9% +/- 0.7% in men assigned to placebo and increased by 0.7% +/- 0.5% in men assigned to zoledronic acid (P = .004). Similar between-group differences were observed for the femoral neck and trochanter. Serum N-telopeptide, a marker of osteoclast activity, decreased significantly after zoledronic acid treatment.

Thus a single treatment with zoledronic acid significantly increased BMD and durably suppressed serum N-telopeptide levels for 12 months. Annual zoledronic acid may be a convenient and effective strategy to prevent bone loss in hypogonadal men.

In these two common cancers amenable to hormonal manipulation, adding a bisphosphonate improves the quality of life by reducing skeletal morbidities.

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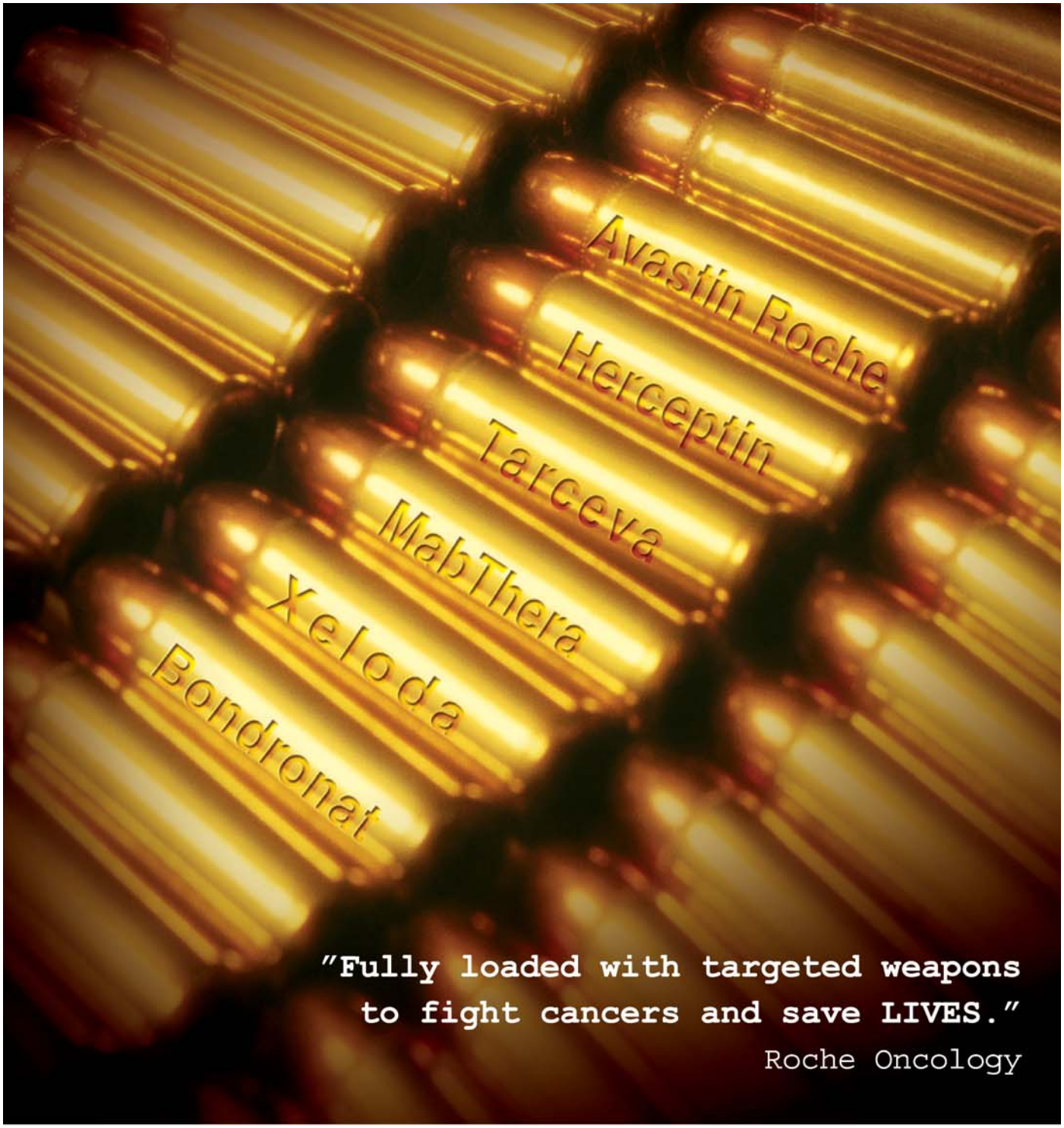

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Systemic Treatment for Colorectal Cancer

Dr. Wai-man Sze

MBChB, FRCR, FHKCR, FHKAM (Radiology), MSc in Palliative Medicine (Wales)
Specialist in Clinical Oncology

Dr . Wai-man Sze

Colorectal cancer ranked number two in incidence in both men and women in the year 2004 in Hong Kong, adding up to 3,500 new patients[1]. In the same year there were about 1,500 deaths attributable to colorectal cancer.

The age-standardised incidence rate of colorectal cancer in Hong Kong is equal to that of the West. For Hong Kong men the age-standardised incidence rate in 2004 was 46.1/10^5, for women it was 32.0/10^5. The same rates for men in North America were 44.4/10^5 and 32.9/105 respectively. We have reached the same level of incidence as in high risk regions.

The median age of diagnosis for Hong Kong men is 70 and women 71. The fact that these are geriatric patients is a concern. A good performance status and minimal co-morbidities are pre-requisite for both successful surgery and systemic treatment. Balancing the risks and benefits of treatment can be difficult.

Surgery remains the mainstay of treatment of colorectal cancer. Surgery clears the tumour burden, helps avoiding bowel complications (obstruction, perforation) and at the same time provides pathological information. The need for adjuvant chemotherapy is based on the pathological findings.

The risk of relapse is dependent on stage. The two most important factors are the depth of penetration to the bowel wall and the number of lymph nodes involved. Stage I denotes node-negative cancer involving at most the muscle layer. Stage II is node-negative cancer with the primary tumour involving subserosa (T3) or serosa and beyond (T4). Stage III is node-positive cancer. Stage IV denotes distant metastasis. The corresponding 5-year survival rates, without adjuvant treatment, are 90%, 80%, 50% and 10% respectively.

Systemic treatment is divided into two scenarios: adjuvant and metastatic settings. In the adjuvant setting one is using systemic treatment to reduce the risk of relapse and improve survival. In the metastatic setting one is improving quality of life and trying to improve survival. So far adjuvant systemic treatment involves chemotherapy only. Biological agents or targeted therapy remains a research option. In treating metastasis chemotherapy and/or targeted therapy is used.

There is no indication for adjuvant treatment for stage I colorectal cancer after resection. Survival is in the region of 90%.

Stage II

For stage II colorectal cancer there is no indication for adjuvant chemotherapy in general. Most of the time survival rate is in the region of 80%. Adjuvant chemotherapy trials failed to demonstrate a survival benefit.

There are however, categories of high-risk stage II colorectal cancers. The high-risk factors are: T4 tumour, presence of perforation, presence of obstruction, presence of lymphovascular permeation or less than 12 lymph nodes examined.

Of note, the number of lymph nodes identified in the surgical specimen correlates with the prognosis[2]. It was demonstrated that in patients with T3N0 disease and only 1 to 2 nodes identified, the 5-year survival rate is 64%, but when more than 25 negative nodes were identified, the 5-year survival rate increases to 80%. It suggests that without adequate node sampling, patients may be under-staged. It was recommended that the minimum number of nodes for adequate staging is 13. Therefore, if a stage II patient has fewer than 13 negative nodes identified, the clinician is well justified in recommending adjuvant chemotherapy because such a case may be understaged. The AJCC TNM staging manual recommended at least 7-14 nodes be available for pathological examination.

A subset analysis of the MOSAIC trial[4] demonstrated that high-risk stage II disease derived the same benefit from FOLFOX4 compared with LV5FU2 as unselected stage III patients (4-year DFS of 84.9% versus 79.8%, respectively; hazard ratio, 0.72).

In well-motivated high-risk stage II patients in good performance status, adjuvant chemotherapy should be seriously considered.

Stage III colorectal cancer

Without adjuvant treatment, patients with stage III colorectal cancer face a relapse rate of 50-60% in 5 years. Fluorouracil-based adjuvant chemotherapy reduces the risk by 30%, translating into an absolute reduction of 10%[3]. Update of the MOSAIC trial comparing FOLFOX4 (oxaliplatin, fluorouracil and folinic acid) to LV5FU2 (fluorouracil and folinic acid) showed that the 6 year survival for stage III was 72.9% vs 68.3%,with a hazard ratio of 0.85.

Choice of adjuvant chemotherapy.

Adjuvant chemotherapy for colorectal cancer evolved a long way (Table 1). It started with single agent fluorouracil. Treatment went on for one year. At some time the antihelminthic levamizole was added but later abandoned. The efficacy of fluorouracil was enhanced by folinic acid. The Mayo clinic regimen of 5 days of bolus injection of fluorouracil and folinic acid every 4 weeks for 6 months became standard for a while. It was associated with toxicities like stomatitis, diarrhoea and alopecia. This was further improved by chronomodulation. With chronomodulation the toxicity was much less.

It was only 10 years later that a new agent was added. Oxaliplatin, when added to chronomodulated fluorouracil and folinic acid, has been shown as the most effective combination chemotherapy in adjuvant treatment (MOSAIC trial[7]) than chronomodulated fluoruracil and folinic acid with an HR of 28%. The drawback is that FOLFOX4 needs to be administered in 3 days every 2 weeks for a total of 12 cycles in 6 months. The repeated hospital admission is inconvenient to both patient and healthcare team. Irinotecan failed to make the adjuvant scene so far.

Modulated fluorouracil-based chemotherapy confers a hazard reduction in relapse by 40% and cancer-specific death by 33%. Oxaliplatin-based treatment7 further reduces the relapse risk by about 28%.

The oral variant of fluorouracil, capecitabine, is a valid alternative. The X-ACT trial[8] shows that single agent capecitabine is at least equivalent to the Mayo Clinic regimen of fluorouracil plus leucovorin in patients younger than 70 years and those 70 years of age or older. The safety advantage of capecitabine over fluorouracil plus leucovorin was also maintained in these subgroups. Capecitabine is taken orally, with a different toxicity profile than intravenous fluorouracil. There is less marrow toxicity, less diarrhoea, less stomatitis and less alopecia with. On the other hand the dose-limiting toxicity is often palmar-plantar erythrodysaesthesia. Clinical trials are on-going to evaluate the combination of capecitabine and oxaliplatin, which can be given in a day-case setting.

Currently the practical choice of adjuvant chemotherapy would lie between oxaliplatin-based, which is more effective but more demanding physically and financially; and capecitabine. Oxaliplatin-based regimens include FOLFOX4[7] and FLOX[9]. These are both combinations of oxaliplatin, fluorouracil and folinic acid in different schedules. Both have been shown to reduce relapse risk by a similar magnitude (HR 25-28%). Capecitabine alone can be given with relative ease, without hospitalisation, and can be better tolerated in those in less favourable performance status or with co-morbidities.

Table 1. Evolution of adjuvant chemotherapy for colorectal cancer

1990	5-FU/lev better than surgery alone
1994	5-FU/LV better than surgery alone
1998	5-FU/LV better than 5-FU/lev
1998	6 months = 12 months
1998	Levamisole unnecessary
1998	HDLV = LDLV
1998	Weekly = monthly
2002	LV5FU2 = monthly bolus

Metastatic Colorectal Cancer

Treatment of metastatic colorectal cancer is based on seven drugs (Table 2): fluorouracil, folinic acid, capecitabine, oxaliplatin, irinotecan on one hand, bevacizumab and cetuximab on the other. The optimal combination and sequence of utilisation remains to be defined.

The basic skeleton is fluorouraicil plus folinic acid. Either oxaliplatin or irinotecan can be added to this skeleton (FOLFOX or FOLFIRI), with a response rate of around 40% and a response duration of around 8 months. When the cancer progresses one can cross to the other. Capecitabine can replace the fluorouracil - folinic acid infusion, reducing the treatment duration of each session (XELOX or XELIRI).

Bevacizumab and cetuximab, being targeted therapy agents, are now incorporated into the scenario of metastatic colorectal cancer.

Bevacizumab is a chimerised monoclonal antibody against the vascular endothelial growth factor (VEGF). In 2006, the U.S. Food and Drug Administration (FDA) approved bevacizumab administered in combination with FOLFOX4 for the second-line treatment of metastatic carcinoma of the colon or rectum. The most serious, and sometimes fatal, bevacizumab toxicities are gastrointestinal perforation, wound-healing complications, haemorrhage, arterial thromboembolic events, hypertensive crisis, nephrotic syndrome, and congestive heart failure.

Cetuximab is a chimeric mouse-human monoclonal antibody targeting the extracellular domain of the epidermal growth factor receptor (EGFR). Cetuximab in combination with irinotecan has been registered in the USA and Europe for the treatment of patients with metastatic colorectal cancer expressing the EGFR after failure of prior irinotecan-based cytotoxic therapy. Important toxicities of cetuximab include an acneiform skin rash and diarrhoea.

Various phase II studies showed efficacy of either bevacizumab or cetuximab added to the chemotherapy combinations containing oxaliplatin or irinotecan.

It has been demonstrated that with the advent of these new drugs, survival in metastatic colorectal cancer is now in the region of 2-3 years, compared to just one year in the fluorouracil era.

Joining the arena of targeted therapy is Panitumumab, is a fully human monoclonal antibody directed against the epidermal growth factor receptor (EGFR). It was recently approved by the FDA for the treatment of chemotherapy refractory, epidermal growth factor expressing colorectal cancer. It was based on a phase III trial[10] comparing panitumumab plus best supportive care (BSC) to that of BSC. Panitumumab significantly prolonged PFS (HR, 0.54; , [$P < .0001$]). Median PFS time was 8 weeks for panitumumab and 7.3 weeks for BSC. Mean PFS time was 13.8 weeks for panitumumab and 8.5 weeks for BSC. After a 12-month minimum follow-up, response rates were 10% for panitumumab and 0% for BSC ($P < .0001$). No difference was observed in

overall survival which was confounded by crossing-over. Panitumumab was well tolerated. Skin toxicities, hypomagnesaemia, and diarrhoea were the most common toxicities observed. No patients had grade 3/4 infusion reactions.

Table 2. Significant phase III trials of chemotherapy for metastatic colorectal cancer.

Regimen	RR (%)	Median PFS or TTP (mo)	Median OS (mo)
5-FU/LV IFL (Saltz trial)	21 39 (P<0.001)	4.3 7.0 (P=0.004)	12.6 14.8 (P=0.04)
5-FU/LV FOLFIRI (Douillard trial)	22 35 (P<0.005)	4.4 6.7 (P<0.001)	14.1 17.4 (P=0.031)
5-FU/LV FOLFOX4 (de Gramont trial)	22 51 (P=0.0001)	6.2 9.0 (P=0.0003)	14.7 16.2 (P=0.12)
IFL IROX FOLFOX4 (N9741 trial)	31 35 45	6.9 (P=0.0014) 6.5 (P=0.001) 8.7	15.0 (P=0.0001) 17.4 (P=0.09) 19.5

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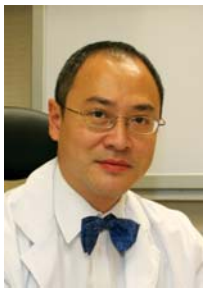
Systemic Adjuvant Therapy for Invasive Breast Cancer

Dr. Michael MC Cheung

MBBS, FRCR, FHKCR, FHKAM (Radiology)
Specialist in Clinical Oncology



Dr . Michael MC Cheung

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 one CME credit under the programme upon returning the completed answer sheet to the Federation Secretariat on or before 31 August 2007.

Introduction

Adjuvant treatment for breast cancer saves lives. Both chemotherapy and endocrine therapy, and independent of each other, are effective in reducing relapse risk and increasing survival.

A working principle is that adjuvant therapy should be considered if the estimated risk of relapse is greater than 10%. The benefits of adjuvant treatment should be balanced against toxicity.

A decade or more ago, postoperative systemic adjuvant therapy of breast cancer was very simple, mainly consisting of 5 years of tamoxifen and /or chemotherapy. Chemotherapy then was CMF - Cyclophosphamide, Methotrexate and Fluorouracil.

Nevertheless, the survival advantage (hazard ratio of 0.79) of the CMF regimen was sustained up to 30 years when the series was updated in 2005[1]. Furthermore the same regimen yielded a hazard ratio of 0.65 at 20 years when used in node-negative oestrogen-receptor negative breast cancer.

This fact was demonstrated time and again by the meta-analysis by the Early Breast Cancer Trialists' Collaborative Group[2] (EBCTCG). Both chemotherapy and endocrine therapy effectively reduced the risk of relapse and improved survival in invasive breast cancer. At 15th year, the relapse rates were 41.1% vs 53.5% in favour of chemotherapy. The corresponding overall mortality rates were 32.4% vs 42.4%. With adjuvant Tamoxifen, which was administered for 5 years in endocrine receptor (ER) positive breast cancer patients, the corresponding relapse risk at 15 years were 33.2% vs 45%, in favour of endocrine therapy. The corresponding mortality rates were 25.6% vs 34.8%.

Research in the last 10 years had made big steps in reducing disease relapse and increasing survival with new pharmaceutical agents. At present, patients after surgery can be categorised according to prognostic factors (Table 1) and major international guidelines are available for a risk-adapted treatment approach[3].

Important pathological parameters include: number of metastatic axillary nodes, grading, endocrine receptor status, tumour size, HER2 over-expression, presence of peri-tumoral vascular invasion and age. Patients are then categorised to low, intermediate and high-risk groups.

What's new in Endocrine Therapy

Aromatase inhibitors are new in adjuvant endocrine therapy for endocrine-receptor positive breast cancer.

The old standard hormonal therapy (5 years of Tamoxifen) for oestrogen receptor (ER) positive disease has the drawback of a slight increase in endometrial cancer (around 1 additional case per 1,000 patient-years of drug use) and side effects like increased thromboembolic events. Furthermore, the risk of relapse of hormonal-dependent tumours is known to extend beyond 10 years after surgery, which is not helped by extending treatment with Tamoxifen beyond 5 years.

Aromatase inhibitors, in postmenopausal patients, are better than Tamoxifen. Several large randomised studies such as ATAC[4], BIG-98[5], IES[6] and MA-17[7] trials have all shown significant survival benefit and better tolerance of aromatase inhibitors (AI) than 5 years of Tamoxifen. In these trials, AIs were either used upfront (Anastrozole or Letrozole), after 2-3 years of Tamoxifen (Exemestane), or as extended adjuvant therapy (Letrozole) after 5 years of Tamoxifen.

Actually, the present guideline from American Society of Clinical Oncology (ASCO) on hormonal therapy recommends the use of an AI at 'some point in time' in the adjuvant hormonal therapy of postmenopausal ER-positive patients.

In premenopausal patients, the use of a luteinising hormone releasing hormone (LHRH) agonist (eg Goserilin) for 2 years has been proven to give equivalent results to CMF chemotherapy[8] - the old standard. This effect was the same in both node-positive and node-negative patients. This reversible medical castration therefore, is an alternative to chemotherapy in low-risk (eg node-negative disease) patients who want to avoid the side-effects of chemotherapy.

What's new in chemotherapy

Since the turn of the century, the anthracycline-containing (adriamycin, epirubicin) regimens have replaced CMF as standard adjuvant chemotherapy. From the EBCTCG meta-analysis anthracyclines provided an extra advantage in survival than CMF, especially in women younger than 50.

One of the latest regimen of anthracycline is FEC100 (epirubicin 100 mg / sq m).It has been shown to be superior to FEC 50 (epirubicin 50 mg / sq m) in a recent 10-year update[11]. The difference in relapse and survival rates were about 5%.

The addition of taxanes (paclitaxel or docetaxel) to anthracycline-containing regimens was shown to give additional survival benefit with an absolute gain of 2% to 7% in different randomised trials.

For paclitaxel, the drug is given for four cycles after four cycles adriamycin and cyclophosphamide (AC) (CALGB protocol 9344[9]) every 3 weeks or given in a 'dose-dense' fashion (every 2 weeks instead of 3) with growth factor (G-CSF) support in between cycles (CALGB protocol 9741[10]), which was shown to give superior survival effects to the same drugs given every 3 weeks.

Docetaxel has also been tested against standard anthracycline-containing regimens and shown to confer survival benefit. It can be given as the TAC[12] regimen (Taxotere, Adriamycin, Cyclophosphamide) every 3 weeks, but growth factor support to prevent severe neutropenia should be given. Alternatively, it can be given in three 3-weekly cycles following three cycles of FEC 100 as in the French PACS-01[13] study. Five-year DFS rates were 73.2% with FEC and 78.4% with FEC-D. Five-year overall survival rates were 86.7% with FEC and 90.7% with FEC-D, demonstrating a 27% reduction in the relative risk of death. At present these regimens, together with the dose-dense regimen giving four cycles of paciltaxel as mentioned above, are the most common 'third generation' chemotherapy administered in high-risk node-positive disease.

Targeted therapy with trastuzumab against the HER2/*neu* receptor.

Following trials showing dramatic improvement of response rates when trastuzumab was combined with chemotherapy in HER2/*neu* oncogene amplified metastatic breast cancer, large-scale randomised studies have been conducted in the use of trastuzumab in the adjuvant setting. Preliminary results of these trials[14-17] have been published with more than 13,000 patients accrued. Even though median follow-up time of some of these trials has been just over 1 year, a significant relapse-free survival gain (absolute gain of up to 18%) was reported for all of these trials. Although the optimal duration of trastuzumab treatment and the optimal sequence of it use with respect to chemotherapy is not known, it is generally recommended that one year of adjuvant trastuzumab should be considered for high-risk HER2/*neu* amplified or over-expressed breast cancer after acknowledging the potential cardiac risk of the drug, especially when is it used concurrently with chemotherapy.

Risk-adapted systemic adjuvant therapy for invasive breast cancer

In summary, the most appropriate systemic adjuvant treatment depends on the estimated risk of relapse of the breast cancer. At present this is done by evaluating the clinical prognostic factors, including the number of metastatic axillary nodes, the ER status, the grading of tumour and age, and placing patients into risk categories such as the St Gallen 2005 risk categories. In international guidelines of adjuvant treatment, the aggressiveness of recommended therapy depend on the estimated risk, and the exact treatment needed would depend on predictive factors: ER and Her2/neu oncogene status.

Finally the patient's general condition, co-morbidities and wishes are the most important modifying factors. Aggressive chemotherapy might not be tolerated in elderly patients with significant medical conditions and might not be appropriate even if the prognostic factors suggest a very aggressive cancer. Medical castration, which is likely to have reversible effects on ovarian function, might be the preferred treatment in those with few involved axillary nodes and who do not want the side-effects of chemotherapy (eg alopecia and potential infertility). However, even good guidelines cannot replace detailed personalised discussion with the patient, and the optimal therapy should be a highly individualised decision for each patient.

Table 1. Risk categories of invasive breast cancer (adapted from International Expert Consensus on the Primary Therapy of Early Breast Cancer 2005)

RISK CATEGORY	NODAL STATUS	FACTORS	OTHER PROGNOSTIC
LOW	Negative	AND	Tumour ≤2 cm AND grade 1 AND No vascular invasion AND HER2/*neu* not amplified nor over-expressed AND age ≥ 35
INTERMEDIATE	Negative	AND	Tumour >2 cm OR grade 2-3 OR Presence of vascular invasion OR HER2/*neu* amplified or over-expressed OR age >35
	OR 1-3 positive	AND	HER2/*neu* not amplified nor over-expressed
HIGH	1-3 positive	AND	HER2/*neu* amplified or over-expressed
	OR > 4 positive		

Table 2. Guidelines of systemic adjuvant therapy according to the risk

RISK CATEGORY	HORMONE SENSITIVE CANCER	HORMONE-RESISTANT CANCER
LOW	Hormonal therapy or none*	Not applicable
INTERMEDIATE	Hormonal therapy alone, OR Chemotherapy then hormonal therapy (trastuzumab therapy considered in HER2/*neu* amplified or over-expressed)	Chemotherapy alone (trastuzumab therapy considered in HER2/*neu* amplified or over-expressed)
HIGH	Chemotherapy then hormonal therapy OR Hormonal therapy alone*, (trastuzumab therapy considered in HER2/*neu* amplified or over-expressed)	HER2/*neu* amplified or over-expressed

* Indicates alternative treatment option in the case of preference of physician or patient, or medical contraindications.

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MCHK CME Programme Self-assessment Questions

Please read the article entitled "Systemic Adjuvant Therapy for Invasive Breast Cancer" by Dr. Michael MC Cheung , and complete the following self-assessment questions. Participants in the MCHK CME Programme will be awarded 1 CME credit under the Programme for returning completed answer sheets via fax (2865 0345) or by mail to the Federation Secretariat on or before 31 August 2007. 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. Adjuvant therapy for breast cancer improves relapse-free survival only.

2. The effect of adjuvant treatment lasts for only 5 years.

3. Only the number of positive axillary nodes matters in prognosis.

4. Aromatase inhibitors are effective only in post-menopausal breast cancer patients.

5. In pre-menopausal patients, LHRH agonists are superior to chemotherapy in reducing relapse risk.

6. Anthracycline-containing chemotherapy has replaced the CMF regimen in adjuvant therapy.

7. Taxane-containing regimens have a higher efficacy than anthracycline-containing regimens.

8. Adjuvant trastuzumab should be given for at least one year.

9. The critical toxicity for adjuvant trastuzumab is cardiac toxicity.

10. Adjuvant therapy should be given to all breast cancer patients.

ANSWER SHEET FOR AUGUST 2007

Please return the completed answer sheet to the Federation Secretariat on or before 31 August 2007 for documentation. 1 CME point will be awarded for answering the MCHK CME programme (for non-specialists) self-assessment questions.

Systemic Adjuvant Therapy for Invasive Breast Cancer

Dr. Michael MC Cheung

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Specialist in Clinical Oncology

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

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Answers to July 2007 issue

Head & Neck Surgery

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- Tolerability was acceptable in patients receiving SUTENT[1,2]

*PFS - Progression free survival
$^{\Delta}$TTP- Time to tumour progression

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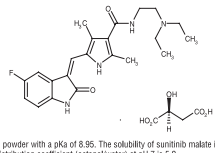
DESCRIPTION

SUTENT®, an oral multi-kinase inhibitor targeting several receptor tyrosine kinases (RTK), is the malate salt of sunitinib. Sunitinib malate is described chemically as Butanedioic acid, hydroxy-, (2S)-, compound with *N*-[2-(diethylamino)ethyl]-5-[(*Z*)-(5-fluoro-1,2-dihydro-2-oxo-3*H*-indol-3-ylidine)methyl]-2,4-dimethyl-1*H*-pyrrole-3-carboxamide (1:1). The molecular formula is $C_{22}H_{27}FN_4O_2 \cdot C_4H_6O_5$ and the molecular weight is 532.6 Daltons. The chemical structure of sunitinib malate is:



Sunitinib malate is a yellow to orange powder with a pKa of 8.95. The solubility of sunitinib malate in aqueous media over the range pH 1.2 to pH 6.8 is in excess of 25 mg/mL. The log of the distribution coefficient (octanol/water) at pH 7 is 5.2.

SUTENT (sunitinib malate) capsules are supplied as printed hard shell capsules containing sunitinib malate equivalent to 12.5 mg, 25 mg or 50 mg of sunitinib together with mannitol, croscarmellose sodium, povidone (K-25) and magnesium stearate as inactive ingredients.

The orange gelatin capsule shells contain titanium dioxide, and red iron oxide. The caramel gelatin capsule shells also contain yellow iron oxide and black iron oxide. The printing ink contains shellac, propylene glycol, sodium hydroxide, povidone and titanium dioxide.

CLINICAL PHARMACOLOGY

Mechanism of Action

Sunitinib malate is a small molecule that inhibits multiple RTKs, some of which are implicated in tumor growth, pathologic angiogenesis, and metastatic progression of cancer. Sunitinib was evaluated for its inhibitory activity against a variety of kinases (>80 kinases) and was identified as an inhibitor of platelet-derived growth factor receptors (PDGFRα and PDGFRβ), vascular endothelial growth factor receptors (VEGFR1, VEGFR2 and VEGFR3), stem cell factor receptor (KIT), Fms-like tyrosine kinase-3 (FLT3), colony stimulating factor receptor Type 1 (CSF-1R), and the glial cell-line derived neurotrophic factor receptor (RET). Sunitinib inhibition of the activity of these RTKs has been demonstrated in biochemical and cellular assays, and inhibition of function has been demonstrated in cell proliferation assays. The primary metabolite exhibits similar potency compared to sunitinib in biochemical and cellular assays.

Sunitinib inhibited the phosphorylation of multiple RTKs (PDGFRβ, VEGFR2, KIT) in tumor xenografts expressing RTK targets *in vivo* and demonstrated inhibition of tumor growth or tumor regression and/or inhibited metastases in some experimental models of cancer. Sunitinib demonstrated the ability to inhibit growth of tumor cells expressing dysregulated target RTKs (PDGFR, RET, or KIT) *in vitro* and to inhibit PDGFRβ- and VEGFR2-dependent tumor angiogenesis *in vivo*.

Pharmacokinetics

The pharmacokinetics of sunitinib and sunitinib malate have been evaluated in 135 healthy volunteers and in 266 patients with solid tumors.

Absorption, Distribution, Metabolism, and Elimination

Maximum plasma concentrations (C_{max}) of sunitinib are generally observed between 6 and 12 hours (T_{max}) following oral administration. Food has no effect on the bioavailability of sunitinib. Sunitinib may be taken with or without food.

Binding of sunitinib and its primary metabolite to human plasma protein *in vitro* was 95% and 90%, respectively, with no concentration dependence in the range of 100 - 4000 ng/mL. The apparent volume of distribution (Vd/F) for sunitinib was 2230 L. In the dosing range of 25 - 100 mg, the area under the plasma concentration-time curve (AUC) and C_{max} increase proportionately with dose.

Sunitinib is metabolized primarily by the cytochrome P450 enzyme, CYP3A4, to produce its primary active metabolite, which is further metabolized by CYP3A4. The primary active metabolite comprises 23 to 37% of the total exposure. Elimination is primarily via feces. In a human mass balance study of [^{14}C] sunitinib, 61% of the dose was eliminated in feces, with renal elimination accounting for 16% of the administered dose. Sunitinib and its primary active metabolite were the major drug-related compounds identified in plasma, urine, and feces, representing 91.5%, 86.4% and 73.8% of radioactivity in pooled samples, respectively. Minor metabolites were identified in urine and feces but generally not found in plasma. Total oral clearance (CL/F) ranged from 34 to 62 L/hr with an inter-patient variability of 40%.

Following administration of a single oral dose in healthy volunteers, the terminal half-lives of sunitinib and its primary active metabolite are approximately 40 to 60 hours and 80 to 110 hours, respectively. With repeated daily administration, sunitinib accumulates 3- to 4-fold while the primary metabolite accumulates 7- to 10-fold. Steady-state concentrations of sunitinib and its primary active metabolite are achieved within 10 to 14 days. By Day 14, combined plasma concentrations of sunitinib and its active metabolite ranged from 62.9 – 101 ng/mL. No significant changes in the pharmacokinetics of sunitinib or the primary active metabolite were observed with repeated daily administration or with repeated cycles in the dosing regimens tested.

The pharmacokinetics were similar in healthy volunteers and in the solid tumor patient populations tested, including patients with gastrointestinal stromal tumor (GIST) and metastatic renal cell carcinoma (MRCC) (see CLINICAL STUDIES).

Special Populations

Population pharmacokinetic analyses of demographic data indicate that there are no clinically relevant effects of age, body weight, creatinine clearance, race, gender or ECOG score on the pharmacokinetics of SUTENT or the active metabolite.

The pharmacokinetics of sunitinib have not been evaluated in pediatric patients.

Hepatic Insufficiency

No clinical studies were conducted in patients with impaired hepatic function. Studies that were conducted excluded patients with ALT or AST > 2.5 x ULN or, if due to underlying disease, > 5.0 x ULN.

Renal Insufficiency

No clinical studies were conducted in patients with impaired renal function. Studies that were conducted excluded patients with serum creatinine > 2.0 x ULN. Population pharmacokinetic analyses have shown that sunitinib pharmacokinetics were unaltered in patients with calculated creatinine clearances in the range of 42 – 347 mL/min.

Drug-Drug Interactions

In vitro studies indicate that sunitinib does not induce or inhibit major CYP enzymes.

In Vitro Studies of CYP Inhibition and Induction: The *in vitro* studies in human liver microsomes and hepatocytes of the activity of CYP isoforms CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1, CYP3A4/5, and CYP4A9/11 indicated that sunitinib and its primary active metabolite are unlikely to have any clinically relevant drug-drug interactions with drugs that may be metabolized by these enzymes.

CYP3A4 Inhibitors: Concurrent administration of sunitinib malate with the strong CYP3A4 inhibitor, ketoconazole, resulted in 49% and 51% increases in the combined (sunitinib + primary active metabolite) C_{max} and $AUC_{0-\infty}$ values, respectively, after a single dose of sunitinib malate in healthy volunteers. A dose reduction for SUTENT should be considered when it must be co-administered with strong CYP3A4 inhibitors (see DOSAGE AND ADMINISTRATION).

CYP3A4 Inducers: Concurrent administration of SUTENT with the strong CYP3A4 inducer, rifampin, resulted in a 23% and 46% reduction in the combined (sunitinib + primary active metabolite) C_{max} and $AUC_{0-\infty}$ values, respectively, after a single dose of SUTENT in healthy volunteers. A dose increase for SUTENT should be considered when it must be co-administered with CYP3A4 inducers (see DOSAGE AND ADMINISTRATION).

CLINICAL STUDIES

The clinical safety and efficacy of SUTENT have been studied in patients with gastrointestinal stromal tumor (GIST) after progression on or intolerance to imatinib mesylate, and in patients with metastatic renal cell carcinoma (MRCC) after failure of cytokine-based therapy.

Gastrointestinal Stromal Tumor (GIST)

Study A

Study A was a two-arm, international, randomized, double-blind, placebo-controlled trial of SUTENT in patients with GIST who had disease progression during prior imatinib mesylate (imatinib) treatment or who were intolerant of imatinib. The primary objective was to compare time-to-tumor progression (TTP) in patients receiving SUTENT plus best supportive care versus patients receiving placebo plus best supportive care. Secondary objectives included progression-free survival (PFS), objective response rate (ORR), and overall survival (OS). Patients were randomized (2:1) to receive either 50 mg SUTENT or placebo orally, once daily, on a schedule of 4 weeks on treatment followed by 2 weeks off (Schedule 4/2) until disease progression or withdrawal from the study for another reason. Treatment was unblinded at the time of disease progression. Patients randomized to placebo were then offered crossover to open-label SUTENT, and patients randomized to SUTENT were permitted to continue treatment per investigator judgment.

The intent-to-treat (ITT) population included 312 patients. Two-hundred seven patients were randomized to the SUTENT arm, and 105 patients were randomized to the placebo arm. Baseline age, gender, race and ECOG performance status were comparable between the placebo and SUTENT groups. Prior exposure to imatinib was similar between the two study arms. Demographics and patient characteristics are shown in Table 1.

Table 1. Baseline Demographics in Study A

	SUTENT (N=207)	Placebo (N=105)
Gender [N (%)]		
Male	132 (64)	64 (61)
Female	75 (36)	41 (39)
Self-identified Race [N (%)]		
White	183 (88)	92 (88)
Asian	10 (5)	5 (5)
Black	8 (4)	4 (4)
Not reported	6 (3)	4 (4)
Age Group [N (%)]		
< 65 years	143 (69)	76 (72)
≥ 65 years	64 (31)	29 (28)
Performance Status [N (%)]		
0	92 (44)	48 (46)
1	113 (55)	55 (52)
2	2 (1)	2 (2)
Prior Treatment [N (%)]		
Surgery (other than biopsy)	194 (94)	98 (93)
Radiotherapy	16 (8)	16 (15)
Imatinib outcome [N (%)]		
Intolerance	9 (4)	4 (4)
Progression within 6 months	36 (17)	17 (16)
Progression beyond 6 months	162 (78)	84 (80)

A planned interim efficacy and safety analysis was performed after 149 TTP events had occurred. There was a statistically significant advantage for SUTENT over placebo in the primary endpoint of TTP, as well as in the secondary endpoint of progression-free survival. Data were not mature enough to determine the overall survival benefit. Efficacy results are summarized in Table 2.

Table 2. GIST Efficacy Results (interim analysis)

Efficacy Parameter	Study A			
	SUTENT (N = 207)	Placebo (N = 105)	P-value (log-rank test)	HR (95% CI)
Time to Tumor Progression[a] [median, weeks (95% CI)]	27.3 (16.0, 32.1)	6.4 (4.4, 10.0)	<0.0001*	0.33 (0.23, 0.47)
Progression Free Survival[b] [median, weeks (95% CI)]	24.1 (11.1, 28.3)	6.0 (4.4, 9.9)	<0.0001*	0.33 (0.24, 0.47)
Objective Response Rate (PR) [%, (95% CI)]	6.8 (3.7, 11.1)	0	0.006[c]	

CI=Confidence interval, HR=Hazard ratio, PR=Partial response

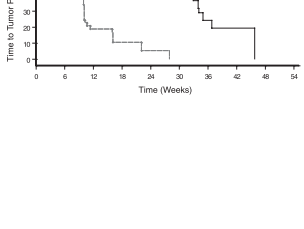
* A comparison is considered statistically significant if the p-value is < 0.0042 (O'Brien Fleming stopping boundary)

[a] Time from randomization to progression; deaths prior to documented progression were censored at time of last radiographic evaluation

[b] Time from randomization to progression or death due to any cause

[c] Pearson chi-square test

Figure 1. Kaplan-Meier Curve of TTP in Study A (Intent-to-Treat Population)



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CLINICAL STUDIES *(continued)*

Study B

Study B was an open-label, multi-center, single-arm, dose-escalation study conducted in patients with GIST following progression on or intolerance to imatinib. Following identification of the recommended Phase 2 regimen (50 mg once daily on Schedule 4/2), 55 patients in this study received the 50 mg dose of SUTENT on treatment Schedule 4/2. Partial responses were observed in 5 of 55 patients [9.1% PR rate, 95% CI (3.0, 20.0)].

Metastatic Renal Cell Carcinoma (MRCC)

The use of single agent SUTENT in the treatment of cytokine-refractory MRCC was investigated in two single-arm, multi-center studies. All patients enrolled into these studies experienced failure of prior cytokine-based therapy. In Study 1, failure of prior cytokine therapy was based on radiographic evidence of disease progression defined by RECIST or World Health Organization (WHO) criteria during or within 9 months of completion of 1 cytokine therapy treatment (interferon-α, interleukin-2, or interferon-α plus interleukin-2; patients who were treated with interferon-α alone must have received treatment for at least 28 days). In Study 2, failure of prior cytokine therapy was defined as disease progression or unacceptable treatment-related toxicity. The primary endpoint for both studies was ORR. Duration of response (DR) was also evaluated.

One hundred six patients were enrolled into Study 1, and 63 patients were enrolled into Study 2. Patients received 50 mg SUTENT on Schedule 4/2. Therapy was continued until the patients met withdrawal criteria or had progressive disease. The baseline age, gender, race and ECOG performance statuses of the patients were comparable between Studies 1 and 2. Approximately 86-94% of patients in the two studies were white. Men comprised 65% of the pooled SUTENT population. The median age was 57 years and ranged from 24 to 87 years in the studies. All patients had an ECOG performance status <2 at the screening visit.

The baseline malignancy and prior treatment history of the patients were comparable between Studies 1 and 2. Across the two studies, 95% of the pooled population of patients had at least some component of clear-cell histology. All patients in Study 1 were required to have a histological clear-cell component. Most patients enrolled in the studies (97% of the pooled population) had undergone nephrectomy; prior nephrectomy was required for patients enrolled in Study 1. All patients had received one previous cytokine regimen. Metastatic disease present at the time of study entry included lung metastases in 81% of patients. Liver metastases were more common in Study 1 (27% vs. 16% in Study 2) and bone metastases were more common in Study 2 (51% vs. 25% in Study 1); 52% of patients in the pooled population had at least 3 metastatic sites. Patients with known brain metastases or leptomeningeal disease were excluded from both studies.

Results of Studies 1 and 2

The ORR and DR data from Studies 1 and 2 are provided in Table 3.

Table 3. MRCC Efficacy Results

Efficacy Parameter	Study 1 (N = 106)	Study 2 (N = 63)
Objective Response Rate (PR) [%, (95% CI)]	25.5[1] (17.5, 34.9)	36.5[2] (24.7, 49.6)
Duration of Response [median, weeks (95% CI)]	27.1 (24.4, *)	54 (34.3, 70.1)

CI=Confidence interval, PR=Partial response

[1] Assessed by blinded core radiology laboratory

[2] Assessed by investigators

* Data not mature enough to determine upper confidence limit

There were 27 PRs in Study 1 as assessed by a core radiology laboratory for an ORR of 25.5% (95% CI 17.5, 34.9). There were 23 PRs in Study 2 as assessed by the investigators for an ORR of 36.5% (95% CI 24.7-49.6). The majority (>90%) of objective disease responses were observed during the first four cycles; the latest reported response was observed in cycle 10. DR data from Study 1 is premature as only 4 of 27 patients (15%) responding to treatment had experienced disease progression. At the time of the data cutoff, Study 1 was ongoing with 44 of 106 patients (41.5%) continuing treatment, and 11 of the 63 patients (17.5%) enrolled on Study 2 continued to receive SUTENT on continuation protocols.

INDICATIONS AND USAGE

SUTENT is indicated for the treatment of gastrointestinal stromal tumor after disease progression on or intolerance to imatinib mesylate.

SUTENT is indicated for the treatment of advanced renal cell carcinoma. Approval for advanced renal cell carcinoma is based on partial response rates and duration of responses. There are no randomized trials of SUTENT demonstrating clinical benefit such as increased survival or improvement in disease-related symptoms in renal cell carcinoma.

CONTRAINDICATIONS

Use of SUTENT is contraindicated in patients with hypersensitivity to sunitinib malate or to any other component of SUTENT.

WARNINGS

Pregnancy Category D

Sunitinib was evaluated in pregnant rats (0.3, 1.5, 3.0, 5.0 mg/kg/day) and rabbits (0.5, 1, 5, 20 mg/kg/day) for effects on the embryo. Significant increases in the incidence of embryolethality and structural abnormalities were observed in rats at the dose of 5 mg/kg/day (approximately 5.5 times the systemic exposure in patients administered the recommended daily doses [RDD]). Significantly increased embryolethality was observed in rabbits at 5 mg/kg/day while developmental effects were observed at ≥1 mg/kg/day (approximately 0.3 times the AUC in patients administered the RDD of 50 mg/day). Developmental effects consisted of fetal skeletal malformations of the ribs and vertebrae in rats. In rabbits, cleft lip was observed at 1 mg/kg/day and cleft lip and cleft palate were observed at 5 mg/kg/day (approximately 2.7 times the AUC in patients administered the RDD). Neither fetal loss nor malformations were observed in rats dosed at ≤3 mg/kg/day (approximately 2.3 times the AUC in patients administered the RDD).

As angiogenesis is a critical component of embryonic and fetal development, inhibition of angiogenesis following administration of SUTENT should be expected to result in adverse effects on pregnancy. There are no adequate and well-controlled studies of SUTENT in pregnant women. If the drug is used during pregnancy, or if the patient becomes pregnant while receiving this drug, the patient should be apprised of the potential hazard to the fetus. Women of childbearing potential should be advised to avoid becoming pregnant while receiving treatment with SUTENT.

PRECAUTIONS

Adverse events described in the following sections for MRCC patients are derived from Study 1 and Study 2. Adverse events discussed for GIST patients are derived from Study A, the randomized, placebo-controlled trial.

Left Ventricular Dysfunction

In the two MRCC studies, twenty-five patients (15%) had decreases in left ventricular ejection fraction (LVEF) to below the lower limit of normal (LLN). In GIST Study A, 22 patients (11%) on SUTENT and 3 patients (3%) on placebo had treatment-emergent LVEF values below the LLN. Nine of twenty-two GIST patients on SUTENT with LVEF changes recovered without intervention. Five patients had documented LVEF recovery following intervention (dose reduction- 1 patient; addition of antihypertensive or diuretic medications- 4 patients). Six patients went off study without documented recovery. Additionally, three patients (1%) on SUTENT had Grade 3 reductions in left ventricular systolic function to LVEF < 40%; two of these patients died without receiving further study drug. No GIST patients on placebo had Grade 3 decreased LVEF. In GIST Study A, 1 patient (<1%) on SUTENT and 1 patient (1%) on placebo died of diagnosed heart failure; 2 patients (1%) on SUTENT and 2 patients (2%) on placebo died of treatment-emergent cardiac arrest.

Patients who presented with cardiac events within 12 months prior to SUTENT administration, such as myocardial infarction (including severe/unstable angina), coronary/peripheral artery bypass graft, symptomatic congestive heart failure (CHF), cerebrovascular accident or transient ischemic attack, or pulmonary embolism were excluded from SUTENT clinical studies. It is unknown whether patients with these concomitant conditions may be at a higher risk of developing drug-related left ventricular dysfunction. Physicians are advised to weigh this risk against the potential benefits of the drug. **These patients should be carefully monitored for clinical signs and symptoms of CHF while receiving SUTENT. Baseline and periodic evaluations of LVEF should also be considered while the patient is receiving SUTENT. In patients without cardiac risk factors, a baseline evaluation of ejection fraction should be considered.**

In the presence of clinical manifestations of CHF, discontinuation of SUTENT is recommended. The dose of SUTENT should be interrupted and/or reduced in patients without clinical evidence of CHF but with an ejection fraction <50% and >20% below baseline.

Hemorrhagic Events

Bleeding events occurred in 44/169 patients (26%) receiving SUTENT for MRCC and 37/202 patients (18%) receiving SUTENT in GIST Study A, compared to 17/102 patients (17%) receiving placebo. Epistaxis was the most common hemorrhagic adverse event reported. Less common bleeding events in MRCC or GIST patients included rectal, gingival, upper GI, genital, and wound bleeding. Most events in MRCC patients were Grade 1 or 2; there was one Grade 3 event (bleeding foot wound). In GIST Study A, 14/202 patients (7%) receiving SUTENT and 9/102 patients (9%) on placebo had Grade 3 or 4 bleeding events. In addition, one patient in Study A taking placebo had a fatal gastrointestinal bleeding event during cycle 2.

Tumor-related hemorrhage has been observed in patients treated with SUTENT. These events may occur suddenly, and in the case of pulmonary tumors may present as severe and life threatening hemoptysis or pulmonary hemorrhage. Fatal pulmonary hemorrhage occurred in 2 patients receiving SUTENT on a clinical trial of patients with metastatic non-small cell lung cancer (NSCLC). Both patients had squamous cell histology. SUTENT is not approved for use in patients with NSCLC. In treatment-emergent Grade 3 and 4 tumor hemorrhage occurred in 5 of 202 patients (3%) with GIST receiving SUTENT on Study A. Tumor hemorrhages were observed as early as cycle 1 and as late as cycle 6. One of these five patients received no further drug following tumor hemorrhage. None of the other four patients discontinued treatment or experienced dose delay due to tumor hemorrhage. No patients with GIST in the Study A placebo arm were observed to undergo intratumoral hemorrhage. Tumor hemorrhage has not been observed in patients with MRCC. Clinical assessment of these events should include serial complete blood counts (CBCs) and physical examinations.

Serious, sometimes fatal gastrointestinal complications including gastrointestinal perforation, have occurred rarely in patients with intra-abdominal malignancies treated with SUTENT.

Hypertension

Hypertension (all grades) was reported in 48/169 MRCC patients (28%), 31/202 GIST patients on SUTENT (15%), and 11/102 GIST patients on placebo (11%). Grade 3 hypertension was reported in 10 MRCC patients (6%), 9 GIST patients on SUTENT (4%), and none of the GIST patients on placebo. No Grade 4 hypertension was reported. SUTENT dosing was reduced or temporarily delayed for hypertension in 6/169 MRCC patients (4%) and none of the patients in GIST Study A. No patients were discontinued from treatment with SUTENT due to systemic hypertension. Severe hypertension (>200 mmHg systolic or 110 mmHg diastolic) occurred in 10/169 MRCC patients (6%), 8/202 GIST patients on SUTENT (4%), and 1/102 GIST patients on placebo (1%).

Patients should be monitored for hypertension and treated as needed with standard anti-hypertensive therapy. In cases of severe hypertension, temporary suspension of SUTENT is recommended until hypertension is controlled.

Adrenal Function

Adrenal toxicity was noted in non-clinical repeat dose studies of 14 days to 9 months in rats and monkeys at plasma exposures as low as 0.7 times the AUC observed in clinical studies. Histological changes of the adrenal gland were characterized as hemorrhage, necrosis, congestion, hypertrophy and inflammation. In clinical studies, CT/MRI obtained in 336 patients after exposure to one or more cycles of SUTENT demonstrated no evidence of adrenal hemorrhage or necrosis. ACTH stimulation testing was performed in approximately 400 patients across multiple clinical trials of SUTENT. Among patients with normal baseline ACTH stimulation testing, one patient developed consistently abnormal test results during treatment that are unexplained and may be related to treatment with SUTENT. Eleven additional patients with normal baseline testing had abnormalities in the final test performed, with peak cortisol levels of 12-16.4 mcg/dL (normal >18 mcg/dL) following stimulation. None of these patients were reported to have clinical evidence of adrenal insufficiency. Physicians prescribing SUTENT are advised to monitor for adrenal insufficiency in patients who experience stress such as surgery, trauma or severe infection.

Information for Patients

Gastrointestinal disorders such as diarrhea, nausea, stomatitis, dyspepsia, and vomiting were the most commonly reported gastrointestinal events occurring in patients who received SUTENT. Supportive care for gastrointestinal adverse events requiring treatment may include anti-emetic or anti-diarrheal medication.

Skin discoloration possibly due to the drug color (yellow) occurred in approximately 1/3 of patients. Patients should be advised that depigmentation of the hair or skin may occur during treatment with SUTENT. Other possible dermatologic effects may include dryness, thickness or cracking of skin, blister or rash on the palms of the hands and soles of the feet.

Other commonly reported adverse events included fatigue, high blood pressure, bleeding, swelling, mouth pain/irritation and taste disturbance.

Patients should be advised to inform their health care providers of all concomitant medications, including over-the-counter medications and dietary supplements (see Drug Interactions).

Laboratory Tests

CBCs with platelet count and serum chemistries including phosphate should be performed at the beginning of each treatment cycle for patients receiving treatment with SUTENT.

Drug Interactions

Co-administration of SUTENT with strong inhibitors of the CYP3A4 family (e.g., ketoconazole, itraconazole, clarithromycin, atazanavir, indinavir, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin, voriconazole) may increase sunitinib concentrations. Grapefruit may also increase plasma concentrations of SUTENT (see CLINICAL PHARMACOLOGY). Co-administration of SUTENT with inducers of the CYP3A4 family (e.g., dexamethasone, phenytoin, carbamazepine, rifampin, rifabutin, rifapentin, phenobarbital, St. John's Wort) may decrease sunitinib concentrations (see CLINICAL PHARMACOLOGY). St. John's Wort may decrease SUTENT plasma concentrations unpredictably. Patients receiving SUTENT should not take St. John's Wort concomitantly. SUTENT dose modification is recommended in patients using concomitant CYP3A4 inhibitors or inducers (see DOSAGE AND ADMINISTRATION).

Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenicity studies with sunitinib have not been performed.

Sunitinib did not cause genetic damage when tested in *in vitro* assays (bacterial mutation [AMES Assay], human lymphocyte chromosome aberration) and an *in vivo* rat bone marrow micronucleus test.

Effects on the female reproductive system were identified in a 3-month repeat dose monkey study (2, 6, 12 mg/kg/day), where ovarian changes (decreased follicular development) were noted at 12 mg/kg/day (approximately 5.1 times the AUC in patients administered the RDD), while uterine changes (endometrial atrophy) were noted at ≥2 mg/kg/day (approximately 0.4 times the AUC in patients administered the RDD). With the addition of vaginal atrophy, the uterine and ovarian effects were reproduced at 6 mg/kg/day in the 9-month monkey study (0.3, 1.5 and 6 mg/kg/day administered daily for 28 days followed by a 14 day recovery; the 6 mg/kg dose produced a mean AUC that was approximately 0.8 times the AUC in patients administered the RDD). A no effect level was not identified in the 3 month study; 1.5 mg/kg/day represents a no effect level in monkeys administered sunitinib for 9 months.

Although fertility was not affected in rats, SUTENT may impair fertility in humans. In female rats, no fertility effects were observed at doses of ≤5.0 mg/kg/day [(0.5, 1.5, 5.0 mg/kg/day) administered for 21 days up to gestational day 7; the 5.0 mg/kg dose produced an AUC that was approximately 5 times the AUC in patients administered the RDD], however significant embryolethality was observed at the 5.0 mg/kg dose. No reproductive effects were observed in male rats dosed (1, 3 or 10 mg/kg/day) for 58 days prior to mating with untreated females. Fertility, copulation, conception indices, and sperm evaluation (morphology, concentration, and motility) were unaffected by sunitinib at doses ≤10 mg/kg/day (the 10-mg/kg/day dose produced a mean AUC that was approximately 25.8 times the AUC in patients administered the RDD).

Pregnancy Category D: see WARNINGS.

Nursing Mothers

Sunitinib and/or its metabolites are excreted in rat milk. In lactating female rats administered 15 mg/kg, sunitinib and its metabolites were extensively excreted in milk at concentrations up to 12-fold higher than in plasma. It is not known whether SUTENT or its primary active metabolite are excreted in human milk. Because drugs are commonly excreted in human milk and because of the potential for serious adverse reactions in nursing infants, women should be advised against breastfeeding while taking SUTENT.

Pediatric Use

The safety and efficacy of SUTENT in pediatric patients have not been studied in clinical trials.

Physeal dysplasia was observed in Cynomolgus monkeys with open growth plates treated for ≥3 months (3 month dosing 2, 6, 12 mg/kg/day; 8 cycles of dosing 0.3, 1.5, 6.0 mg/kg/day) with sunitinib at doses that were >0.4 times the RDD based on systemic exposure (AUC). In developing rats treated continuously for 3 months (1.5, 5.0 and 15.0 mg/kg) or 5 cycles (0.3, 1.5, and 6.0 mg/kg/day), bone abnormalities consisted of thickening of the epiphyseal cartilage of the femur and an increase of fracture of the tibia at doses ≥5 mg/kg (approximately 10 times the RDD based on AUC). Additionally, caries of the teeth were observed in rats at >5 mg/kg. The incidence and severity of physeal dysplasia were dose-related and were reversible upon cessation of treatment however findings in the teeth were not. A no effect level was not observed in monkeys treated continuously for 3 months, but was 1.5 mg/kg/day when treated intermittently for 8 cycles. In rats the no effect level in bones was ≤2 mg/kg/day.

PRECAUTIONS *(continued)*

Geriatric Use

Of the 450 patients with solid tumors reported from clinical studies of SUTENT, 115 (25.6%) were 65 and over. No overall differences in safety or effectiveness were observed between younger and older patients.

ADVERSE REACTIONS

Overview

Four hundred fifty (450) patients with solid tumors including 257 patients (57%) with GIST and 169 patients (38%) with cytokine-refractory MRCC have been treated in 7 completed non-randomized, open-label, single arm clinical trials and 1 randomized, double-blind, placebo-controlled clinical trial. All patients received SUTENT once daily as a 50-mg oral capsule on Schedule 4/2 (see CLINICAL STUDIES). One hundred two (102) patients received placebo in the randomized, double-blind, placebo-controlled clinical trial conducted in patients with GIST.

Adverse events occurring in GIST and MRCC studies are described below.

Adverse Events in GIST Study A

Median duration of blinded study treatment was two cycles for patients on SUTENT (mean 3.0, range 1-9) and one cycle (mean 1.8, range 1-6) for patients on placebo. Dose reductions occurred in 23 patients (11%) on SUTENT and none on placebo. Dose interruptions occurred in 59 patients (29%) on SUTENT and 31 patients (30%) on placebo. The rates of treatment-emergent, non-fatal adverse events resulting in permanent discontinuation were 7% and 6% in the SUTENT and placebo groups, respectively.

Most treatment-emergent adverse events in both study arms were Grade 1 or 2 in severity. Grade 3 or 4 treatment-emergent adverse events were reported in 56% vs. 51% of patients on SUTENT versus placebo, respectively. Diarrhea, hypertension, bleeding, mucositis, skin abnormalities, and altered taste were more common in patients receiving SUTENT. Table 4 compares the incidence of common (>10%) treatment-emergent adverse events for patients receiving SUTENT versus those on placebo.

Table 4. Treatment-Emergent Adverse Events Reported in at Least 10% of GIST Patients Who Received SUTENT or Placebo in Study A*

	GIST			
	SUTENT (n=202)		Placebo (n=102)	
Adverse Event, n (%)	**All Grades**	**Grade 3/4[a]**	**All Grades**	**Grade 3/4[b]**
Any		114 (56)		52 (51)
Constitutional				
Fatigue	84 (42)	17 (8)	48 (47)	8 (8)
Fever	36 (18)	3 (2)	17 (17)	1 (1)
Gastrointestinal				
Diarrhea	81 (40)	9 (4)	27 (27)	0 (0)
Nausea	63 (31)	3 (2)	33 (32)	5 (5)
Mucositis/stomatitis	58 (29)	2 (1)	18 (18)	2 (2)
Vomiting	49 (24)	4 (2)	24 (24)	3 (3)
Constipation	41 (20)	0 (0)	14 (14)	2 (2)
Abdominal pain[c]	67 (33)	22 (11)	39 (38)	12 (12)
Cardiac				
Hypertension	31 (15)	9 (4)	11 (11)	0 (0)
Dermatology				
Rash	28 (14)	2 (1)	9 (9)	0 (0)
Skin Discoloration	61 (30)	0 (0)	23 (23)	0 (0)
Hand-foot syndrome	28 (14)	9 (4)	10 (10)	3 (3)
Neurology				
Altered taste	42 (21)	0 (0)	12 (12)	0 (0)
Headache	26 (13)	3 (2)	23 (23)	0 (0)
Musculoskeletal				
Arthralgia	24 (12)	2 (1)	16 (16)	0 (0)
Back pain	23 (11)	2 (1)	16 (16)	4 (4)
Myalgia/limb pain	28 (14)	1 (1)	9 (9)	1 (1)
Respiratory				
Dyspnea	20 (10)	0 (0)	19 (19)	3 (3)
Cough	17 (8)	0 (0)	13 (13)	0 (0)
Metabolism/Nutrition				
Anorexia[d]	67 (33)	1 (1)	30 (29)	5 (5)
Asthenia	45 (22)	10 (5)	11 (11)	3 (3)
Hemorrhage/bleeding				
Bleeding, all sites	37 (18)	14 (7)	17 (17)	9 (9)

* Common Toxicity Criteria for Adverse Events (CTCAE), Version 3.0

[a] Grade 4 AEs in patient on SUTENT included abdominal pain (2%) and bleeding (2%).

[b] Grade 4 AEs in patients on placebo included fatigue (3%), mucositis (1%), vomiting (1%), abdominal pain (3%), back pain (1%), and bone pain (1%).

[c] Includes abdominal quadrant, gastric, hypochondrial, abdominal, flank, and cancer-related pain

[d] Includes decreased appetite

Oral pain other than mucositis/stomatitis occurred in 12 patients (6%) on SUTENT versus 3 (3%) on placebo. Hair color changes occurred in 15 patients (7%) on SUTENT versus 4 (4%) on placebo. Alopecia was observed in 10 patients (5%) on SUTENT versus 2 (2%) on placebo.

Table 5 provides common (≥10%) treatment-emergent laboratory abnormalities.

Table 5. Treatment-Emergent Laboratory Abnormalities (≥10%) from Study A*

	SUTENT (n=202)		Placebo (n=102)	
Adverse Event, n (%)	**All Grades**	**Grade 3/4[a]**	**All Grades**	**Grade 3/4[b]**
Any		68 (34)		22 (22)
Gastrointestinal				
AST / ALT	78 (39)	3 (2)	23 (23)	1 (1)
Alkaline phosphatase	48 (24)	7 (4)	21 (21)	4 (4)
Total Bilirubin	32 (16)	2 (1)	8 (8)	0 (0)
Indirect Bilirubin	20 (10)	0 (0)	4 (4)	0 (0)
Amylase	35 (17)	10 (5)	12 (12)	3 (3)
Lipase	50 (25)	20 (10)	17 (17)	7 (7)
Cardiac				
Decreased LVEF	21 (10)	2 (1)	3 (3)	0 (0)
Renal / Metabolic				
Creatinine	25 (12)	1 (1)	7 (7)	0 (0)
Hypokalemia	24 (12)	1 (1)	4 (4)	0 (0)
Hypernatremia	20 (10)	0 (0)	4 (4)	1 (1)
Uric acid	31 (15)	16 (8)	16 (16)	8 (8)
Hematology				
Neutropenia	107 (53)	20 (10)	4 (4)	0 (0)
Lymphopenia	76 (38)	0 (0)	16 (16)	0 (0)
Anemia	52 (26)	6 (3)	22 (22)	2 (2)
Thrombocytopenia	76 (38)	10 (5)	4 (4)	0 (0)

*Common Toxicity Criteria for Adverse Events (CTCAE), Version 3.0

[a] Grade 4 AEs in patients on SUTENT included alkaline phosphatase (1%), lipase (2%), creatinine (1%), hypokalemia (1%), neutropenia (2%), anemia (2%), and thrombocytopenia (1%).

[b] Grade 4 AEs in patients on placebo included amylase (1%), lipase (1%), anemia (2%), and thrombocytopenia (1%).

Grade 3 or 4 treatment-emergent laboratory abnormalities were observed in 68 (34%) versus 22 (22%) patients on SUTENT and placebo, respectively. Elevated liver function tests, pancreatic enzymes, and creatinine were more common in patients treated with SUTENT than placebo. Decreased LVEF and myelosuppression were also more common with SUTENT treatment. Treatment-emergent electrolyte disturbances of all types were more common in patients on SUTENT than on placebo, including hyperkalemia (6% vs. 4%), hypokalemia (12% vs. 4%), hypernatremia (10% vs. 4%), hyponatremia (6% vs. 1%), and hypophosphatemia (9% vs. 0%). Three SUTENT patients (1.5%) had Grade 3 hypophosphatemia. Acquired hypothyroidism was noted in 8 patients (4%) on SUTENT versus 1 (1%) on placebo.

Adverse Events in the MRCC Studies

The data described below reflect exposure to SUTENT in 169 patients with MRCC enrolled in Studies 1 and 2. The median duration of treatment was 5.5 months (range: 0.8-11.2) for Study 1 and 7.7 months (range: 0.2-16.1) for Study 2. Dose interruptions occurred in 48 patients (45%) on Study 1 and 45 patients (71%) on Study 2; one or more dose reductions occurred in 23 patients (22%) on Study 1 and 22 patients (35%) on Study 2. Table 6 summarizes treatment emergent adverse events for at least 10% of all patients with MRCC who received at least one 50-mg dose of SUTENT. Hematology laboratory abnormalities are presented separately, in Table 7.

Table 6. Treatment-Emergent Adverse Events Reported in at Least 10% of MRCC Patients Treated with SUTENT*

	MRCC (N=169)	
Adverse Event, n (%)	**All Grades**	**Grade 3**
Any	169 (100)	123 (73)
Constitutional		
Fatigue	125 (74)	19 (11)
Fever	26 (15)	2 (1)
Gastrointestinal		
Diarrhea	93 (55)	8 (5)
Nausea	92 (54)	4 (2)
Mucositis/stomatitis	90 (53)	7 (4)
Dyspepsia	77 (46)	1 (1)
Vomiting	63 (37)	7 (4)
Constipation	57 (34)	1 (1)
Abdominal pain	34 (20)	5 (3)
Glossodynia	25 (15)	0 (0)
Flatulence	24 (14)	0 (0)
Cardiac		
Hypertension	48 (28)	10 (6)
Edema, peripheral	28 (17)	1 (1)
Dermatology		
Rash	64 (38)	1 (1)
Skin Discoloration	55 (33)	0 (0)
Dry skin	29 (17)	0 (0)
Hair color changes	29 (17)	0 (0)
Hand-foot syndrome	21 (12)	5 (3)
Alopecia	20 (12)	0 (0)
Neurology		
Altered taste	73 (43)	0 (0)
Headache	43 (25)	2 (1)
Dizziness	27 (16)	3 (2)
Musculoskeletal		
Arthralgia	48 (28)	2 (1)
Pain in limb	31 (18)	1 (1)
Back pain	29 (17)	1 (1)
Myalgia	29 (17)	1 (1)
Respiratory		
Dyspnea	47 (28)	8 (5)
Cough	29 (17)	1 (1)
Metabolism/Nutrition		
Anorexia	53 (31)	1 (1)
Dehydration	19 (11)	5 (3)
Hemorrhage/bleeding		
Bleeding, all sites	44 (26)	1 (1)

* Common Toxicity Criteria for Adverse Events (CTCAE), Version 3.0

** There were no Grade 4 adverse events among the events reported with a ≥10% incidence in the MRCC population.

Other significant adverse events occurring in MRCC patients receiving SUTENT included peripheral neuropathy (10%), appetite disturbance (9%), blistering of the skin (7%), periorbital edema (7%) and increased lacrimation (6%).

Table 7. Treatment-Emergent Grade 3 and 4 Hematology Laboratory Abnormalities* from Studies 1 and 2

		MRCC (N=169)		
Laboratory Test	**Unit**	**Grade 3**	**Grade 4**	**Total (Grade 3 + 4)**
Hematology, n (%)		54 (32)	4 (2)	58 (34)
Neutropenia	10^9/L	21 (12)	1 (1)	22 (13)
Anemia	g/L	9 (5)	3 (2)	12 (7)
Lymphopenia	10^9/L	33 (20)	2 (1)	35 (21)
Thrombocytopenia	10^9/L	5 (3)	0 (0)	5 (3)
Leukopenia	10^9/L	12 (7)	0 (0)	12 (7)

* Common Toxicity Criteria for Adverse Events (CTCAE), Version 3.0

SUTENT™
(sunitinib malate) capsules

ADVERSE REACTIONS *(continued)*

Common treatment-emergent Grade 3 and 4 chemistry laboratory abnormalities in the MRCC studies included increased lipase (16%), increased amylase (5%), hypophosphatemia (10%), and hyperuricemia (10%).

Cardiovascular

See PRECAUTIONS section for information on left ventricular dysfunction.

Two patients with MRCC experienced Grade 3 myocardial ischemia, one had Grade 2 "cardiovascular toxicity" reported as an adverse event and one patient experienced a fatal myocardial infarction while on treatment.

Data from non-clinical (*in vitro* and *in vivo*) studies indicate that sunitinib has the potential to inhibit the cardiac action potential repolarization process (e.g., prolongation of QT interval). In GIST Study A, 23 patients (11%) on SUTENT versus 12 (12%) on placebo had observed QT prolongation greater than 20 milliseconds from baseline. No consistent, clinically significant QTc prolongation has been observed in completed clinical studies.

Venous Thromboembolic Events

Four patients (2%) on the two MRCC studies had venous thromboembolic events reported; two patients with pulmonary embolism (both Grade 4) and two patients with deep venous thrombosis (DVT) (both Grade 3). Dose interruption occurred in one of these cases. Seven patients (3%) on SUTENT and none on placebo in GIST Study A experienced venous thromboembolic events; five of the seven were Grade 3 DVTs, and two were Grade 1 or 2. Four of these seven GIST patients discontinued treatment following first observation of DVT.

Seizures

In clinical studies of SUTENT, seizures have been observed in subjects with radiological evidence of brain metastases. In addition, there have been rare (<1%) reports of subjects presenting with seizures and radiological evidence of reversible posterior leukoencephalopathy syndrome (RPLS). None of these subjects had a fatal outcome to the event. Patients with seizures and signs/symptoms consistent with RPLS, such as hypertension, headache, decreased alertness, altered mental functioning, and visual loss, including cortical blindness should be controlled with medical management including control of hypertension. Temporary suspension of SUTENT is recommended; following resolution, treatment may be resumed at the discretion of the treating physician.

Laboratory Abnormalities/Testing

Hematologic Events

Grade 3 and 4 neutropenia were reported in 21 (13%) and 1 (1%) patients with MRCC, 19 (9%) and 3 (2%) patients with GIST on SUTENT, respectively. In Study A, one patient each in the SUTENT and placebo groups had febrile neutropenia. Grade 3 and 4 thrombocytopenia was reported in 5 (3%) and 0 patients with MRCC, 7 (4%) and 1 (1%) patients with GIST on SUTENT, respectively. No GIST patients receiving placebo experienced either Grade 3 or 4 neutropenia or thrombocytopenia. The rates of dose reductions and delays for hematologic abnormalities were 4% and 2% for neutropenia, 2% and 0% for anemia, and 1% and 1% for thrombocytopenia for MRCC and GIST patients, respectively. One MRCC patient with an adverse event report of Grade 4 thrombocytopenia discontinued treatment.

Patients receiving SUTENT should be monitored regularly for myelosuppression.

Hypothyroidism

Hypothyroidism was reported as an adverse event in 7 patients (4%) across the two MRCC studies. Additionally, TSH elevations were reported in 4 patients (2%). Overall, 7% of the MRCC population had either clinical or laboratory evidence of treatment-emergent hypothyroidism. Treatment-emergent acquired hypothyroidism was noted in 8 GIST patients (4%) on SUTENT versus 1 (1%) on placebo.

Patients with symptoms suggestive of hypothyroidism should have laboratory monitoring of thyroid function performed and be treated as per standard medical practice.

Pancreatic Function

Grade 3 and 4 increases in serum lipase were observed in 23 (14%) and 4 (2%), respectively, of 169 patients receiving SUTENT for MRCC. Grade 3 and 4 increases in serum amylase were observed in 8 (5%) and 1 (1%) MRCC patients, respectively. Increases in lipase levels were transient and were generally not accompanied by signs or symptoms of pancreatitis in subjects with either MRCC or GIST. Pancreatitis has been observed rarely (<1%) in patients receiving SUTENT for GIST or MRCC. If symptoms of pancreatitis are present, patients should have SUTENT discontinued and be provided with appropriate supportive care.

OVERDOSAGE

No overdose of SUTENT was reported in completed clinical studies. In non-clinical studies mortality was observed following as few as 5 daily doses of 500 mg/kg (3000 mg/m^2) in rats. At this dose, signs of toxicity included impaired muscle coordination, head shakes, hypoactivity, ocular discharge, piloerection and gastrointestinal distress. Mortality and similar signs of toxicity were observed at lower doses when administered for longer durations. Treatment of overdose with SUTENT should consist of general supportive measures. There is no specific antidote for overdosage with SUTENT. If indicated, elimination of unabsorbed drug should be achieved by emesis or gastric lavage.

DOSAGE AND ADMINISTRATION

The recommended dose of SUTENT for GIST and advanced RCC is one 50-mg oral dose taken once daily, on a schedule of 4 weeks on treatment followed by 2 weeks off. SUTENT may be taken with or without food.

Dose Modification

Dose increase or reduction of 12.5-mg increments is recommended based on individual safety and tolerability.

Strong CYP3A4 inhibitors such as ketoconazole may **increase** SUTENT plasma concentrations. Selection of an alternate concomitant medication with no or minimal enzyme inhibition potential is recommended. A dose reduction for SUTENT to a minimum of 37.5 mg daily should be considered if SUTENT must be co-administered with a strong CYP3A4 inhibitor (see CLINICAL PHARMACOLOGY and PRECAUTIONS, Drug Interactions).

CYP3A4 inducers such as rifampin may **decrease** SUTENT plasma concentrations. Selection of an alternate concomitant medication with no or minimal enzyme induction potential is recommended. A dose increase for SUTENT to a maximum of 87.5 mg daily should be considered if SUTENT must be co-administered with a CYP3A4 inducer. If dose is increased, the patient should be monitored carefully for toxicity (see CLINICAL PHARMACOLOGY and PRECAUTIONS, Drug Interactions). St. John's Wort may decrease SUTENT plasma concentrations unpredictably. Patients receiving SUTENT should not take St. John's Wort concomitantly.

STORAGE

Please refer to outer package for the recommended storage condition.

Rx only

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Cancer Incidence in Hong Kong

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Overview

The Hong Kong Cancer Registry ("the Registry") was established in 1963 as a population-based cancer registry. We compile reports on cancer statistics using demographic, morphologic and histologic data collected from medical institutions in Hong Kong in strict accordance with the Personal Data (Privacy) Ordinance.

The Registry is a full member of the International Association of Cancer Registries (IACR) under the auspices of WHO. Our data quality meet the standard of IACR. Together with the Shanghai Cancer Registry, we are the first in China to have our results accepted and published in the "*Cancer in Five Continents*" since its 4th edition in 1982.

As cancer reporting is not mandatory by law in Hong Kong, collecting clinical data is both labour intensive and resource demanding. The Registry annually collects over 200,000 episodes of cancer for meticulous matching and checking to come up with the reported figures. Over the years with the aid of computer technology, we have reduced the reporting lag time to 24 months by releasing the 2004 data in December 2006. Compared to other cancer registries in the world, our efficiency is already above par despite resource constraint.

Incidence figures are important in public heath. Our strength lies in the good quality data accumulated over the past quarter century, which, together with the population figures regularly updated by the Census of the Government, form the basis of all our calculations. Hence we are able to show trends with reasonable validity to guide health care service development and epidemiological research.

Incidence data

In 2004, a total of 12,206 men and 10,317 women were diagnosed with cancer. In the same period, 7,183 men and 4,608 women died of the disease. The number of new cancer cases in Hong Kong is rising by 2% per year. The cumulative rates up to age 75 were 28.4% for males and 20.3% for females. Thus 1 in 4 men and 1 in 5 women would develop a cancer by age 75.

The ranking of different cancers is of interest to the media and public. Over the years the cancer pattern is following the footsteps of the developed countries in the West, probably due to changes in socio-economic factors like ageing population, urbanisation and adoption of western lifestyle. In men, the commonest cancers are from lung, colorectum, liver, prostate and nasopharynx (Table 1). Colorectal cancer overtook liver cancer to become the second commonest cancer in the mid-1990s. Prostate cancer was not in the league of the top ten in earlier period but has also become increasingly common. In women, cancers of the breast, colorectum, lung, cervix and corpus uteri are the leading types. Breast and colorectal cancers replaced lung cancer to become number one and two, respectively, since the mid-1990s. Corpus cancer has also overtaken stomach cancer in ranking.

The age-specific rates vary widely among cancers. Knowing the age-specific rates, or the changes of the rate with time, improves clinical judgment, helps service planning and raises public awareness. For instance, the overall age-specific incidence rate in female rises more rapidly than that of males from age 20 until age 50 (Fig. 1a). Thereafter, the incidence in males increases steeply. The female predominance in the 20 to 50 year age group is mainly due to the high incidence of breast and gynaecological cancers in middle-aged women.

Calculated from age-specific rates, the age-standardised rates allow fair comparison of incidence rates not only in different populations but also within the same population but in different times. Studying the trends in age-standardised rate forms the basis of epidemiological studies. In 2000-2004, the age-standardised incidence rate (adjusted to the 2000 world standard population) for all cancers combined was 292.5 per 100,000 for men while for female, it was 216.0 per 100,000. Compared to other developed countries, Hong Kong has a relatively high incidence rates in Asia, approaching that of the West. (Fig. 2)

Epidemiology of the principal cancers

The time trend of age-standardised incidence rates for all cancers combined shows that despite the rising numbers or crude rates, the cancer risks have been falling steadily over the years (Fig. 3), with a few exceptions like breast, colorectal, corpus, ovarian and prostate cancers. The incidence of traditional cancers such as nasopharynx, cervix and stomach is falling (Fig. 4). Overall, the five leading cancers are the lung, colorectum, breast, liver and stomach, which altogether accounted for over 55% of all new cases in 2000-2004.

Table 1. Ten most common cancers in different 5-year periods, 1985-2004

Male

1985-1989			1990-1994			1995-1999			2000-2004		
Site	No. / year	ASR	Site	No. / year	ASR	Site	No. / year	ASR	Site	No. / year	ASR
Lung	2,178	88.3	Lung	2,408	83.9	Lung	2,519	71.5	Lung	2,694	65.4
Liver	1,082	41.7	Liver	1,198	40.2	Colorectum	1,576	44.7	Colorectum	1,873	45.6
Colorectum	982	40.8	Colorectum	1,187	41.8	Liver	1,265	35.4	Liver	1,262	30.8
Nasopharynx	800	28.9	Nasopharynx	785	24.8	Nasopharynx	819	21.9	Prostate	835	20.1
Stomach	590	24.1	Stomach	586	20.7	Stomach	626	18.0	Nasopharynx	725	17.4
Oesophagus	464	18.2	Oesophagus	440	15.0	Prostate	460	13.6	Stomach	662	16.1
Bladder	426	18.3	Bladder	424	15.3	Bladder	450	13.0	Bladder	487	11.8
Larynx	254	9.9	Non-Hodgkin's	271	9.2	Oesophagus	409	11.6	Oesophagus	391	9.6
Non-Hodgkin's lymphoma	254	9.8	lymphoma			Non-Hodgkin's lymphoma	317	9.2	Non-Hodgkin's lymphoma	334	8.5
Leukaemia	201	7.5	Prostate	255	9.9	Leukaemia	206	6.2	Non-melanoma skin	249	6.1
			Larynx	231	7.9						
All sites	9,148	365.8	All sites	9,746	336.6	All sites	10,951	311.5	All sites	11,889	292.5

Female

1985-1989			1990-1994			1995-1999			2000-2004		
Site	No. / year	ASR	Site	No. / year	ASR	Site	No. / year	ASR	Site	No. / year	ASR
Lung	1,095	37.7	Lung	1,154	34.7	Breast	1,585	42.5	Breast	2,071	46.8
Breast	964	36.5	Breast	1,152	37.8	Colorectum	1,306	32.6	Colorectum	1,496	31.9
Colorectum	872	30.6	Colorectum	1,062	32.7	Lung	1,182	28.8	Lung	1,279	26.6
Cervix	494	18.6	Cervix	468	15.3	Cervix	469	12.6	Cervix	434	9.8
Stomach	356	12.4	Liver	355	11.0	Liver	390	10.1	Corpus uteri	414	10.0
Liver	306	10.8	Stomach	346	10.4	Stomach	382	9.4	Stomach	383	7.9
Nasopharynx	298	11.4	Nasopharynx	298	9.9	Nasopharynx	320	8.5	Ovary	377	9.0
Ovary	221	8.2	Thyroid	241	7.8	Ovary	300	8.3	Liver	361	7.9
Corpus uteri	203	7.8	Ovary	235	7.7	Corpus uteri	296	8.5	Thyroid	325	7.8
Thyroid	198	7.1	Corpus uteri	218	7.5	Thyroid	288	7.8	Non-melanoma skin	303	5.9
All sites	6,929	249.2	All sites	7,458	235.2	All sites	8,678	224.7	All sites	9,796	216.0

Both

1985-1989			1990-1994			1995-1999			2000-2004		
Site	No. / year	ASR	Site	No. / year	ASR	Site	No. / year	ASR	Site	No. / year	ASR
Lung	3,273	61.1	Lung	3,561	58.0	Lung	3,701	49.2	Lung	3,974	45.1
Colorectum	1,853	34.8	Colorectum	2,249	36.8	Colorectum	2,882	38.3	Colorectum	3,369	38.4
Liver	1,388	26.0	Liver	1,553	25.6	Liver	1,656	22.8	Breast	2,086	24.0
Nasopharynx	1,098	20.5	Breast	1,158	18.9	Breast	1,593	21.3	Liver	1,623	19.2
Breast	978	18.5	Nasopharynx	1,082	17.6	Nasopharynx	1,140	15.4	Stomach	1,045	11.8
Stomach	946	17.8	Stomach	932	15.2	Stomach	1,008	13.4	Nasopharynx	998	11.8
Bladder	592	11.1	Bladder	571	9.3	Bladder	605	8.0	Prostate	835	9.2
Oesophagus	578	10.7	Oesophagus	552	9.1	Non-Hodgkin's lymphoma	556	7.6	Bladder	643	7.1
Cervix	494	9.2	Non-Hodgkin's	480	7.9				Non-Hodgkin's lymphoma	585	7.0
Non-Hodgkin's lymphoma	438	8.1	lymphoma			Oesophagus	508	6.9			
			Cervix	468	7.6	Cervix	469	6.3	Non-melanoma skin	552	6.1
All sites	16,077	300.4	All sites	17,205	281.7	All sites	19,630	264.8	All sites	21,685	251.7

ASR = Age-standardized rate is calculated based on the 2000 world standard population and expressed per 100,000.

Lung cancer

Lung cancer has long been the most common cancer in Hong Kong, ranking first in men and third in women. It represents over 18% of total malignant neoplasms registered each year. Like many other cancers, its incidence is rising continuously after age 50 (Fig. 1b). Environmental factors particularly smoking are responsible in men. Compared with other countries, the rate of lung cancer in Hong Kong women exceeded those recorded in most other registries and was also high in men. Nevertheless, the age-standardised incidence rates are decreasing in both genders (Fig. 4). A previous study[1] showed that the decline occurred mainly in squamous cell and small cell carcinomas, which are closely associated with smoking. This pattern corresponds to the decline in smoking prevalence in Hong Kong. Nowadays, the most common histological type is adenocarcinoma, particularly in women.

Colorectal cancer

Colorectal cancer was the most rapidly increasing in terms of numbers among all cancers in Hong Kong over the last 20 years. The age-specific rate rates in both sexes are nearly identical before 50 years. Then the rate rises sharply afterwards to reach around 400 per 100,000 for men and 280 for women beyond age 70 (Fig. 1c). The age-standardised rates, however, remained stable in the past decade (Fig. 4). Further analysis of the time trends by age-specific rate showed that the biggest climb was found only in the groups aged 60 and over, while those of age 30 to 59 recorded only a small change or even a decline. Thus the common perception that people are getting colorectal cancer at younger age is untrue. The predominant histological type is adenocarcinoma (75%). Stage at diagnosis is 8.6% stage I, 25.9% stage II, 29.7% stage III, 20.4% stage IV and 15.3% unknown.

Female breast cancer

Like most Western countries, breast cancer is now the leading women cancer in Hong Kong. In 2004, there were 2,200 new cases diagnosed. Breast cancer occurs in women at an earlier age compared with other cancers. The age-specific incidence rises dramatically between the age groups 20-49 and thereafter remains stable (Fig. 1d). The age-standardised rates are also increasing since the mid-1990s (Fig. 4b). Factors other than ageing population such as westernised lifestyle and "Baby boom" generation" could account for such rise. The most common histological type is invasive ductal carcinoma (75%). Stage at diagnosis is 24.5% stage I, 37.4% stage II, 15.4% stage III, 4.0% stage IV and 18.7% unknown.

Liver cancer

The number of liver cancer is stable over the years. Its incidence rises sharply after the age of 40 and continues into the older age group (Fig. 1e). The age-standardised incidence rates began to drop significantly in the mid-1990s for both genders (Fig. 4). As hepatitis B virus is the main causative agent in Hong Kong, the incidence is

expected to drop further in a few decades after the launching of the vaccination programme against hepatitis B at birth in 1988. About 85% of the cases are hepatocellular carcinoma.

Stomach cancer

Stomach cancer remains the number 5 common cancer despite its falling age-standardised incidence over the past two decades (Fig. 4). Its incidence starts to rise after 40s and continues into the older age group (Fig. 1f). The most common histological type is adenocarcinoma.

Conclusion

Study on the epidemiological trend of cancer incidence is essential to evaluate and monitor changes in population lifestyle, environmental risks and cancer burden over time. The Registry is a rich source of information for these studies. The Registry was an incident-only registry in the past and is now transforming to a full registry, initially by collecting staging and individual follow-up information. Our future success counts on the support of all clinicians in Hong Kong. Special thanks must be given to all medical institutions, public and private, which have been so cooperative to facilitate our data collection. In return we have developed our own website at http://www.ha.org.hk/cancereg, making the data accessible to all the contributors, the professionals and the public. It is the Asian's first web-based query and reporting system to disseminate cancer statistical and epidemiological information for the purpose of epidemiological research and education. It has always been the policy of the Registry to provide free access of relevant data to everybody.

Fig. 1. Average age-specific incidence curves (per 100,000) of principal cancers, 2000-2004

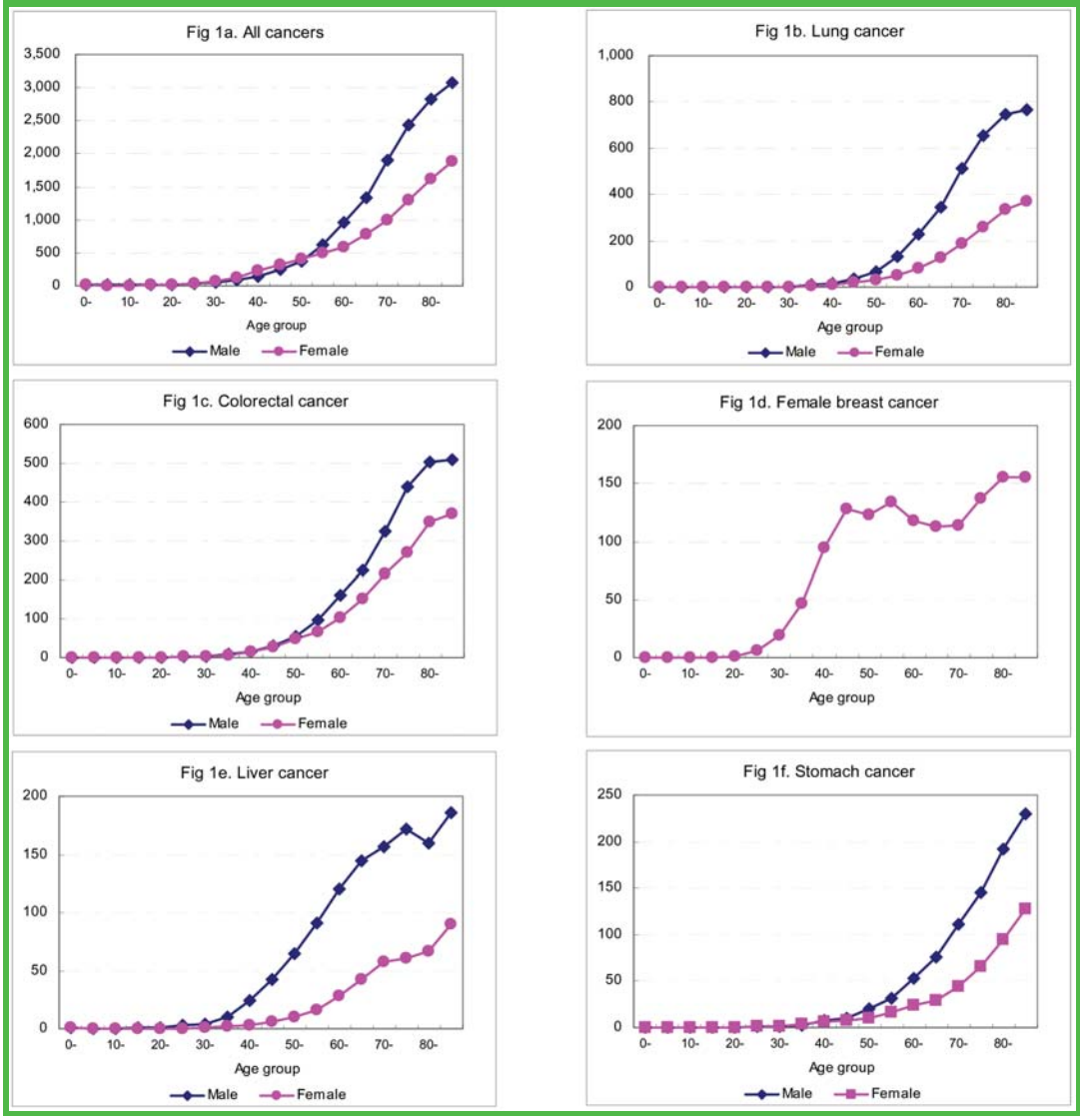
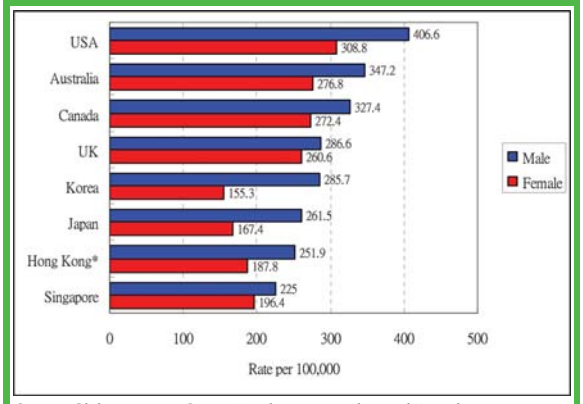


Fig. 2. World age-standardized incidence for selected countries in 2002 (All cancers except non-melanoma skin)



Source: Globocan 2002: Cancer Incidence, Mortality and Prevalence Worldwide, IARC, WHO
*Hong Kong Cancer Registry 2002 figures
Rates are standardized to the 1966 world standard population.

Fig. 3. Trends in crude and age-standardized (ASR) incidence rates of all cancers in Hong Kong, 1985-2004

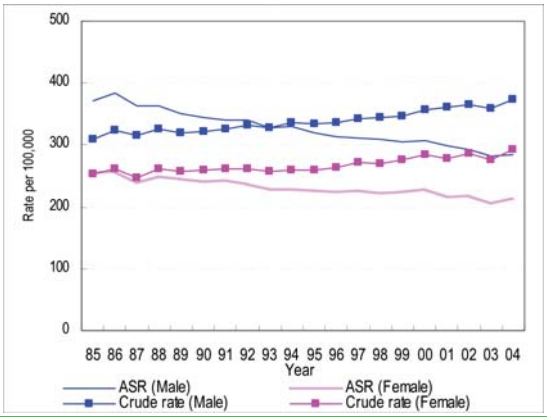


Fig. 4a. Trends in age-standardized incidence rates for leading cancers in Men

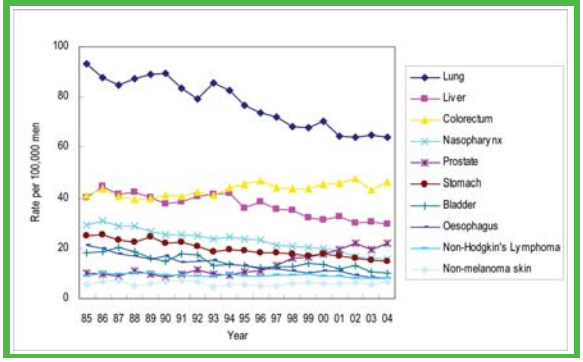
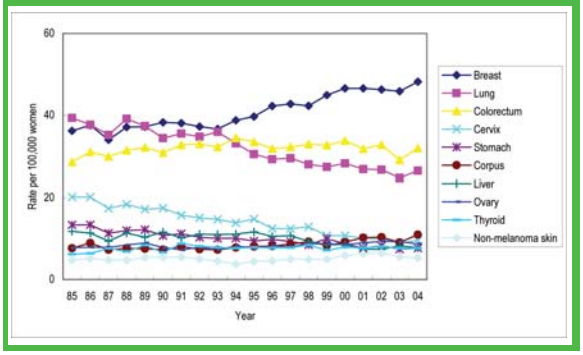


Fig. 4b. Trends in age-standardized incidence rates for leading cancers in Women



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Upcoming Certificate Courses of the Federation of Medical Societies of Hong Kong

Date	Course No	Course Name	Co-organiser	Target Participants
25 Aug 2007	C126	Certificate Course in Nutrition	Hong Kong Nutrition Association	General Public
3 Oct 2007 - 7 Nov 2007	C124	Certificate Course on Infectious Disease	The Hong Kong Society for Infectious Diseases	General Practitioners & Paramedic
8 Oct 2007 - 19 Nov 2007	C122	Enhancing Medical Practice: The Role of Psychotherapy in Promoting Physical and Mental Health	Psychotherapy Society of Hong Kong	Medical & Health Professionals & Practitioner
20 Oct 2007 - 20 Nov 2007	C118	Certificate Course on Ophthalmology	The Hong Kong Ophthalmological Society	General Practitioners & Paramedic

Practical Management of Non-Small Cell Lung Cancer

Dr. Paddy TM Chan

Specialist in Clinical Oncology

Dr. Paddy TM Chan

Hong Kong saw just over 4,000 new cases of lung cancer in 2004. It is the first-ranking incident cancer in men and number 3 in women. However it tops the cancer mortality chart, responsible for over 3,500 deaths in the same year. Most, around 90%, are non-small cell lung cancers (NSCLC). Most male lung cancer patients are smokers while most female are non-smokers. The aetiology of non-smoking female having lung cancer is still a hot topic of epidemiological studies.

Diagnosis and Staging

Lung cancers tend to present in an advanced stage. Most adenocarcinomas are situated in the periphery of the lung. Thus they seldom produce classical textbook symptoms like cough, shortness of breath, haemoptysis, which are more 'central' or 'proximal' airway symptoms. Nowadays non-small cell carcinomas tend to present with constitutional symptoms like weight loss, anorexia and sometimes with advanced disease like pleural effusion and distant metastasis. These non-specific symptoms may evade early detection by clinicians.

Bronchoscopy becomes less and less useful for obtaining pathological diagnosis, since the tumours are in the peripheral airways. More and more transcutaneous biopsies under CT scan guidance are performed. In some instances mediastinoscopy is used to biopsy enlarged mediastinal nodes. Supraclavicular adenopathy, if present, are also convenient sites to obtain cytological (fine needle aspiration) or histological (core biopsy) diagnosis. Sputum cytology, or in the case of presence of pleural effusion, pleural cytology are also sources for pathological diagnosis.

The most important point for staging is to determine the mode of treatment. Stage I is primary lung cancer without metastasis. Stage II permits hilar adenopathy only. Stage III denotes presence of pleural effusion or mediastinal adenopathy. Stage IV means presence of distant metastasis, including intra-pulmonary metastasis.

The most favourable situation would be stage I or II lung cancer which would be treatable by surgery. These are few and far between. Most are incidental findings on radiological imaging for other purposes. Screening for lung cancer, using high resolution computerised tomography, remains a controversial issue, with the effect on mortality remaining to be proven. The 'who, when, with what, how often...' are still undetermined.

The practical way to stage lung cancer is determined by the starting point at diagnosis. If distant metastasis is obvious there is no point to use highly sophisticated staging modalities. If one may be dealing with early, operable lung cancer, then thorough evaluation is necessary. Useful methods include high resolution CT thorax, PET-CT scan and mediastinoscopy. The common theme is to determine whether metastatic mediastinal nodes are present.

Treatment for Stage I and II NSCLC

Given stage I and II non-small cell lung cancer patients, the next determinant would be whether surgical treatment is appropriate. Important factors include age, performance status and co-morbidities. Adequate lung function is an obvious pre-requisite. Pneumonectomy, lobectomy with mediastinal lymph node sampling are standard thoracic surgical procedures. Video-Assisted Thoracic Surgery is now a common-place procedure.

Adjuvant chemotherapy for pathological stage I and II non-small cell carcinoma are gaining acceptance amongst oncologists[1-6]. Randomised trials strongly support the use of three or four cycles of cisplatin-based chemotherapy after complete surgical resection in patients with NSCLC. The benefit observed is in the same range as the improvement obtained with adjuvant chemotherapy in patients with other cancers, such as breast cancer, colon cancer, and ovarian cancer. Selection of patients is important because the chemotherapy does carry toxicity. There is little place for adjuvant radiotherapy for stage I and II lung cancers. Using the targeted therapy agents - the tyrosine kinase inhibitors, as adjuvant treatment is not established.

Treatment for stage III NSCLC

'Dry' (no pleural effusion) stage III NSCLC are mostly treated with chemotherapy and radiotherapy. Chemotherapy concurrent with thoracic radiotherapy produce the best therapeutic results when compared to the two modalities in sequence. Platinum-based chemotherapy is used. Advance in radiotherapy (3 dimensional radiotherapy, intensity-modulated radiotherapy) enables a high dose of radiation to be delivered more accurately to the target (primary and nodes), and at the same time minimise the dose to critical structures like the spinal cord and the oesophagus. This has improved the outcome i.e. better tumour control with less toxicity, with radiation

therapy to the thorax. Dose-escalating protocols are being worked out, in an attempt to further improve the efficacy.

Other feasible treatments for 'dry' stage III NSCLC include neoadjuvant chemotherapy followed by surgery. This is more of a research topic than everyday practice. Sometimes salvage surgery after definitive chemoradiation is used for residual tumours after chemoradiation.

'Wet' stage III NSCLC (presence of pleural effusion) is usually treated with chemotherapy alone. It is treated more like a stage IV cancer.

Treatment of stage IV NSCLC

For patients in reasonable performance status (PS<2), chemotherapy doublets with platinum as base, is frequently used. Paclitaxel, gemcitabine, vinorelbine and docetaxel are all useful agents of similar efficacy when combined with either cisplatin or paraplatin. These 'modern' combinations of chemotherapy have a lower toxicity profile than 'older' combinations. Adding the vascular endothelial growth factor (VEGF) inhibitor bevacizumab was reported to have an advantage in outcome compared to chemotherapy alone.

For patients in less favourable performance status, single agents using these chemotherapy agents are still useful for palliation. These can be given at weekly intervals with even less toxicity.

Palliative radiotherapy remains a useful tool for distressing symptoms like painful skeletal metastasis, spinal cord compression, brain metastasis, major airway obstruction or superior mediastinal obstruction.

Palliative radiotherapy remains a useful tool for distressing symptoms like painful skeletal metastasis, spinal cord compression, brain metastasis, major airway obstruction or superior mediastinal obstruction.

Treatment for Relapse / Progression

Biological therapy / targeted therapy aiming at epidermal growth factor receptors (EGFR) becomes viable options for second-line treatment after failing first-line chemotherapy. Erlotinib and Gefitinib are similar tyrosine-kinase inhibitors for non-small cell lung cancers. Useful predictors of response include: female, never-smokers, adenocarcinomas and ethnic Asian. Other biologicals are already in the pipeline to be tested in NSCLC.

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Chemoradiation - an overview and examples

(adapted from issues of JOC Bulletin, Joint Oncology Conference)

Chemoradiation for Carcinoma of the Cervix

Dr. William Foo
Specialist in Clinical Oncology

Chemoradiation became the standard treatment for carcinoma of the cervix almost overnight in 1999, replacing radiotherapy. The April 15 1999 issue of The New England Journal of Medicine published three randomised trials of chemoradiation for carcinoma of the cervix. The National Cancer Institute of the United States earlier issued a recommendation that "... strong consideration should be given to the incorporation of concurrent cisplatin-based chemotherapy with radiation therapy in women who require radiation therapy for treatment of cervical cancer". Two more phase III trials were reported later that year, reinforcing the momentum.

Cisplatin, mostly given weekly when added to conventional radiotherapy for the treatment of carcinoma of the cervix, reduced the odds of death ranging from 50% to 28%. The absolute reduction of mortality amounted to 10% to 15%. The practice in Hong Kong followed suit.

A recent Cochrane review (The Cochrane Database of Systematic Reviews 2005 Issue 4) further supports the treatment efficacy of chemoradiation. The database reviewed 24 trials including 4,921 patients. The authors concluded that the evidence "... strongly suggests chemoradiation improves overall survival and progression free survival, whether or not platinum [ie, all we need is chemotherapy] was used, with absolute benefits of 10% and 13%, respectively". They also commented that reports on late toxicities were still lacking. Late radiation toxicity takes years to manifest. The underlying pathology is almost always endarteritis obliterans, stromal atrophy and fibrosis. We are watching cautiously.

Chemoradiation is evolving. Biologics and hypoxic cell killers are now being tested to see if they can be part of the regimen integrated to radiotherapy.

Starting chemoradiation for cancer of the cervix actually gave us an opportunity to familiarise ourselves with this technique. Prior to this, we were trying our hand at advanced head and neck cancers, with the worry that using the two modalities concomitantly might do great harm. The radiotherapy target volume for cancer of the cervix is large, comprising the whole pelvis, including a lot of bowel and bone marrow. Radiation enteritis and bone marrow toxicity were our main concerns; however, these turned out to be manageable. Since then, we have become much more positive and confident in using chemoradiation, extending the application to other cancer sites. The rest is history.

Evolution of Chemoradiation in the Management of Locally Advanced Rectal Cancer in the Post-5-FU Era

Dr. Raymond T T Chan
Specialist in Clinical Oncology

Management of rectal cancer has undergone significant evolution in the last decade. Advances in diagnostic evaluation, meticulous attention to complete excision of mesorectum, judicious use of adjuvant therapy and availability of novel chemotherapeutic agents for patients with advanced disease have culminated in significant improvement in outcomes. In patients with locally advanced rectal cancer, the present standard of care is to offer preoperative fluorouracil (5-FU)-based chemoradiotherapy, which induces downsizing and downstaging that, in turn, facilitates complete resection. Whilst adjuvant chemotherapy with the oxaliplatin-5-FU couplet has become the new standard of care in patients with stage III resected cancer of the colon, the role of novel agents in rectal cancer is still evolving. On a practical level, patients with locally advanced disease harbour significant risks of both local and systemic failures, and in this regard, pre- and postoperative regimens that offer both radiation sensitisation and systemic activity may improve local as well as distant control.

Oxaliplatin is a novel platinum derivative with a 1, 2 diaminocyclohexane (DACH) group. The combination of oxaliplatin and 5-FU has shown superior progression-free survival and 3-year disease-free survival in patients with advanced and stage III colon cancer, respectively. Moreover, oxaliplatin is a potent radiation sensitiser, which renders it an appropriate agent to combine with radiotherapy in rectal cancer. More recently, capecitabine, an oral fluoropyrimidine with selective activation in tumours where there is a relatively high level of thymidine phosphorylase, has been shown to be active in advanced disease, and equivalent to conventional 5-FU plus leucovorin in patients with stage III colon cancer. Moreover, there are data suggesting a synergistic relationship between capecitabine and radiation, a result of the upregulation of thymidine phosphorylase by the latter. The

oxaliplatin and capecitabine couplet has been examined in patients with metastatic colorectal cancer, and preliminary results reveal significant systemic activity in the same order as oxaliplatin plus 5-FU.

Figure 1.3-Dimensional conformal radiotherapy planning in rectal cancer.

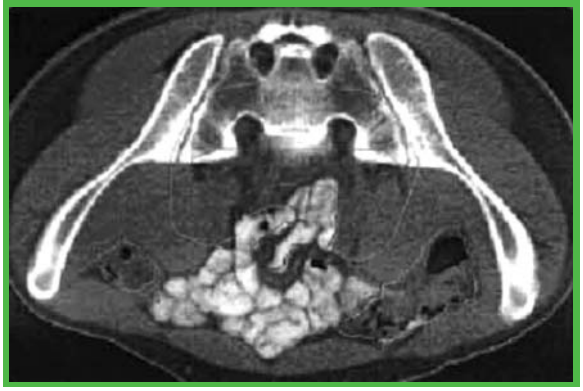
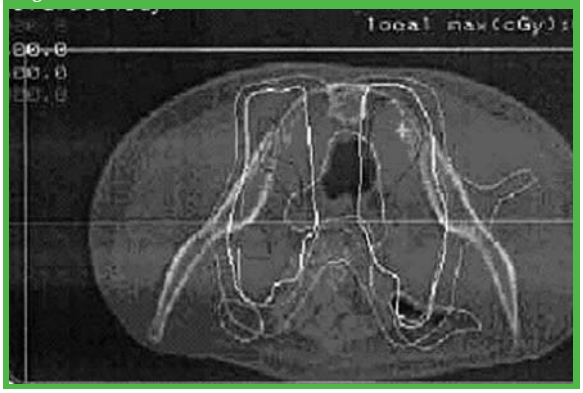


Figure 2. IMRT dose distribution in rectal cancer.



In parallel, there is also momentous innovation in radiotherapy technology, and 3-dimensional radiotherapy planning is increasingly being employed to improve the conformity of radiation dose distribution (Figure 1), a move that has significantly reduced the toxicities over the small bowel and urinary bladder. More advanced conformal techniques, including intensity modulated radiotherapy (IMRT) (Figure 2) and tomotherapy, are also being examined in the field of rectal cancer to further improve the therapeutic ratio.

With such advances in place, are there any clinical data showing benefits of adding oxaliplatin-capecitabine to radiotherapy? There are a number of studies examining the combination of oxaliplatin-capecitabine with radiotherapy in patients with locally advanced rectal cancer and three of these have been published recently. Findings from these studies are summarised in the Table.

An overview of these preliminary data suggests the feasibility and safety of combining radiotherapy with the systemically active oxaliplatin-capecitabine couplet. In addition, the high pathological complete response rates observed across these studies are encouraging, although longer follow-up with specific data on sites of relapses, survival and longterm toxicities are required before it is widely adopted.

In summary, the availability of systemically active agents in the post-5-FU era has shown considerable promise for refining the management of patients with locally advanced rectal cancer, and further data are eagerly awaited.

Table. Recent studies of oxaliplatin-capecitabine with radiotherapy in locally advanced rectal cancer

No. of patients	Patients recruited	Phase of study	Combination studied	pCR rate (%)	RO rate (%)	Significant pathological response (including pCR)	Authors
32	T3-T4 or low-lying rectal cancer	I/II	O: escalating dose between 50mg/m2 and 60mg/m2 weekly C: 825mg/m2 bd on days 1-14 & 22-35 RT: 50.4 Gy	19	79% (T4)	58%	Rodel et al
40 (evaluable:36)	T3-T4 and/or N+	II	O: 50mg/m2 weekly x 5 weeks C: 825mg/m2 bd on each day of RT RT: 45 Gy	14	83% (CRM tumour free)	58% (by Wheeler grade)	Machiels et al
18	Clinically unresectable rectal canceror when histologically clear surgical margins unlikely	I	O: 130mg/m2 on days 1 & 29 C: escalating dose from 500-625-825mg/m2 bd RT: 45 Gy	28	78%	NA	Glynne-Jones et al

O:oxaliplatin; C: capecitabine; RT: radiotherapy; pCR: pathological complete response; RO: complete resection; CRM: drcumferential resection margin; NA: Not available

Chemoradiotherapy of Carcinoma of the Oesophagus

Specialist in Clinical Oncology

The incidence of carcinoma of the oesophagus remains high in Hong Kong with a mortality rate of 5 per 100,000 in 2002. It is the 6th most common cause of cancer morality in Hong Kong. The aggressiveness of the disease can be illustrated by the fact that 356 patients died of this disease in 2002, while 472 new cases were diagnosed in the same year. With a recent rise in the incidence of carcinoma at the gastro-oesophageal junction[1], adenocarcinoma has overtaken squamous cell carcinoma as the commonest histology. Because of its location and advanced stage and age at diagnosis (60% of patients diagnosed were older than 65 years), surgical resection can seldom be performed successfully. Even among the selected surgical candidates, the surgical mortality rate is about 5% and the long-term survival is 10% to 40%. There is an obvious need to develop new treatments to improve local control and survival.

Several randomised studies of preoperative chemoradiotherapy have shown impressive results and a resection rate of 70%.[2,3] Clinical complete remission and pathological complete remission rates up to 25% are reported. Definitive chemoradiotherapy is usually used for those advanced disease cases in which surgical resection is not an option.[4] The treatment result in these patients is expected to be poor because the metastatic rate is high. A randomised study using cisplatinium and 5-fluorouracil (5-FU) plus concurrent radiotherapy has shown a 5-year survival rate of 32% and 10-year survival rate of 20%.[5] The relatively low dose of radiation used (50 Gy) and the good local control of disease in the study have demonstrated the synergistic effect of combined chemotherapy and radiation.

Case 1. A 62-year-old male smoker presented in July 2000 with dysphagia and weight loss of 10 kg. He underwent a barium swallow test and CT scan (Figure 1a), which revealed an occlusive lesion at the mid-oesophagus level. Oesophagastroduodenoscopy (OGD) was performed with biopsy confirming a moderately differentiated carcinoma extending from 22 to 26 cm.
The patient received radical chemoradiation with two cycles of IV cisplatinium 100 mg/m^2 on day 1 and 5-FU 1,000 mg/m^2 on day 1 to day 4 every 3 weeks. 3-D conformal radiotherapy was given concurrently using 50 Gy over 25 fractions, 6 fractions per week with another 10 Gy in 5 fractions as a local boost. An additional two cycles of chemotherapy was given after radiotherapy.
The patient developed severe radiation oesophagitis requiring parenteral nutrition support. His symptoms of dysphagia disappeared 1 month after treatment. Follow-up CT scan and OGD showed no evidence of recurrence. A CT scan 52 months after treatment (Figure 1b) showed complete radiological resolution of the disease. The patient is in remission and asymptomatic at 68 months post-treatment.

Case 2. A 43-year-old male patient presented with haematemesis and dysphagia. A CT scan done in August 2001 showed extensive disease in the oesophagus measuring 12 cm with a right paravertebral mass (Figure 2a). The patient was treated in a similar manner to Case 1 above, and he is completely symptom-free 4 months after treatment with resolution of most of the disease. The latest CT scan from February 2006 (Figure 2b) showed no evidence of recurrence.

Case 3. There is recent evidence to suggest that PET/CT can predict local control and survival[7] after chemoradiation, and may be used to select patients for definitive chemoradiation. To illustrate this, here is an example of a 56-year-old woman who presented recently with severe dysphagia. She was subsequently found to have squamous cell carcinoma with mediastinal lymphadenopathy (Figure 3a). She was treated with chemoradiation as before.
She is in complete remission according to a PET/CT performed 3 months after treatment (Figure 3b). This resolution of disease on PET/CT may predict local control without surgery.

Discussion. The standard treatment for inoperable or medically unfit patients with oesophageal carcinoma is combined chemoradiotherapy. This applies to squamous cell histology and also adenocarcinoma.[5,6] Complete pathological remission rates in the region of 40% can be expected. For resectable tumours, meta-analysis data suggested superior local control and survival with trimodality (chemoradiation followed by surgery) over surgery alone.[3,6] It is of note that the majority of patients in that study suffered from adenocarcinoma. Alternatively, adding surgery to chemoradiation may increase local control but the survival may not improve.[6] As most radiation or chemoradiation patients are either locally advanced or medically unfit, there is patient-selection bias in comparing surgical series. Palliative oesophagectomy should not be performed in patients with locally advanced disease or with distant metastasis because this group of patients can be treated effectively with either oesophageal stenting or chemoradiation.
While surgery remains the standard treatment for resectable early-stage oesophageal carcinoma in medically fit patients, chemoradiation can offer another option, especially for elderly patients or those with an advanced stage of disease.

Fig 1a. CT scan revealing an occlusive lesion at the mid-oesophagus level

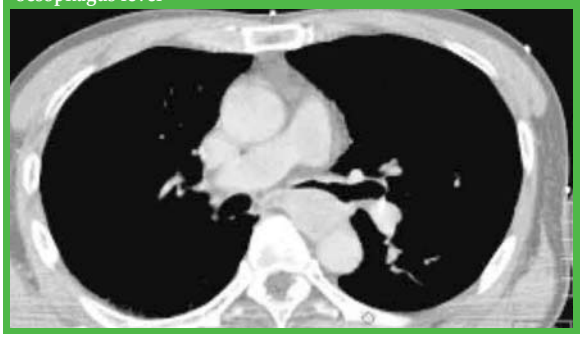


Fig. 1b. Repeat CT scan 52 months after treatment showing complete radiological resolution of disease

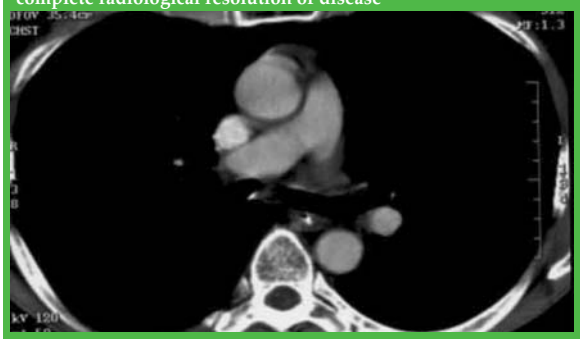


Fig. 2a. CT scan from August 2001 showing extensive disease in the oesophagus measuring 12cm with a right paravertebral mass

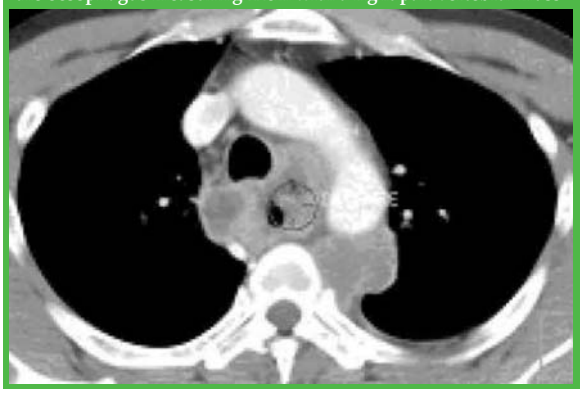


Fig. 2b. Repeat CT scan from February 2006 with no evidence of recurrence

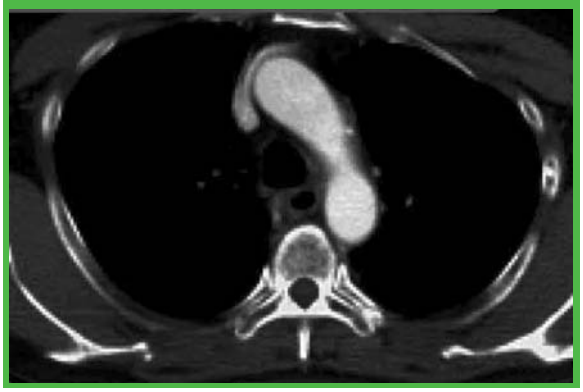


Fig. 3a. PET/CT image reveals squamous cell carcinoma with mediastinal lymphadenopathy

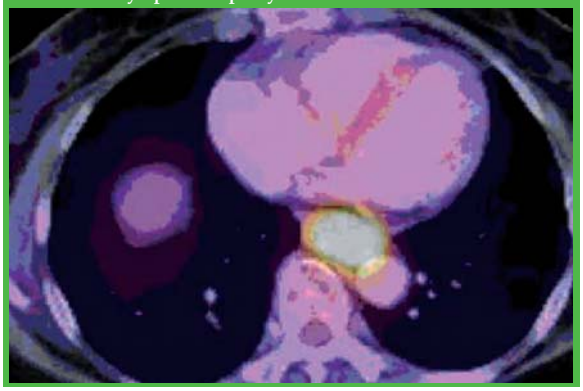
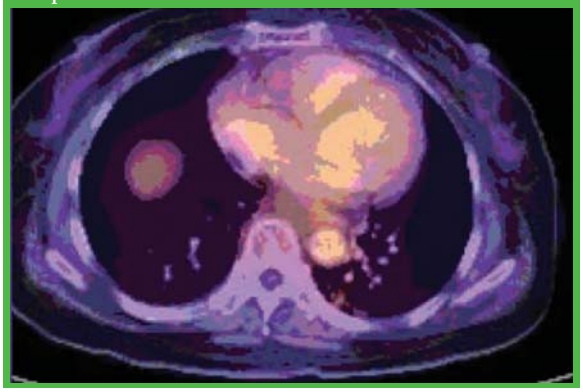


Fig. 3b. Repeat PET/CT done 3 months after treatment shows complete remission



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7. Kostakoglu L, Goldsmith SJ. J Nucl Med 2004;45:56-68.

Pre-operative Chemoradiation for Advanced Rectal Cancer

Dr. Lawrence PK Li
Specialist in Clinical Oncology

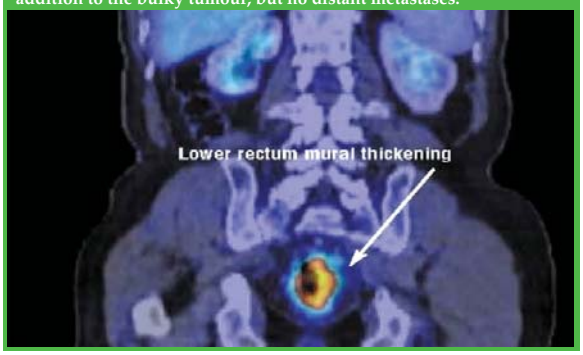
Introduction

There has been a growing trend for the use of pre-operative chemoradiation in the curative treatment of rectal cancer. The aims are to downstage the tumour, enable sphincter preservation in cancers situated in the lower third of the rectum, and possibly to increase the cure rate. Overall, about 15% of patients will achieve pathological complete response to the chemoradiation treatment prior to surgery, and another 60% of patients will achieve partial response. The former group usually has a very favourable long term outcome. Sphincter preservation is achieved in more than half of the patients who would otherwise have to undergo abdominoperineal resection. The following case history is one of the growing number of success stories.

History and investigations

A 71-year-old gentleman was diagnosed with histologically proven adenocarcinoma of the rectum in December 2003. The inferior border of the tumour was at 5 cm from the dentate line, and it was locally advanced, involving the whole circumference of the rectal wall. The tumour measured 7 cm in length. PET-CT scan showed enlarged para-rectal lymph nodes in addition to the bulky tumour, but no distant metastases (Figure 1).

Figure 1. PET-CT scan showing enlarged para-rectal lymph nodes in addition to the bulky tumour, but no distant metastases.



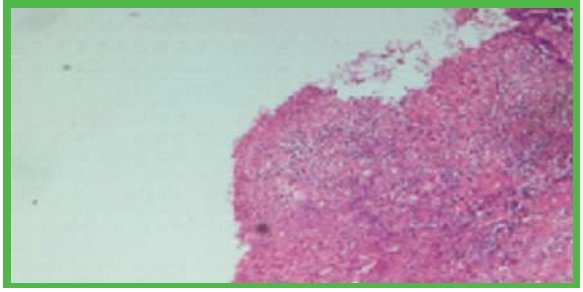
Management

The patient was referred for pre-operative chemoradiation. A total dose of 50 Gy over 25 fractions in 5 weeks was given to the pelvis by multiple beams. Concurrently, intravenous leucovorin and 5-fluorouracil (5FU) were given during the first 5 days and the last 5 days of the radiotherapy treatment.

The patient underwent a low anterior resection 6 weeks after completion of radiotherapy. During the operation, the surgeon could not palpate any tumour, and said he actually felt like he was operating on a disease-free person.

The pathology of the resected specimen showed an 8-cm-long shallow ulcer in the original tumour site. Microscopically, there were no residual carcinoma cells identifiable either in the rectum (Figure 2) or in the para-rectal lymph nodes. The patient has his sphincter preserved, with good function.

Figure 2. Pathology of the original rectal tumour site shows absence of residual carcinoma cells.



A Case of Complete Pathological Remission by Chemoradiotherapy in Inoperable Non-small Cell Lung Cancer

Dr. Victor Hsue

Specialist in Clinical Oncology

Introduction

Inoperable non-small cell carcinoma of the lung has a poor prognosis. Despite the use of radical radiotherapy, the median survival has been about 9 months and the overall 5-year survival rate only 5%. Various methods have been tried including neoadjuvant chemotherapy followed by radiotherapy. However, evidence suggests that the use of concurrent chemotherapy and radiotherapy followed by surgery will offer the best local control and survival. An example of this treatment was reported at the Joint Oncology Conference on October 26, 2004.

History and presentation

A 45-year-old Chinese woman from Vancouver, Canada, was diagnosed with an inoperable adenocarcinoma in July 2003. She is a non-smoker but both of her parents had lung cancer. She presented with dry cough for 3 months with no haemoptysis, dyspnoea or weight loss.

Investigations

Chest x-ray showed a 2.5-cm mass in the left upper zone. Unfortunately, CT thorax showed an enhancing 3.5 x 3.4 x 3.3 cm mass with an irregular margin in the left upper lobe, which was adherent to the aortic arch, and also another adjacent cavitating 2.0 x 1.9 x 1.6 cm mass. There were multiple mediastinal lymph nodes up to 1.5 cm including AP window. The patient also had a PET scan confirming the extensive locoregional disease, but there were no distant metastases. She was seen by a thoracic surgeon and her tumour was considered inoperable.

Management

After detailed discussion with the patient and her family, the decision was made to use neoadjuvant concurrent chemotherapy and radiotherapy (Figure 1). Two cycles of Taxol (paclitaxel) at 175 mg/m2 + carboplatin at AUC 6 every 3 weeks was started from 30 July 2003 together with concurrent radiotherapy (6 fractions/week). A total dose of 56 Gy in 28 fractions was completed on 30 August 2003. There was no significant marrow toxicity or weight loss after treatment. However, the patient experienced moderate radiation oesophagitis.

Two weeks after treatment, a repeat CT scan showed significant reduction of the lung masses and the disappearance of the enlarged mediastinal lymph nodes.

As planned, a left pneumonectomy was performed 4 weeks after treatment and there was no adhesion encountered during the resection.

The surgical pathology showed extensive necrosis of the original tumour with no identifiable viable tumour cells (Figure 2). There was no tumour detected in the resected mediastinal lymph nodes.

After surgery, she received four cycles of Taxol/carboplatin as adjuvant therapy. Two months after chemotherapy, the patient experienced a sudden generalised seizure. The subsequent MRI showed three cerebral deposits (Figure 3), which were all successfully treated with stereotactic radiosurgery.

Outcome

The patient was well when last seen in January 2005.

Figure 1. Patient was treated using chemoradiotherapy before surgery. The primary tumour, the involved lymph node and subclinical disease were covered by the Planning Target Volume (PTV). The isodose lines are also shown.

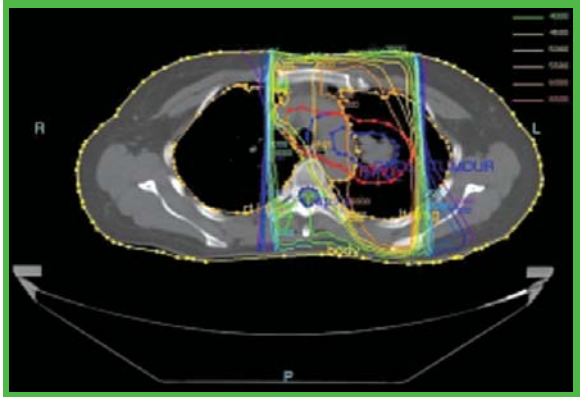


Figure 2. Histology of the resected tumour shows extensive necrosis with no identifiable viable tumour cells.

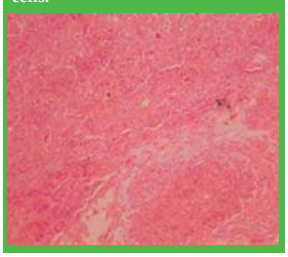
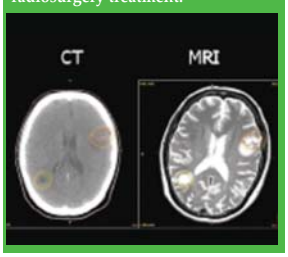


Figure 3. CT and MRI images showing the cerebral deposits, which were well covered by the radiosurgery treatment.



Dermatological Quiz

Dr. Ka-ho Lau

MBBS(HK), FRCP(Glasg), FHKCP, FHKAM(Med)
Yaumatei Dermatology Clinic, Social Hygiene Service

Dr. Ka-ho Lau

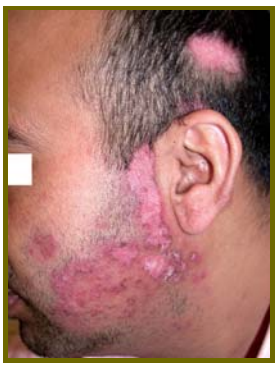


Fig 1
Lesions in the left side of the face

A 40-year-old man developed this slightly itchy skin rash on his face after his business trip in Africa. Beside the skin rash on his face, his left parietal scalp was also affected with loss of hair. He did not have any systemic upset associated with the rash. He consulted his family doctor and received oral and topical antifungal treatment with no improvement.

Questions:

1. What is your diagnosis?
2. How will you confirm your clinical diagnosis?
3. How will you manage this patient?

(See P. 35 for answers)

Federation Soccer Five Tournament 2007

We invite all our member societies and interested parties to participate in the Federation Soccer Five Tournament 2007 which will commence in September 2007. The registration form can be downloaded from our website www.fmshk.org and the registration deadline is 15 August 2007. Please contact Ms. Karen Chu at 2821 3515, karen.chu@fmshk.org for further details and assistance.

Function	Members of the Organizing Committee
Co-Chairman	Mr. Nelson Lam, Hon. Treasurer, FMSHK
Co-Chairman	Dr. Kingsley Chan, Co-Opted Council Member, FMSHK
Immediate Past Chairman	Dr. Godfrey CF Chan, Publicity Chairman, FMSHK
Sports Official (Members)	Dr. Raymond SK Lo, Hon Secretary, FMSHK
Sports Official (Members)	Dr. Liu Wing Hong, Sports Council, Hong Kong Dental Association
Sports Official (Members)	Dr Chan Chi Wing, Timmy
Sports Official (Associate Members)	Dr. Jimmy Lai, Sports Chair, Hong Kong Ophthalmological Society
Sports Official (Associate Members)	Ms Tina Yap, President, The Pharmaceutical Distributors Association of Hong Kong Ltd.
Sports Official (Associate Members)	Mr. Stephen Leung, Country Manager, Pfizer Corp Hong Kong Ltd.

Society News

News from Member Societies:

Association of Private Orthopaedic Surgeons
Updated office-bearers for the year 2007-2008 are as follows: President: Dr. BONG Shu-chun, Hon. Secretary: Dr. LAM Yan-kit, Council Representative: Dr. HO Ho-pak.

Hong Kong Practising Dietitian Union
New office-bearers for the year 2007-2008 are as follows: President: Mr. TING Ho-yan, Terry, Hon. Secretary: Ms. WOO Chi-yan Josephine, Hon. Treasurer & Council Representative: Ms. Sham Yeung Yuk-mei Mimi.

The Hong Kong Association of Blood Transfusion & Haematology Limited
Updated office-bearers for the year 2007-2008 are as follows: President: Dr. YU Pui Hung, Hon. Secretary: Ms. CHENG Wai-sze, Sisi, Council Representative: Mr. CHAN Nam-kwan.

The Hong Kong Society for Colposcopy and Cervical Pathology (HKSCCP)
HKSCCP was established since 2001 for the following objectives:

- To facilitate the interchange of information on colposcopy and cervical pathology among members of the Society, both locally and internationally.
- To research, and offer guidelines for the diagnosis and management of diseases of the female lower genital tract.
- To facilitate training, teaching and accreditation of colposcopists and cervical smear takers.
- To enhance public awareness of cervical cancer screening

Currently, we have 148 members and 56 associate members. Application forms are available at www.hksccp.org.hk or www.香港陰道鏡及子宮頸病理學會.hk

2007

香港醫學組織聯會

FEDERATION PRESIDENT CUP SOCCER FIVE TOURNAMENT

醫聯會長盃 - 五人足球賽

五 5 Soccer 人

Organiser : FMSHK

Date:September -November 2007 **Group Stage** Venue: Kowloon Bay 展貿中心

	Group A	Group B	Group C	Group D	
1					1
2					2
3					3
4					4
5					5

Group A First Place	Group B First Place	Group C First Place	Group D First Place
Group A Second Place	Group B Second Place	Group C Second Place	Group D Second Place

Date: November **2007** **Final Stage**

Group A 1 vs Group C 2	Group B 1 vs Group D 2	Group C 1 vs Group A 2	Group D 1 vs Group B 2

Semi-final 1

Semi-final 2

3rd Place Match

Championship Match

FEDERATION PRESIDENT CUP SOCCER FIVE TOURNAMENT 2007

REGISTRATION APPLICATION FORM
(Tournament matches)

FIRST ANNOUNCEMENT ENTRANCE FEE PER TEAM: To be decided at a later date

NAME OF TEAM:

QUALIFYING MEMBERSHIP TYPE : * ORDINARY/ ASSOCIATE/ STUDENT/OTHER

PLAYERS (10-12) IN THE TEAM with names and ID No (first 5 digits)

CONTACT NAME OF MANAGER:

TELEPHONE:

EMAIL:

ADDRESS:

Would you like to PURCHASE professional Nike size 4 football @HK$140 and how many?

HOW MANY T-shirts (at cost) WOULD YOU LIKE?

Total value for purchasing T-shirts/Nike football

Once you have completed the form (fill in a separate form per team), please fax it to 2865 0345 or mail to the Secretariat, The Federation of Medical Societies of Hong Kong, 4/F, Duke of Windsor Social Services Building, 15 Hennessy Road, Wanchai, Hong Kong, **on or before 15th August 2007.**

(RULES AND REGULATIONS SUBJECT TO THE FEDERATION ORGANISING COMMITTEE CHAIRMAN WITH POSTED RESULTS OF MATCHES ON THE INTERNET)

* Delete as appropriate

Medical Diary of August

Sunday	Monday	Tuesday	Wednesday	Thursday	Friday	Saturday
			1	★ HKMA Council Meeting 2	3	4
★ HKMA Structured CME Programme at Queen Elizabeth Hospital Year 07/08 (V) - O&G and X-Ray 5	6	★ HKMA Newsletter Editorial Meeting 7	★ Hong Kong Neurosurgical Society Monthly Academic Meeting - "An Update on Neuroradiology" 8	★ HKMA Structured CME Programme with Hong Kong Sanatorium & Hospital Year 2007 (VIII) - Intraocular Contact Lens 9	10	★ Refresher Course for Health Care Providers 2006/2007 (XII) - Sexually Transmitted Diseases In The Community 11
★ Trailwalker 3rd Practice Session (Stage 9 & 10) 12	★ FMSHK Officers' Meeting 13	14	★ FMSHK Executive Committee & Council Meetings 15	16	17	18
19	20	21	22	23	★ Advanced Trauma Life Support (ATLS) Student Course 24	★ Advanced Trauma Life Support (ATLS) Student Course ★ Food and Health Day Course ★ Trailwalker 4th Practice Session (Stage 6, 7 & 8) ★ SHMT Dermatology Summit 2007 25
★ Advanced Trauma Life Support (ATLS) Student Course ★ HKMA Structured CME Programme at Kwong Wah Hospital Year 07/08 (V) - Cardiology 26	27	28	29	30	31	

Date / Time	Function	Enquiry / Remarks
2 THU 8:00 pm	**HKMA Council Meeting** Organised by: The Hong Kong Medical Association Chairman: Dr. K CHOI # HKMA Head Office, 5/F., Duke of Windsor Social Service Building, 15 Hennessy Road, Wanchai, Hong Kong	Ms. Christine WONG Tel: 2527 8285
5 SUN 2:00 pm	**HKMA Structured CME Programme at Queen Elizabeth Hospital Year 07/08 (V) - O&G and X-Ray** Organised by: The Hong Kong Medical Association & Queen Elizabeth Hospital Speaker: Various # Lecture Theatre, G/F., Block M, Queen Elizabeth Hospital, Kowloon	Miss Viviane LAM Tel: 2527 8452 (Registration fee is required) 3 CME Points
7 TUE 8:00 pm	**HKMA Newsletter Editorial Meeting** Organised by: The Hong Kong Medical Association Chairman: Dr. H.H. TSE # HKMA Head Office, 5/F., Duke of Windsor Social Service Building, 15 Hennessy Road, Wanchai, Hong Kong	Ms. Tammy TAM Tel: 2527 8941
8 WED 7:30 am	**Hong Kong Neurosurgical Society Monthly Academic Meeting - "An Update on Neuroradiology"** Organised by: Hong Kong Neurosurgical Society Chairman: Dr. Gilbert LEUNG Speaker: Dr. Hector MA # Seminar Room, G/F., Block A, Queen Elizabeth Hospital, Kowloon	Dr. Y.C. PO Tel: 2990 3788 Fax: 2990 3789
9 THU 2 :00 pm	**HKMA Structured CME Programme with Hong Kong Sanatorium & Hospital Year 2007 (VIII) - Intraocular Contact Lens** Organised by: The Hong Kong Medical Association & Hong Kong Sanatorium & Hospital Speaker: Dr. CHANG So Min John # HKMA Dr. Li Shu Pui Professional Education Centre, 2/F., Chinese Club Building, 21-22 Connaught Road Central, Hong Kong	Miss Viviane LAM Tel: 2527 8452 (Registration fee is required) 1 CME Point
11 SAT 2:30 pm	**Refresher Course for Health Care Providers 2006/2007 (XII) - Sexually Transmitted Diseases In The Community** Organised by: The Hong Kong Medical Association & Our Lady of Maryknoll Hospital Chairman: Dr. W.H. YIP Speaker: Dr. LUK Nai Ming Tommy # Training Room II, 1/F., OPD Block, Our Lady of Maryknoll Hospital, 118 Shatin Pass Road, Wong Tai Sin, Kowloon, Hong Kong	Ms. Clara TSANG Tel: 2354 2440 2 CME Points
12 SUN 8:00 am	**Trailwalker 3rd Practice Session (Stage 9 & 10)** Organised by: The Hong Kong Medical Association Chairman: Dr. Y.H. CHOW # Tsuen Wan MTR Station Exit C	Miss Dorothy KWOK Tel: 2527 8285
13 MON 8:00 pm - 10:00pm	**FMSHK Officers' Meeting** Organised by: The Federation of Medical Societies of Hong Kong # Gallop, 2/F., Hong Kong Jockey Club Club House, Shan Kwong Road, Happy Valley, Hong Kong	Ms. Carmen CHEUNG Tel: 2821 3512 Fax: 2865 0345
15 WED 7:00 pm - 10:00pm	**FMSHK Executive Committee & Council Meetings** Organised by: The Federation of Medical Societies of Hong Kong # Council Chambers, 4/F., Duke of Windsor Social Service Building, 15 Hennessy Road, Wanchai, Hong Kong	Ms. Carmen CHEUNG Tel: 2821 3512 Fax: 2865 0345
24 FRI (25,26)	**Advanced Trauma Life Support (ATLS) Student Course** Organised by: Department of Surgery, Li Ka Shing Faculty of Medicine, University of Hong Kong Medical Centre; Queen Mary Hospital & Hong Kong Chapter of the American College of Surgeons # Skills Development Centre, Department of Surgery, Li Ka Shing Faculty of Medicine, University of Hong Kong Medical Centre, Queen Mary Hospital, Pokfulam, Hong Kong	Program Manager Tel: 2855 4885 Fax: 2819 3416 Email: hnsrg@hkucc.hku.hk Website: http://www.hku.hk/surgery
25 SAT 9:00 am - 3:30 pm	**Food and Health Day Course** Organised by: The Federation of Medical Societies of Hong Kong & Hong Kong Nutrition Association Speaker: Various # Lecture Hall, 4/F, Duke of Windsor Social Service Building, 15 Hennessy Road, Wanchai, Hong Kong	Ms. Karen CHU Tel: 2821 3515 Fax: 2865 0345
3:30 pm	**Trailwalker 4th Practice Session (Stage 6, 7 & 8)** Organised by: The Hong Kong Medical Association Chairman: Dr. Y.H. CHOW # Tai Po Road (at the entrance of Kam Shan Road)	Miss Dorothy KWOK Tel: 2527 8285
8:00 am - 5:15 pm	**SHMT Dermatology Summit 2007** Organised by: The Hong Kong Society of Dermatology and Venereology & The Hong Kong Association of Specialists in Dermatology Speaker: Various # Lecture Theatre, Cheung Kung Hai Conference Centre, G/F., William M.W. Mong Block, Li Ka Shing Faculty of Medicine Building, The University of Hong Kong, 21 Sassoon Road, Pokfulam, Hong Kong	Ms. Sigourney LIU Tel: 2290 1717 Fax: 2810 6913
26 SUN 2:00 pm	**HKMA Structured CME Programme at Kwong Wah Hospital Year 07/08 (V) - Cardiology** Organised by: The Hong Kong Medical Association & Kwong Wah Hospital Speaker: Various # Lecture Theatre, 10/F., Yu Chun Keung Memorial Medical Centre, Kwong Wah Hospital, Kowloon	Miss Viviane LAM Tel: 2527 8452 (Registration fee is required) 3 CME Points

Meetings

8/9/2007	**9th Joint Annual Scientific Meeting** Organised by: The Hong Kong Society of Gastroenterology, The Hong Kong Society of Digestive Endoscopy, Hong Kong Society for Coloproctology, Hong Kong Association for the Study of Liver Diseases & The Hong Kong Society of Gastrointestinal Motility Chairman: Dr. YUEN Man Fung Speaker: Various # Level 7, Langham Place Hotel, Mongkok, Kowloon Enquiry: Ms. Celia TAM Tel: 2869 5133 Fax: 2869 9533 CME Accreditation: Various
20/9/2007 7:00 pm	**Annual General Meeting** Organised by: Hong Kong Society for Coloproctology # World Trade Centre Club Hong Kong, 38/F., World Trade Centre, 280 Gloucester Road, Causeway Bay, Hong Kong Enquiry: Miss Christina LO Tel: 2595 6416 Fax: 2515 3195 Email: cloyy@ha.org.hk
29/9/2007 9:00 am - 6:00 pm	**Health Research Symposium 2007** Organised by: Health, Welfare and Food Bureau Speaker: Various # Hong Kong Academy of Medicine, 99 Wong Chuk Hang Road, Aberdeen, Hong Kong Enquiry: Ms. Lenora YUNG Tel: 2871 8841 Fax: 2871 8898
19-22/10/2007	**16th Asian Congress of Surgery & 3rd Chinese Surgical Week** Organised by: Asian Surgical Association & The Chinese Surgical Society of the Chinese Medical Association # Grand Epoch City, Beijing, China Enquiry: ASA Congress Secretariat Tel: 2855 4235 / 2855 4993 Fax: 2818 1186 Email: info@AsianSurgAssoc.org Website: www.AsianSurgAssoc.org
20/10/2007 1:00 pm - 5:30 pm	**The Federation's Annual Scientific Meeting 2007 - Targeted Therapy in Cancer** Organised by: The Federation of Medical Societies of Hong Kong # M/F, Lecture Theatre, Hospital Authority Building, Kowloon Enquiry: Ms. Karen CHU Tel: 2821 3515 Fax: 2865 0345 Website: www.fmshk.org
17-18/11/2007	**Annual Scientific Meeting in Anaesthesiology 2007 - Expanding the Boundaries** Organised by: The Hong Kong College of Anaesthesiology & The Society of Anaesthetists of Hong Kong # Hong Kong Convention and Exhibition Centre Enquiry: CMPMedica Pacific Limited Tel: 2559 5888 Fax: 2559 6910 Email: meeting.hk@asia.cmpmedica.com Website: www.hkca.edu.hk/asm2007.htm
24-25/11/2007	**4th Asian Pacific Diabetic Limb Problems** Organised by: Various Associations # Wiliam MW Mong Block, Li Ka Shing Faculty of Medicine, The University of Hong Kong, 21 Sassoon Road, Hong Kong Website: http://www.diabeticlimb.hk/

Courses

28,29,30,31/9/2007 1,2/10/2007	**PALS Course 2007** Organised by: Hong Kong College of Paediatricians Speaker: Various # Hong Kong Academy of Medicine, 99 Wong Chuk Hang Road, Aberdeen, Hong Kong Enquiry: Miss Karen YU Tel: 2871 8773 Fax: 2785 1850 CME Accreditation: 12 Points for Hong Kong College of Paediatricians

Answer to Dermatological Quiz

Answer :

1. The correct diagnosis is cutaneous lupus erythematosus, in the discoid form (DLE). The clinical picture shows multiple well defined erythematous scaly plaques with atrophic centres at his left cheek especially at the pre-auricular area. Careful examination of the active plaques at the left lateral cheek around the angle of the jaw reveals the presence of follicular plugging with destruction of hair follicles of the beard area by the disease process. Similar disease process is seen at the left parietal area of the scalp resulting in scarring alopecia. The sign of follicular plugging is a helpful clue suggesting the correct diagnosis. The onset of disease after his sunny trip and the location of the involved areas (face and scalp) suggest photosensitivity. The lack of systemic symptoms makes SLE unlikely. Differential diagnoses include tinea facei/ capitis (which should have responded to the antifungal treatment), eczema/ contact dermatitis and psoriasis.

2. Diagnosis can be confirmed by skin biopsy taken at lesional skin for histology and direct immunofluorescence studies. The epidermis shows atrophic changes with the presence of scattered amorphous eosinophilic colloid bodies representing damaged keratinocytes. The dermo-epidermal junction shows the characteristic interphase dermatitis with vacuolar degeneration of basal keratinocytes. The basement membrane is thickened with mucin deposition. In the dermis, there are mild perivascular and periappendigeal infiltration with lymphohistiocytic cells. Hair follicles may exhibit damage to keratinocytes resulting in follicular plugging, hence the clinical morpholoigical clue to the correct diagnosis. In more established lesions, follicular structures are destroyed and become atrophic or absent, hence giving rise to the clinical manifestation of scarring alopecia. Direct immunofluorescence shows the lupus band with granular deposits of IgG and /or IgM and/ or IgA and C3 at the dermo-epidermal junction.

3. Full autoimmune profiles and systemic work up are indicated to rule out any systemic involvement by LE. DLE needs potent (such as mometasone furoate) or ultrapotent (such as clobetasol propionate) topical corticosteroids to control the inflammatory disease process so as to prevent scarring. After controlling the disease, less potent preparations can then be used for maintenance if necessary. For those lesions which do not respond to topical steroids, intralesional injections of triamcinolone are indicated. This may be considered in treating active DLE at the scalp which may lead to permanent scarring alopecia as seen in our patient. Extensive lesions sometimes require oral antimalarials (such as hydroxychloroquine), but rarely the drug may cause retinopathy. Hence opthalmological assessment is required before and during treatment. Sun avoidance and sun protection with suitable sun screens are important measures for optimising disease control.

Dr. Ka-ho Lau
MBBS(HK), FRCP(Glasg), FHKCP, FHKAM(Med)
Yaumatei Dermatology Clinic, Social Hygiene Service

CERTIFICATE COURSE FOR GENERAL PRACTITIONERS & PARAMEDIC

Commonly Encountered Infections In Daily Practice

常見的感染及傳染病

Course No. C124

Jointly organized by:

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

The Hong Kong Society for Infectious Diseases
香港傳染病醫學會

Objective: To provide updated information on commonly encountered infections in Hong Kong to local healthcare providers.

Date & Time	Topic	Speaker
3 Oct 2007	Respiratory Tract Infection 呼吸道感染	Dr. Ada Lin 連慰慈醫生
10 Oct 2007	Urinary Tract and Other Intra-abdominal Infection 泌尿系統及其他腹內感染	Dr. WS Leung 梁偉成醫生
17 Oct 2007	CNS Infection 中樞神經系統感染	Dr. Wilson Lam 林緯遜醫生
24 Oct 2007	Skin, Soft Tissue, Bone and Joint Infection 皮膚，皮下組織，骨骼及關節感染	Dr. Iris Li 李慧芯醫生
31 Oct 2007	Common Communicable Diseases in Hong Kong 本港常見的傳染病	Dr. Ada Lin 連慰慈醫生
7 Nov 2007	Infection Related to Travelers 與旅遊關聯的感染	Dr. Wilson Lam 林緯遜醫生

Date : 3 October 2007 - 7 November 2007
Time : 7:00 p.m. - 8:30 p.m.
Venue : Lecture Hall, 4/F, Duke of Windsor Social Service Building, 15 Hennessy Road, Wanchai, Hong Kong
Course Fee : HK$750 (6 Sessions)
Language : Cantonese with supplemented by English
Certificate : Awarded to participants with a minimum attendance of 70%
Enquiry : The Secretariat of the Federation of Medical Societies of Hong Kong
Tel. : 2527 8898 Fax : 2865 0345 Email : info@fmshk.org

CME/CPD Accreditation applied for
To download the application form, please visit our website: http://www.fmshk.org

THE FEDERATION OF MEDICAL SOCIETIES OF HONG KONG
香 港 醫 學 組 織 聯 會

The Federation's Annual Scientific Meeting 2007
Targeted Therapy in Cancer

20 October, 2007 (SAT) 1:00 p.m. - 5:30 p.m.
Lecture Theatre, M/F, Hospital Authority Building,147B Argyle Street, Kowloon

APPLICATION FORM

Surname: Prof. / Dr. / Mr. / Ms. _____ First name: _____
(block letters please) (block letters please)

Position: _____

Address: _____

_____ E-mail: _____

Tel. No.: _____ Fax No.:_____

Please tick as appropriate:

☐ I will attend the Federation's Annual Scientific Meeting 2007.
☐ I will have/not have lunch.

☐ I am a member of _____
(member society of the Federation of Medical Societies of Hong Kong)
Enclosed please find a cheque in the amount of _____. (HK$100 for medical, dental, nursing and healthcare professionals).

☐ I am not a member of member society of the Federation of Medical Societies of Hong Kong. Enclosed please find a cheque in the amount of _____. (HK$200 for medical, dental, nursing and healthcare professionals).

_____ _____
Signature Date

Remarks: Please send registration form with cheque made payable to "**The Federation of Medical Societies of Hong Kong**" to 4/F, Duke of Windsor Social Service Building, 15 Hennessy Road, Wanchai, Hong Kong. Registration will be on first-come-first-served basis. No refund will be made if you have to cancel your registration afterwards.

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For office use:

Registration confirmed on _____ Registration Number _____

Cheque Issuing Bank _____ Cheque Number _____

4/F, Duke of Windsor Social Service Building, 15 Hennessy Road, Wanchai, Hong Kong
Tel: (852) 2527 8898 Fax: (852) 2865 0345 Homepage: www.fmshk.org E-mail: info@fmshk.org

THE FEDERATION OF MEDICAL SOCIETIES OF HONG KONG

The Federation's Annual Scientific Meeting 2007

Targeted Therapy in Cancer

20 October, 2007 (SAT)
1:00 p.m. - 5:30 p.m.
Lecture Theatre, M/F,
Hospital Authority Building,
147B Argyle Street, Kowloon

- ***Overview and Breast Cancer***
  Prof. Richard J. Epstein
  Department of Medicine, Queen Mary Hospital, The University of Hong Kong
- ***Head and Neck Cancer***
  Dr. Daniel TT Chua
  Department of Clinical Oncology, Queen Mary Hospital, The University of Hong Kong
- ***Lung Cancer***
  Dr. James CM Ho
  Department of Medicine, Queen Mary Hospital, The University of Hong Kong
- ***Gastrointestinal Tract Cancers***
  Prof. Benjamin CY Wong
  Department of Medicine, Queen Mary Hospital, The University of Hong Kong
- ***Haematological Malignancies***
  Dr. James CS Chim
  Department of Medicine, Queen Mary Hospital, The University of Hong Kong
- ***Childhood Malignancies***
  Dr. Godfrey CF Chan
  Department of Paediatrics, Queen Mary Hospital, The University of Hong Kong

Registration Fee
HK$100 Members of member societies
HK$200 Non-member

Registration
Registration forms can be obtained by calling our Secretariat at 2527 8898 or the homepage http://www.fmshk.org Please send registration form and cheque to: The Federation of Medical Societies of Hong Kong, 4/F, Duke of Windsor Social Service Building, 15 Hennessy Road, Wanchai, Hong Kong. Registration will be on first-come-first-serve basis.

CME/CPE: Please refer to our homepage http://www.fmshk.org for details