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

References

1. IRESSA HK Prescribing Information, Oct 2009.
2. Mok TS, et al. *N Engl J Med* 2009;361:947-957.

Abbreviated Prescribing Information

Presentation: Gefitinib film-coated tablet. **Indications:** 1) First-line treatment of locally advanced or metastatic NSCLC who have activating mutations of the EGFR TK. 2) Treatment of locally advanced or metastatic NSCLC who have previously received chemotherapy. **Dosage:** 250 mg once daily. Tablet can be dispersed in half a glass of drinking water (non-carbonated) without crushing it. Stir until the tablet is dispersed and drink immediately. The liquid can also be administered through a nasogastric tube. **Contraindications:** Severe hypersensitivity to any ingredients of this product; pregnancy & lactation. **Precautions:** EGFR mutation assessment is recommended for first-line treatment; interstitial lung disease; worsening of respiratory symptoms; asymptomatic increase in liver transaminases. **Interactions:** CYP3A4 inhibitors e.g. itraconazole, ketoconazole, clobimazole & ritonavir; CYP3A4 inducers e.g. rifampicin, phenytoin, carbamazepine, barbiturates & St John's wort; drugs that increase gastric pH; warfarin; metoprolol. **Undesirable effects:** Diarrhoea, nausea, vomiting, stomatitis, elevations in alanine aminotransferase, anorexia, rash, asthenia. Full local prescribing information is available upon request. API.HK.IRE.1009



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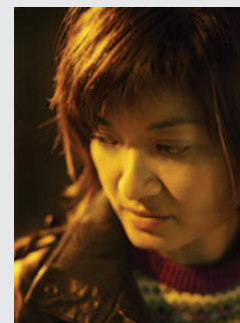
SPRING CLEANING

This photo captures the soft misty colors of an early spring morning, in Xitang, Jiaxing, China, where women work laundry by the river side.

The image focuses on the woman with most action. The outfocused leaves of the willow tree in the foreground frames the subjects in action. In the background, an outfocused watermill is seen.

This is very much the atmosphere of traditional water village life in rural China.

Reflex lens 250mm, f-stop 1.8, 1/800, ISO 400



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Cancer Treatment in the Era of Targeted Therapy: the March is on!

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Editor



Dr. James CS CHIM

In general, cancers including haematological cancers are characterised by either of the following three mechanisms: 1. activation of oncogenes; 2. loss of function of tumour suppressor genes or 3. inhibition of cellular differentiation.^{1,2} Oncogenes confer proliferative or survival advantages while tumour suppressors normally prevent development of cancer by activating apoptosis. Therefore, cancer cells often have constitutive activation of oncogenes together with inactivation of tumour suppressor genes. On the other hand, failure of proper differentiation of precursor cells may result in cancers.

Haematological cancers comprise cancers arising from lymphoid (lymphoma, acute lymphoblastic leukaemia, chronic lymphocytic leukaemia and multiple myeloma) or myeloid origin (acute myeloid leukaemias [AML] and chronic myeloid leukaemias [CML], myelodysplastic syndrome). Many either arise from progenitors or stem cells that are naturally residing in the bone marrow or metastasise to the bone marrow (lymphoma, multiple myeloma). On the other hand, solid cancers arise from transformed epithelium including carcinomas of the breast, lung, liver and colon.

Basic research has enormously impacted the modern management of both haematological and solid cancers. Because of the understanding of the molecular pathogenesis of cancers that usually involve concomitant activation of oncogenes and inactivation of tumour suppressor genes, numerous therapeutic targets have been identified in cancers. For instance, imatinib, a tyrosine kinase inhibitor, is the first small molecule found to inhibit the pathogenic fusion gene, BCR/ABL, which is the primary oncogenic event in chronic myeloid leukaemia. Indeed, since the first randomised controlled trial, the International Randomized Study of Interferon and STI571 (IRIS) trial, published in 2003,³ which showed a much higher rate of response (both haematological and cytogenetic) in CML patients randomised to receive imatinib. Moreover, a substantial number of patients receiving imatinib may actually achieve molecular remission, which has been a mission impossible with conventional chemotherapy. Indeed the updated survival for patients enrolled in that trial showed that the 8-year overall survival is 80% in patients receiving imatinib,⁴ which is comparable or superior to survivals achieved by the use of allogeneic haematopoietic stem cell transplantation in young CML patients transplanted with stem cells from an HLA-identical sibling. Because of the significant response rate including molecular remission and the remarkable survival associated with the use of imatinib, allogeneic HSCT is no longer the first line therapy in CML patients but reserved for patients with accelerated phase or blastic transformation. Moreover, while intensive chemotherapy or allogeneic HSCT is only applicable in relatively young patients, imatinib and many other targeted therapies are generally non-myelotoxic or minimally myelotoxic, and hence can be used in both young and elderly patients alike. Therefore, the scale of impact of the advent of targeted therapy has been enormous, and the momentum is still on. Other major targeted therapies in haematological cancers include the monoclonal antibodies such as rituximab and alemtuzumab, and small molecules like bortezomib, which is an nuclear factor kappa B inhibitor and very effective in the treatment



of myelomas and lymphomas. Moreover, epigenetic therapy has come of age too. Epigenetics refers to the alteration of gene expression not associated with gene mutation but due to either promoter DNA methylation or histone modifications at the promoter regions of tumour suppressor genes. Demethylating therapy such as 5-Azacitidine (Vidaza) or Decitabine (Dacogen) is now the choice of therapy in patients suffering from myelodysplastic syndrome, a disease of the elderly characterised by peripheral cytopenia and a propensity of leukaemia transformation. Indeed, 5-azacytidine has been shown to result in less transfusion requirements, increased response rate, and hence better quality of life. Moreover, it also suppresses leukaemia transformation, and hence improves overall survival.

Similar advances have been made in solid cancers too.⁵ For instance, therapeutic antibodies have emerged as an important part of treatment in multiple solid cancers. In breast cancer, trastuzumab is a welcome addition to the treatment of HER2-overexpressing breast cancers. In colorectal cancer, cetuximab, an inhibitor of EGFR signalling, has been shown to be useful in metastatic colorectal cancers and head and neck cancers. Similarly, small molecules have made substantial impact in cancer therapy too. For instance, in bronchogenic carcinoma, the era of targeted therapy has come for the treatment of non-small cell lung cancers, best exemplified by the story of epidermal growth factor receptor inhibitors like gefitinib (Iressa) and erlotinib (Tarceva) in addition to anti-angiogenesis. Moreover, the future of lung cancer treatment will certainly rest on a personalised approach with more molecularly targeted agents on the horizon. Finally, in

hepatocellular carcinoma, a cancer highly associated with hepatitis B infection, which is a prevalent disease in Hong Kong, this has been met with astounding success with the use of multiple kinase inhibitors like sorafenib and sunitinib.⁶

Therefore, the emergence of targeted therapy has markedly improved the treatment outcome of both haematological and epithelial cancers. We look forward to further improvement with the emergence of new targeted therapies, or after optimisation of their use in different phases of treatment such as the role of maintenance therapy with targeted therapy, or their role in combination with chemotherapy or even with other targeted therapies. Therefore, the march is on!

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Dermatological Quiz



Dermatological Quiz

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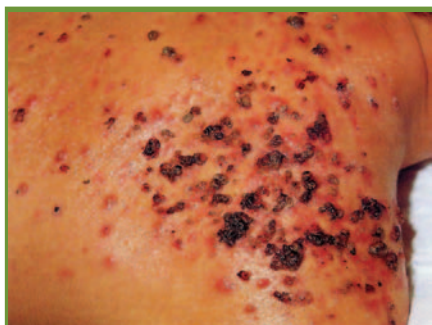


Fig 1: Multiple haemorrhagic crusted lesions over the upper back

This 20-year-old man had refractory acne which failed to respond to treatments with various oral antibiotics. He had been given oral isotretinoin at a dose of 1mg/kg/day (Body weight: 60kg). After 2 weeks' treatment, his condition deteriorated and he developed extensive painful and haemorrhagic papulo-nodular lesions over his upper trunk (Fig 1) and face. There was no systemic upset.

Questions:

1. What is your preliminary diagnosis?
2. What are the main differential diagnoses?
3. How can this condition be prevented in practice?
4. What are the important systemic side-effects of oral isotretinoin that must be monitored?

(See P. 41 for answers)

Take Life Further

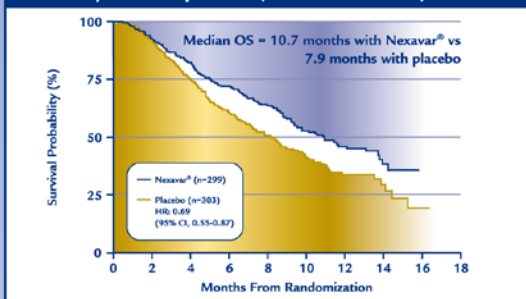


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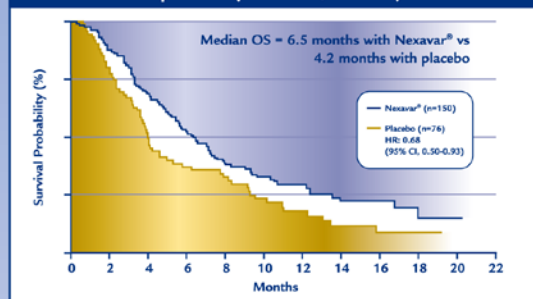
SHARP Trial

Nexavar® extended overall survival (OS) by 44% vs placebo (HR: 0.69; $P < .001$)^{1,b,c}



AP Study

Nexavar® extended OS by 47%^a vs placebo (HR: 0.68; $P = .014$)²



HR=hazard ratio; CI=confidence interval.

*Sorafenib HCC Assessment Randomized Protocol (SHARP), a randomized, double-blind, placebo-controlled, international, multicenter, phase III study of 602 patients with HCC.¹

†Asia Pacific (AP) Liver Cancer Study, a randomized, placebo-controlled, phase III study conducted in 226 patients with HCC in China, Taiwan, and South Korea.²

^aFormula: $(1.0/\text{HR} - 1) \times 100\%$.

^bPatients were ineligible or had disease progression after surgery or locoregional therapies.¹

^cStatistically significant because the prespecified O'Brien-Fleming stopping boundary of $\alpha = .0077$ was met.¹

The magnitude of the Nexavar® overall survival result in the AP Study was consistent with the result seen in the SHARP Trial, despite more advanced disease and different etiologies (eg, HBV infection) in AP Study patients^{1,2} —Based on hazard ratios, the survival benefit represented a 31% (HR: 0.69) and 32% (HR: 0.68) reduction in risk of death in the SHARP Trial and the AP Study, respectively.^{1,2}

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To Optimise Myeloma Treatment in the Era of Targeted Therapy

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This article has been selected by the Editorial Board of the Hong Kong Medical Diary for participants in the CME programme of the Medical Council of Hong Kong (MCHK) to complete the following self-assessment questions in order to be awarded one CME credit under the programme upon returning the completed answer sheet to the Federation Secretariat on or before 31 March 2011.

Multiple myeloma is a cancer with multifocal proliferation of plasma cells in the bone marrow¹. Plasma cells are important in normal immune defence because of its ability to produce immunoglobulin, which is responsible for defence against offensive micro-organisms. Patients with myeloma often present with bone pain, fractures and high blood calcium levels, resulting in impairment of kidney function, anaemia and infection.

Diagnosis of myeloma is based on the demonstration of excessive (>10%) plasma cells in the marrow, presence of monoclonal gammopathy and lytic bone lesions on X-ray. The disease is incurable, mainly due to the low complete remission (CR) rate (used to be in the region of 5%). Therefore, the main goal of treatment used to be symptomatic relief. This has been achieved with combination chemotherapy with melphalan and prednisolone. (Figure 1)



Figure 1. Myeloma is characterised by the presence of excessive plasma cells in the marrow. (Upper panel showing abnormal plasma cells infiltrating the marrow) Clinically, osteolytic bone lesions may manifest as pathological fractures (arrow in the lower panel points to a fracture beneath the head of humerus).

Pathogenesis involves immortalisation of a post-germinal centre B-lymphocyte, which homes to the bone marrow. Upon interaction with the marrow stroma, a paracrine cytokine loop involving IL-6 and IGF1 is triggered, which confers survival and proliferative advantage to the neoplastic plasma cell². At this stage, clinically the disease manifests as monoclonal gammopathy of unknown significance (MGUS), which transforms into clinically myeloma at the rate of 1% per year. At the early stage, myeloma plasma cells rely on the marrow micro-environment for its survival². However, upon acquisition of secondary genetic alterations or mutations including FGFR3 mutation, secondary translocations involving MYC, etc, the myeloma plasma cells will be able to survive in extramedullary sites and manifest as extramedullary plasmacytoma or plasma cell leukaemia. (Figure 2)

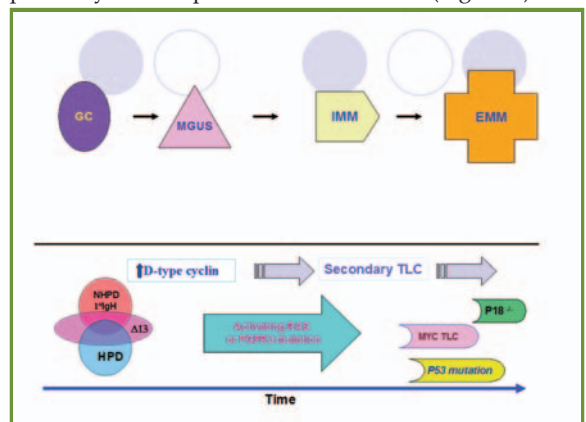


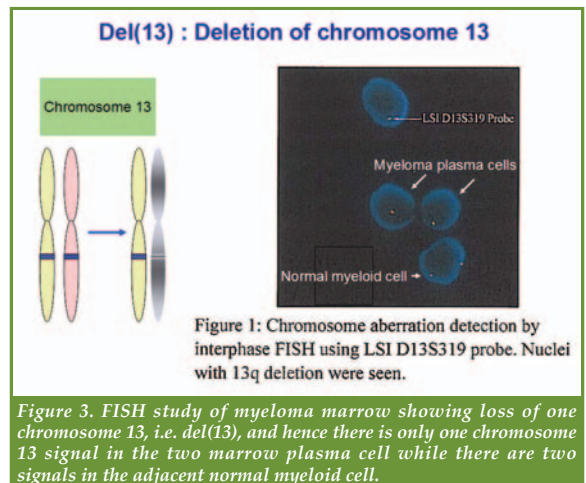
Figure 2. Myeloma pathogenesis starts with immortalisation of a post-germinal centre plasma cell (GC), which homes to the marrow and manifests clinically as monoclonal gammopathy of unknown significance (MGUS). When these plasma cells metastasise to different parts of the bone marrow, the disease manifests as intramedullary myeloma (IMM). Upon acquisition of secondary genetic mutations such as RAS or MYC mutations or secondary translocations involving MYC, the plasma cells may reside in extramedullary sites, and clinically manifest as extramedullary myeloma (EMM) including plasma cell leukaemia or extramedullary plasmacytoma.

Major advances in the recent decade include the advent of autologous bone marrow transplantation and targeted therapy, which result in a much higher complete remission (CR) rate¹. Autologous haematopoietic stem cell transplantation (auto-HSCT) is performed after

adequate initial control of myeloma by the use of chemotherapy that results in substantial eradication of tumour cells. This is followed by mobilisation and collection of stem cells from the patients, after which, the patients will undergo high-dose chemotherapy, and then infusion of stem cells collected earlier on, which is the essence of auto-HSCT). Targeted therapy (including bortezomib, thalidomide or lenalidomide) enables effective killing of myeloma tumour cells, and hence results in a high CR rate in particular those with bortezomib-containing regimens¹. Moreover, unlike chemotherapy, targeted therapy is not toxic to the marrow, and hence can be used in both young and old patients alike. Finally, initial control of myeloma can be substantially increased by the combination of targeted therapy together with chemotherapy. Therefore, targeted therapy alone may result in a CR rate of about 20+%. The use of auto-BMT results in an additional CR rate of 20+%. Therefore, the CR rate will be increased to up to 50% if myeloma patients are treated with targeted therapy initially, followed by auto-HSCT.

In Hong Kong, we have shown in an earlier study that use of targeted therapy for initial disease control, followed by auto-HSCT, results in a CR rate of 48% (compared with 5% in the past)³. Moreover, 75% of patients survive at 4 years from diagnosis, compared with 40% for myeloma patients not receiving targeted therapy or auto-BMT⁴. One important finding from this study was that this CR rate (48%) and overall survival (75% at 4 years) were comparable to large studies in the US and UK while only 52% patients required the use of the expensive targeted therapy, bortezomib. Therefore, it is a strategy potentially able to maintain a high CR rate and favourable survival with a much lower cost.

Finally, there is substantial evidence that targeted therapy may overcome the adverse impact of high-risk cytogenetic alterations including deletions of chromosome 13, i.e. del(13), or the short arm of chromosome 17, i.e. del(17p), and reciprocal translocations between chromosomes 4 and 14, t(4;14) or translocations between chromosomes 14 and 16, t(14;16). (Figure 3) Patients carrying these chromosomal alterations have a low CR rate and a poor survival because of more drug resistant cases and more frequent relapse of disease⁵. Therefore, targeted therapy will be an important component of therapy for myeloma patients carrying high-risk cytogenetic features. For instance, in a French randomised controlled trial in which newly diagnosed myeloma patients were randomised to receive the conventional combinational chemotherapy regimen, VAD (vincristine, adriamycin and dexamethasone), or targeted therapy, bortezomib and dexamethasone (velcade/dexamethasone), it was shown that bortezomib/dexamethasone treated patients had similar CR rates and survivals in patients with or without del(13) or t(4;14)/t(14;16). On the other hand, in patients randomised to receive velcade/dexamethasone only, the CR rate and survival of patients carrying these high-risk chromosomal alterations were much inferior to those without. These findings testify that the incorporation of targeted therapy had overcome the adverse impact of these high risk chromosomal alterations in myeloma, and hence is particularly important as a frontline therapy in myeloma patients with high-risk chromosomal aberrations.



In Hong Kong, as bortezomib is an expensive drug, in order to make judicious use of it and maximise its clinical benefit, one possible way is to risk-stratify the patients. Therefore, bortezomib should be used as a frontline therapy in myeloma patients carrying these high-risk chromosomal aberrations including del(13), t(4;14) or t(14;16). However, to execute this cost-effective treatment approach, there are several hurdles to further improve myeloma treatment in Hong Kong at present. First, the high-risk cytogenetic alterations can only be detected by a special technique called Fluorescent In-situ Hybridisation (FISH), which is an expensive test currently unavailable for myeloma patients in HA hospitals. Secondly, frontline use of targeted therapy, especially bortezomib, which is approved by the FDA for frontline treatment of myeloma, is not possible in the HA setting yet. Therefore, it will be important to make the FISH test available for myeloma patients. As targeted therapy has been shown to overcome the adverse prognostic impact of the high-risk cytogenetic alterations, it is important to treat these patients with frontline bortezomib-containing regimens, followed by auto-HSCT in those transplant-eligible patients. With the current financial constraints, judicious frontline use of targeted therapy with bortezomib-based regimens in high-risk myeloma patients does not only benefit the patients (as it increases the CR rate, and also reduces risk of relapse, and hence improves the quality-of-life of patients) but will also be cost-effective from the healthcare financing perspective as these "high-risk" myeloma patients are the ones who will progress/relapse quickly and require frequent hospital admissions for further disease and symptomatic control. Frontline use of bortezomib-based regimens in myeloma patients with high-risk cytogenetic features will translate into reduced hospital admissions and hence less hospital expenditure. Therefore, despite that myeloma is an incurable disease, significant advances have been made. Moreover, judicious frontline application of bortezomib-based therapy will be a cost-effective approach, and hence, the FISH test should be made freely available to all myeloma patients in the HA setting.

In addition, advances are being developed or actively sought in diagnostic techniques and imaging. To address developments in these different sectors, the Hong Kong Society of Myeloma has been established in March, 2010 to arouse public awareness of the disease,



educate oncologists about latest advances in myeloma, and improve patient care in the whole of Hong Kong. In summary, to make judicious use of expensive targeted drugs in myeloma, it is important to make FISH test available to all myeloma patients, and bortezomib-based therapy should be used upfront in those carrying high-risk chromosomal aberrations such as del(13), t(4;14) and t(14;20).

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MCHK CME Programme Self-assessment Questions

Please read the article entitled "To Optimise Myeloma Treatment in the Era of Targeted Therapy" by Dr. James CS CHIM 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 March 2011. 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. Myeloma is a neoplastic proliferation of lymphocytes like lymphoma.
2. The elevated monoclonal immunoglobulin leads to an enhanced immunity and protection against infections.
3. Myeloma is now a curable disease.
4. MGUS is a precursor of symptomatic myeloma.
5. Extramedullary myeloma usually only occurs at advanced stage of myeloma.
6. Autologous haematopoietic stem cell transplantation may increase the complete remission rate and prolong survival of myeloma patients.
7. Targeted therapy could only be applied to younger myeloma patients.
8. Karyotypic aberration detected by Fluorescent In-situ Hybridisation (FISH) is an important prognostic factor to myeloma patients.
9. Targeted therapy like bortezomib may overcome the adverse prognostic impacts of high-risk karyotypic abnormalities like del(13) or t(4;14).
10. If targeted agents like bortezomib could be used upfront, autologous haematopoietic stem cell transplantation might be omitted even in transplant-eligible patients.

ANSWER SHEET FOR MARCH 2011

Please return the completed answer sheet to the Federation Secretariat on or before 31 March 2011 for documentation. 1 CME point will be awarded for answering the MCHK CME programme (for non-specialists) self-assessment questions.

To Optimise Myeloma Treatment in the Era of Targeted Therapy

Dr. James CS CHIM

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 Department of Medicine, Queen Mary Hospital, The University of Hong Kong
 Founding Chairman, the Hong Kong Society of Myeloma

1 2 3 4 5 6 7 8 9 10

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

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Answers to February 2011 Issue

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



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Reference:

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The Myelodysplastic Syndrome (MDS)

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Dr. Herman Sung-yu LIU

Myelodysplastic Syndrome (MDS) is a group of malignant haematopoietic disorders sharing an ineffective production of one or more myeloid cell lines with a variable percentage of leukaemic blasts. There is usually a discrepancy between a cellular marrow and peripheral cytopenia with a risk of transformation to acute myeloid leukaemia (AML). It is primarily a disease affecting the elderly with a median age of 76 years old¹ at diagnosis. Clinically, it may overlap with a number of disease entities including aplastic anaemia, paroxysmal nocturnal haemoglobinuria (PNH), large granular lymphocytic (LGL) leukaemia and myeloproliferative neoplasms (MPN).

Classification

According to the 2008 revised WHO classification², a new subtype is refractory cytopenia with unilineage dysplasia (RCUD) which includes: Refractory anaemia (RA) (unilineage erythroid dysplasia), refractory neutropenia (RN) (unilineage dysgranulopoiesis), and refractory thrombocytopenia (RT) (unilineage dysmegakaryocytopoiesis). (Table 1)

Table 1: 2008 WHO Classification of MDS

Subtype	Blood	Bone Marrow
(1) Refractory cytopenia with unilineage dysplasia (RCUD): RA/RN/RT	Single or bicytopenia	Dysplasia in $\geq 10\%$ of one cell line, $< 5\%$ blasts
(2) Refractory anaemia with ring sideroblasts (RARS)	Anaemia, no blasts	$\geq 15\%$ of erythroid precursors with ring sideroblasts, erythroid dysplasia only, $< 5\%$ blasts
(3) Refractory cytopenia with multilineage dysplasia (RCMD)	Cytopenia(s), $< 1 \times 10^9/L$ monocytes	Dysplasia in $\geq 10\%$ of cells in ≥ 2 haematopoietic lineages +/- 15% ring sideroblasts, $< 5\%$ blasts
(4) Refractory anaemia with excess blasts-1 (RAEB-1)	Cytopenia(s), $\leq 2-4\%$ blasts, $< 1 \times 10^9/L$ monocytes	Unilineage or multilineage dysplasia, no Auer rods, $5-9\%$ blasts
(5) Refractory anaemia with excess blasts-2 (RAEB-2)	Cytopenia(s), $5-19\%$ blasts, $< 1 \times 10^9/L$ monocytes	Unilineage or multilineage dysplasia, +/- Auer rods, $10-19\%$ blasts
(6) Myelodysplastic Syndrome, unclassified (MDS-U)	Cytopenias	Unilineage dysplasia or no dysplasia but characteristic MDS cytogenetics, $< 5\%$ blasts
(7) MDS associated with isolated del(5q)	Anaemia, platelets normal or increased	Unilineage erythroid dysplasia, isolated del(5q), $< 5\%$ blasts

Work-up

Diagnosis of MDS was established based on morphological examination of the peripheral blood and bone marrow. Patients with significant cytopenias and karyotypes t(8;21), t(15;17) and/or inversion 16 or variants should be considered to be suffering from AML.

Special tests may be required in certain circumstances: (a) HLA tissue typing if the patient is a candidate of haemopoietic stem cell transplant (HSCT). (b) HLA-DR15 positivity is potentially predictive for determining the responsiveness to immunosuppressive therapy (IST), particularly in young patients with normal cytogenetics and hypoplastic MDS (c) Flow cytometry to evaluate the presence of PNH clone or to assess the existence of LGL leukaemia (d) Genetic screening for patients with family history of cytopenias e.g. Fanconi anaemia or dyskeratosis congenita.

Prognosis

Survival and risk of AML transformation are predicted by the International Prognostic Scoring System (IPSS)³ and the World Health Organization Prognostic Scoring System (WPSS)⁴.

The IPSS was based on the French-American-British (FAB) morphologic criteria and thus marrow blasts of 21-30% was included in the prognostic variable which was previously classified as Refractory anaemia with excess blasts in transformation (RAEB-t). Based on the three prognostic variables: marrow blasts, karyotype and cytopenia, the patient can be sub-divided into 4 risk categories according to the summation of the scores (Table 2). There is a wide range of median survival and risk of AML progression in between the 4 different risk categories (Figure 1, Table 3). Among the individual risk categories, there is also significant inferiority in the median survival if the patient's age is above 60.

Table 2: IPSS Score value (Cytopenia: Hb $< 10g/dL$; ANC $< 1800/uL$, platelet $< 100,000/uL$)

Prognostic variable	0	0.5	1.0	1.5	2.0
(1) Marrow blasts %	$< 5\%$	5-10%	--	11-20%	21-30%
(2) Karyotype	Good [normal, -Y alone, del(5q) alone, del(20q) alone]	Intermediate (Others)	Poor (complex ie. ≥ 3 abnormalities or chromosome 7 anomalies)	--	--
(3) Cytopenia	0/1	2/3	--	--	--

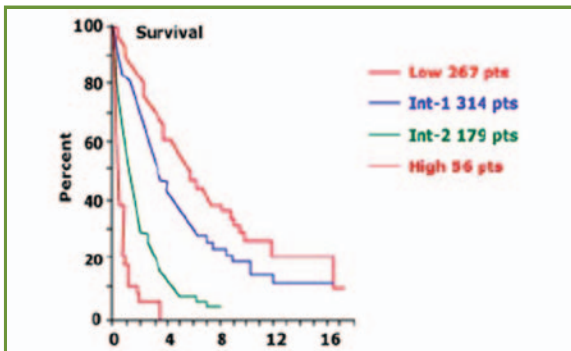


Figure 1: Median Survival (IPSS)

Table 3: Median Survival and AML Progression Risk (in years) by IPSS and Age

Age (n)	Low (score 0)	Int-1 (Score 0.5-1.0)	Int-2 (Score 1.5-2.0)	High (Score ≥ 2.5)
All ages (816)	5.7	3.5	1.2	0.4
<60 (205)	11.8	5.2	1.8	0.3
>60 (611)	4.8	2.7	1.1	0.5
25% AML progression (in years) without therapy	9.4	3.3	1.1	0.2

Recently, the WPSS incorporates the WHO-based morphologic categories, the IPSS cytogenetic categories and the patient's RBC transfusion dependence (Table 4). As opposed to 4 different risk groups in IPSS, patients can be sub-divided into 5 risk groups. Once again, the individual patient can be risk categorised with significant differences in overall survival and AML progression risks (Table 5). Yet, whether WPSS is a better prognostic tool than IPSS remains to be seen.

Table 4: WPSS score value

Parameter	0	1	2	3
WHO category	RA, RARS, 5q-	RCMD, RCMD-RS	RAEB-1	RAEB-2
Karyotype (same as IPSS)	Good	Intermediate	Poor	--
RBC transfusion requirement (≥ 1 RBC transfusion every 8 weeks over a 4 month period)	No	Regular	--	--

Table 5: Median overall survival (OS) in months and AML progression risk (WPSS)

WPSS Risk Group	WPSS Score	Median OS (months)	AML Progression (Cumulative Probability)	
			2 year	5 year
Very low	0	141	0.03	0.03
Low	1	66	0.06	0.14
Intermediate	2	48	0.21	0.33
High	3-4	26	0.38	0.54
Very high	5	9	0.80	0.84

Management

The patient's IPSS risk category, patient's age, performance status, co-morbidities are important issues in considering the different therapeutic options for an individual patient. The WPSS provides a dynamic estimation of prognosis during the monitoring of the patient.

(A) Supportive Care

Supportive care includes red cell transfusions for symptomatic anaemia or platelet transfusions for severe thrombocytopenia or symptomatic bleeding. Granulocyte colony stimulating factor (G-CSF) may be considered for recurrent episodes of neutropenic fever. For patients with chronic red cell transfusion, serum ferritin levels and corresponding organ dysfunction should be monitored, especially in the low or intermediate-1 risk group who has a much longer survival and lesser risk of AML transformation. In general, iron chelation therapy should be considered in low or intermediate-1 patients who have received or anticipated to receive more than 20 units of red cell transfusion with a serum ferritin level of more than 1000ng/ml.

(B) Drugs

Currently, 3 drugs: Azacitidine, Decitabine and Lenalidomide were approved by the U.S. Food and Drug Administration (FDA) specifically for MDS-related indications (Table 6).

Table 6: Drugs approved by FDA for treatment of MDS

	Azacitidine	Lenalidomide	Decitabine
Indication	All MDS subtypes (FAB classification): IPSS Int-1 or above	Low risk MDS(IPSS low or intermediate-1) with del(5q) and transfusion dependence	All MDS subtypes (FAB classification), IPSS: Int-1 or above
Route	Subcutaneous/ Intravenous	Oral	Intravenous
Dosing	75mg/m ² /day for 7 days every 28 days	10mg/day for 21 to 28 days every 28 days	20mg/m ² daily infusion over 5 days every 28 days
Mode of action	DNA hypomethylation	Immune modulation Angiogenesis inhibition	DNA hypomethylation

(I) Erythropoiesis Stimulating Agent (ESA)

For lower risk MDS patients, when the patient develops transfusion dependence, ESA should be considered. However, not all patients benefit from ESA. In the study by Hellstrom-Lindberg⁵, predictors of response included (i) <2 units red cell transfusion monthly and (ii) low baseline serum EPO level: < 500IU). There was a 74% chance of response compared with only 7% if the patient had high transfusion requirement and high baseline EPO level.

(II) Immunosuppressive Therapy (IST)

Again for lower risk MDS patients, IST in the form of cyclosporine A or Antithymocyte globulin (ATG) should be considered if there is a good probability of response: IPSS low/int-1, WPSS very low, low or intermediate, age less than 60, hypocellular marrow, HLA-DR15 or PNH clone positivity. However, if the patient lacks the above predictors to ESA and IST, hypomethylating agents should be considered early in the treatment plan.

(III) Hypomethylating Agents

(i) Epigenetics

Epigenetics is genetic information that is not conveyed through DNA sequence. There are 2 important epigenetic processes: DNA methylation and histone modifications. The former involves addition of methyl group to cytosine in DNA, resulting in reduced gene expression or gene silencing. DNA methylation typically occurs in a CpG dinucleotide context. Unmethylated



CpGs are grouped in clusters called CpG islands that are present in the promoter regions of many genes. Both azacitidine and decitabine exert their effects by binding to and inactivating the DNA methyltransferase 1 (DNMT1), leading to hypomethylation of DNA.

(ii) Azacitidine

The efficacy of Azacitidine (75mg/m²/day) subcutaneously for 7 days every 28 days in MDS has been shown in the pivotal phase III crossover study (9221)⁶ conducted by the Cancer and Leukaemia Group B (CALGB). There were 99 and 92 patients randomised to the azacitidine group and supportive care group respectively. All MDS subtypes were included. A significantly greater number of patients achieved an overall response (complete response + partial response + haematological improvement or clinical benefit) in the azacitidine arm compared to the group receiving only supportive care (60% Vs 5% respectively, p <0.001). Differences were also seen in patients who crossed over to azacitidine, with 47% of patients responding. A number of different quality of life (QoL) parameters, fatigue and dyspnoea also showed improvement in the azacitidine treated group (Figure 2). Time to AML progression or death was longer in the azacitidine group (21 vs 12 months in supportive group, p=0.007). However, no significant overall survival advantage for azacitidine was demonstrated, probably due to the crossover effect for the supportive care group and the mixed MDS population.

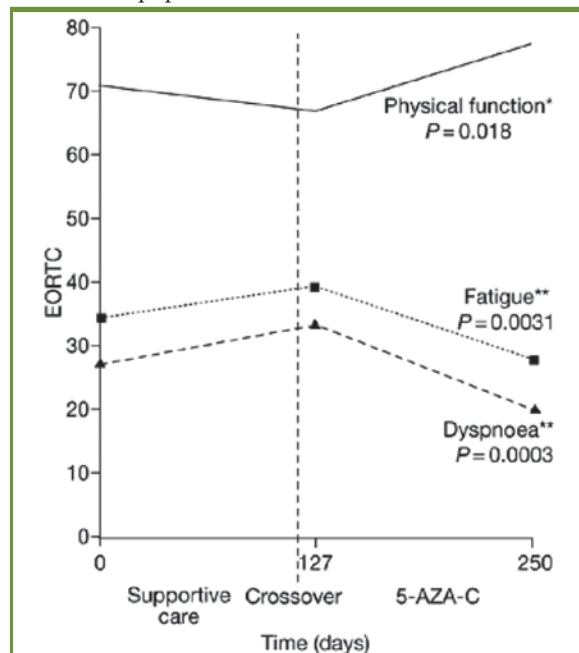


Figure 2: EORTC fatigue, dyspnoea and physical functioning of crossover patients on supportive care for 4 months prior to crossover (n=30)

The median number of cycles from first treatment with azacitidine to any response was 3 cycles (range: 1 to 17 cycles). For the responders, 75% responders achieved a response by cycle 4, 90% by cycle 6, the rest up to cycle 17. Thus, patients should receive at least 6 cycles of therapy before the azacitidine was withdrawn and considered to be non-beneficial.

In the AZA-001 Phase III study⁷, higher-risk MDS patients, FAB-defined as RAEB, RAEB-T, or CMML 10-29% marrow blasts) with an IPSS of Int-2 or High were enrolled. Before randomisation, investigators pre-selected patients to 1 of the 3 Conventional Care Regimens (CCR): BSC only (transfusions, antibiotics, and G-CSF for neutropenic infections); low-dose ara-C (LDAC, 20mg/m²/day x 14 days, every 28 days); or standard chemotherapy (conventional induction/consolidation). Patients were stratified by FAB/IPSS and randomised to Azacitidine (75mg/m²/day for 7 days every 28 days) or CCR. The trial did not allow erythropoietin. Three hundred and fifty eight patients were randomised to Azacitidine (N=179) or CCR (N=179): BSC only (N=105, 58%), LDAC (N=42, 27%), or standard chemotherapy (N=25, 14%). Median age was 69 years (range: 38-88). Azacitidine was administered for a median of 9 cycles, LDAC for 4 cycles. Azacitidine showed a median Kaplan-Meier overall survival time of 24.4 months against 15.0 months with CCR (Figure 3). At 2 years, there was a 2-fold overall survival advantage: Azacitidine (51%) against CCR (26%). Median overall survival per IPSS cytogenetic subgroup showed similar results (Table 7).

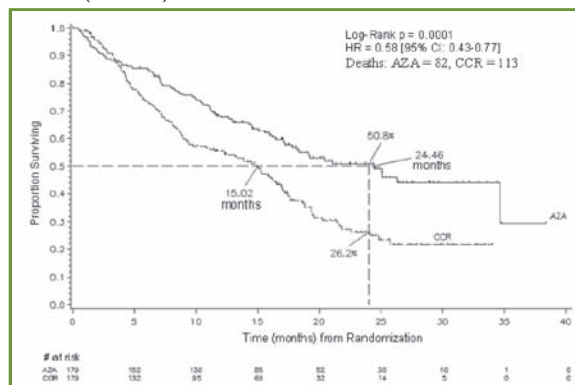


Figure 3: Overall survival (Azacitidine Vs CCR) of AZA-001 study

Table 7: OS analysis per IPSS Cytogenetic Group

Group	% (n/N patients)	Azacitidine Median (months)	CCR Median (months)	HR (95% CI)	Log-rank p
Good	46 (166/358)	Not reached	17.1	0.61 (0.39, 0.96)	0.030
Intermediate	21 (76/358)	26.3	17.0	0.43 (0.21, 0.88)	0.017
Poor	28 (100/358)	17.2	6.0	0.52 (0.32, 0.87)	0.011

When analysed by International Working Group (IWG) best response, all response categories including stable disease (SD) showed an OS benefit with AZA treatment: CR (96.7%), PR (85.5%), HI (96%), or SD (73.3%), while only 28.6% of AZA patients with disease progression (DP) were alive at 1 year.⁸ This data showed that achievement of CR is not an obligate state for extended survival in higher-risk MDS.

(iii) Decitabine

Decitabine was developed in 1964 and was once explored in the management of AML. Being a hypomethylating agent, its activity is similar to that of azacitidine

In a multicentre phase III trial in advanced MDS, patients were randomised to receive supportive care plus decitabine (n=89) or supportive care alone (n=81)⁹, the overall response rate was 17% in the decitabine group compared to 0% in the supportive care group (p<0.001). Decitabine was delivered at a dose of 15mg/m² every 8 hours over 3 days (a total of 9 doses), with a cycle repeated every 6 weeks. Using the IWG criteria, complete response and partial response rates were 9% and 8% respectively in the decitabine group. An additional 13% of those receiving decitabine had haematological improvement, making the overall improvement rates of 30% in the decitabine group versus 7% in the supportive care group (p<0.001).

A more user friendly and less myelotoxic dosing schedule: Decitabine 20mg/m² daily infusion over 5 days every 28-day cycle has been explored in higher risk patients with a median of > 5 cycles. Ninety-nine patients¹⁰ (IPSS score of 0.5 or above) were enrolled; the ORR was 32%, and the overall improvement rate was 51%, which included 18% haematological improvement. Similar response rates were observed in all FAB subtypes and IPSS risk categories. Among patients who improved, 82% demonstrated responses by the end of cycle 2. Among 33 patients assessable for a cytogenetic response, 17 (52%) experienced cytogenetic CR (n = 11) or partial response (n = 6).

(iv) Lenalidomide

Lenalidomide is a 4-amino-glutarimide analog of thalidomide. In the MDS-003 phase II study¹⁰, it is given at a dose of 10mg/day for a 28 days cycle or 10mg/day for 21 days of a 28 days cycle to the lower-risk transfusion dependent MDS with the del(5q) abnormality. Among the 148 patients enrolled, 67% achieved transfusion independence, including every patient who experienced a cytogenetic response. The median haemoglobin increase from baseline was 5.2g/dL. The cytogenetic CR rate was 45% (including some patients with complex karyotypes) and the median response duration was more than 2 years.

(C) Allogeneic Stem Cell Transplantation

Although majority of patients belong to the elderly group with co-morbidities, a minority of younger patients should be considered to be candidate of stem cell transplantation for potential cure. Important determinants include age, performance status and availability of donor. The role of induction chemotherapy and hypomethylating agent before transplantation has not been well established.

In conclusion, MDS is a very heterogeneous disease and the management should be individualised according to the risk category (Table 8)

- (i) Lower-risk MDS (RA, RARS, RCUD, RCMD, MDS-U, MDS del(5q), IPSS low, Int-1): The aim is to sustain residual haematopoiesis with minimising transfusions and improving QoL
- (ii) Higher-risk MDS (RAEB-1, RAEB-2, IPSS Int-2, high): The aim is to achieve response, delaying AML transformation, prolonging survival and improving QoL.

Meanwhile, supportive care should be provided to all MDS patients.

Table 8: Management of MDS based on risk-category

	IPSS: Low/Int-1 RA, RARS, RCUD, RCMD, MDS-U, MDS del(5q)	IPSS: Int-2/High RAEB-1, RAEB-2
Treatment Goal	Haematopoiesis	Survival
Clinical Endpoint	Haematological improvement Quality of life	Alter natural history Delay AML transformation
Management Considerations	Erythropoiesis stimulating agent Immunosuppressive therapy Hypomethylating agent	Hypomethylating agent Allogeneic SCT Chemotherapy
Supportive	Iron chelation	

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Aplastic Anaemia

Dr. Harold Kwok-kuen LEE

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Associate Consultant, Department of Medicine & Geriatrics, Princess Margaret Hospital



Dr. Harold Kwok-kuen LEE

Introduction

Acquired aplastic anaemia (AA) is an unusual form of marrow failure with pancytopenia and a hypocellular bone marrow with no increase in reticulin. By definition, other causes of marrow failure must be excluded, especially malignant diseases of the haematopoietic system and cancer of other organs metastatic to the marrow. The most important differential diagnoses are between aplastic anaemia and hypocellular myelodysplasia. The widely accepted Camitta criteria defined for Severe Aplastic Anaemia (SAA) are: absolute neutrophil count (ANC) below $1.0 \times 10^9/l$, platelet count (PLT) below $20 \times 10^9/l$, reticulocyte count (Retic) below 0.1 percent, and less than 20 percent cellularity on trephine bone marrow biopsy.¹ Such patients have little chance of spontaneous recovery and a very high mortality. Symptoms of anaemia: fatigue, palpitation, dyspnoea or mucocutaneous haemorrhage: ecchymoses, gingival bleeding, epistaxis lead to the initial medical consultation.

Epidemiology and Aetiology

The annual incidence of aplastic anaemia in Europe was established in a large international study at 2 to 4 per million.² The incidence in Thailand is 4 per million and closer to 6 in some rural regions of the country.³ The median age of onset is 20 - 25 years. Men and women are equally affected. The Thailand study also showed that low socio-economic status was associated with an increased risk of AA. The study pointed out that the low socio-economic status could well be the surrogate marker for other environmental factors. An industry-based national survey in Japan found the annual incidence of 14 per million of the population.⁴ The average incidence rate of 2.1 per million per year was the only local data published in 1998.⁵

Aplastic anaemia is a disorder with a manifestation of a variety of insults which result in bone marrow failure. In about one-third of the patients with acquired AA, suspicion may be directed to a particular agent, usually a drug or virus. Table 1 indicates the drugs where the association with AA is strong.¹ An association with viral infections, particularly hepatitis, has also been suggested, but how remains very vague.⁶ Thus, in at least two-thirds of patients, no aetiological agent can be identified. Japanese workers have found an association between a particular DR2 haplotype and response to cyclosporin therapy. It may be that there are subtle genetic associations with the disease and indeed it

would be expected that a certain genetic make-up would render an individual susceptible to the varying environmental stress.⁷ What these environmental stresses are remains unknown.

Pathophysiology

Marrow failure in aplastic anaemia could be the consequence of damage either to haematopoietic cells or to the cells from the microenvironment. However, most of the evidence points strongly to effects on haematopoietic cells, stromal cell function and growth factor production are normal in almost all patients with AA. The important pathophysiologic inferences have been derived from clinical observation: the success of stem cell transfer focused attention on a haematopoietic deficit; recovery after antithymocyte globulin (ATG) and cyclosporin implied an immune mechanism of marrow destruction. Cytotoxic T lymphocytes is likely one of the mediated component in causing marrow failure.⁸ However, so far an increase in these cell types or their direct implication in marrow suppression has not been demonstrated. It is possible that cytokines such as interferon gamma may be released inappropriately in AA and suppresses bone marrow function. The large numbers of clinical associations with AA suggest that a variety of events can activate the immune system to cause marrow destruction and haematopoietic failure. Mutations in genes of the telomere repair complex have been reported in some adults with acquired AA. Some observations suggest that AA thus is a model of genetic factors interacting with environment, resulting in organ failure and malignant transformation.⁸

Treatment for Severe Aplastic Anaemia

Prompt diagnosis is important; both to treat the serious consequences of pancytopenia and to initiate treatment to correct the underlying bone marrow failure. Patients with moderate cytopenia, not requiring transfusions can be offered supportive care or outpatient treatment with anabolic steroids and/or low dose steroids or cyclosporin. Patients with cytopenia requiring transfusions should be treated with either immunosuppressive therapy or haematopoietic stem cell transplant.⁹ Age and severity of cytopenia affect the choice of treatment.

(1) Supportive Care

The major cause of death in AA patients is infection. The major risk factor for developing infection is the

degree and duration of the neutropenia. When the patient is refractory to conventional therapy or cannot undergo Haematopoietic Stem Cell Transplant (HSCT), infection is inevitable. Recovery from neutropenia is directly related to survival, and supportive care has a vital role in a state of neutropenia. Bacterial infections in neutropenic patients can be rapidly fatal. Invasive aspergillosis is the most common and serious fungal infection with a mortality rate of 80-90%.¹⁰ Suspicion of infection should lead to immediate institution of broad spectrum parenteral antibiotics. If fever persists, antifungal agents should also be added.

Bleeding from thrombocytopenia is also life threatening. Some patients can tolerate low platelet counts with very few serious symptoms. There is no evidence that a prophylactic programme of regular transfusions is superior to transfusion for symptoms. Haemoglobin concentration should be maintained to allow full activity. Transfusion policy must be carefully considered in order to avoid sensitisation to transplantation antigens and transmission of viral diseases. A multidisciplinary approach should be taken when caring for this specific group of patients. Further epidemiological research will help to elucidate the current patterns and characteristics of infections in AA patients.¹¹

(2) Androgens and Corticosteroids

Historically androgens, or anabolic steroids, were the first specific form of therapy used in aplastic anaemia. They have a temporary benefit in the initial management. Androgen response and even dependence are observed but have not improved survival in any controlled trial.¹² In some cases, they can accelerate bone marrow recovery after treatment with Antilymphocyte Globulin (ALG).¹³ Androgens have recently been shown to increase telomerase activity in human CD34+ cells, which may explain their effects in some patients.⁹

Corticosteroids in conventional doses may ameliorate the serum sickness of ALG therapy, but have little activity alone in the disease. The use of low dose corticosteroids to enhance vascular stability has little basis in either laboratory experiments or clinical experience. Again, the side effects of long term usage is the major concern.

(3) Haematopoietic Growth Factors

The use of haematopoietic growth factors (HGFs) to support blood counts is of limited value in SAA as predicted by *in vitro* studies and measurement of endogenous serum levels of HGFs, which are markedly elevated. HGFs administered alone play no role in the treatment of SAA.¹⁴ Granulocyte colony-stimulating factor (G-CSF), Granulocyte-macrophage colony-stimulating factor (GM-CSF) and Interleukin-3 can lead to an increased number of granulocytes in patients who still have sufficient committed precursor cells. In patients with total aplasia, there is usually no improvement. The prognosis and survival of SAA are not influenced by such therapy. However, G-CSF has been described in conjunction with ATG and Cyclosporin (CsA) as a first-line treatment.¹⁵ In this study, the response to G-CSF appeared to have prognostic values.

(4) Bone Marrow Transplantation

For young patients, if an HLA-identical sibling donor is

available, their prognosis is improved by an allogeneic bone marrow transplantation (BMT), with a long term survival rate of 60 - 90 percent.^{8, 16} The major drawback is less than 25% of the patients have donors available and the age limitation policy in most centres. However, the survival of unrelated donor transplants has almost doubled in the past decade for improved donor/recipient matching. The preparative regimen consists of high dose cyclophosphamide combined with ALG or ATG. Better survival and low morbidity in young patients make allogeneic BMT the treatment of choice for children and adolescents. The age effect has remained significant with survivals of about 50% for patients over the age of 40. The major cause of excess mortality is chronic graft-versus-host disease (GVHD).¹⁷ The European Group for Blood and Marrow Transplantation (EBMT) is exploring the use of lower dose of cyclophosphamide in combination with low dose fludarabine and ATG in patients older than 30 years of age. The initial results are encouraging for lowering the transplantation-related toxicity.¹⁸

(5) Immunosuppressive Therapy

Immunosuppressive therapy (IST) has proven to yield superior survivals when compared with supportive care.⁸ The combinations of ATG, or CsA and steroids improve the overall response rate.^{13, 19} Up to 67 percent of the SAA patients receiving combination immunosuppressive treatment may respond within 3 months.¹⁵ Responses can be subdivided into complete (CR) and partial (PR): the former with nearly normal blood counts.¹⁵ Partial responses requires at least transfusion independence. The immunosuppressant is with immunoglobulin preparations purified from the plasma of animals immunised with children's thymocytes in the case of ATG and thoracic duct lymphocytes for ALG. Although relatively non-specific in their reactivity for human cells, ATG and ALG lyse human lymphocytes.²⁰ Both horse ATG and rabbit ATG have been used successfully in patients with acquired AA.⁸ CsA is a more specific immunosuppressive agent which blocks T-cell proliferation and lymphocyte function. When combined with ATG or ALG, CsA intensifies immunosuppression and increases the haematological response rate to about 70%.²¹

The standard first-line immunosuppressive therapy is currently horse ATG plus CsA and second-line treatment is rabbit ATG plus CsA, although the latter has been successfully used as a first-line therapy.²²

Conclusions

SAA can be treated effectively with either immunosuppressive therapy (IST) or Haematopoietic stem cell transplant (HSCT). IST can be readily administered but is not curative. It is recommended for older patients or younger patients who do not have an HLA-identical sibling donor. HSCT produces long-lasting haematologic recovery but requires a suitable donor, large financial resources, and may cause long-lasting GVHD. Age remains a major predictor in deciding treatment strategy. The final important message is early diagnosis and prompt treatment that will improve the outcome.



Table 1: Drugs associated with idiosyncratic acquired aplastic anaemia¹

Class	Example
Antibiotics	Chloramphenicol Sulphonamides Cotrimoxazole Nitrofurantoin
Anti-malarials	Quinacrine (atabrine) Chloroquine
Anti-helminthics	Mebendazole
Anti-inflammatory	Phenylbutazone Indomethacin Sulindac Diclofenac Ibuprofen Piroxicam
Anti-rheumatics	Gold salts D-penicillamine
Anti-thyroids	Potassium perchlorate Carbimazole Methimazole Methylthiouracil Propylthiouracil
Psychotropic/antidepressants	Phenothiazines Mianserin Remoxipride Dothiepin
Anti-convulsants	Carbamazepine Phenytoin Mesantoin Ethosuximide
Anti-diabetics	Tolbutamide Carbutamide Chlorpropamide
Carbonic anhydrase inhibitors	Acetazolamide Methazolamide
Miscellaneous	Allopurinol

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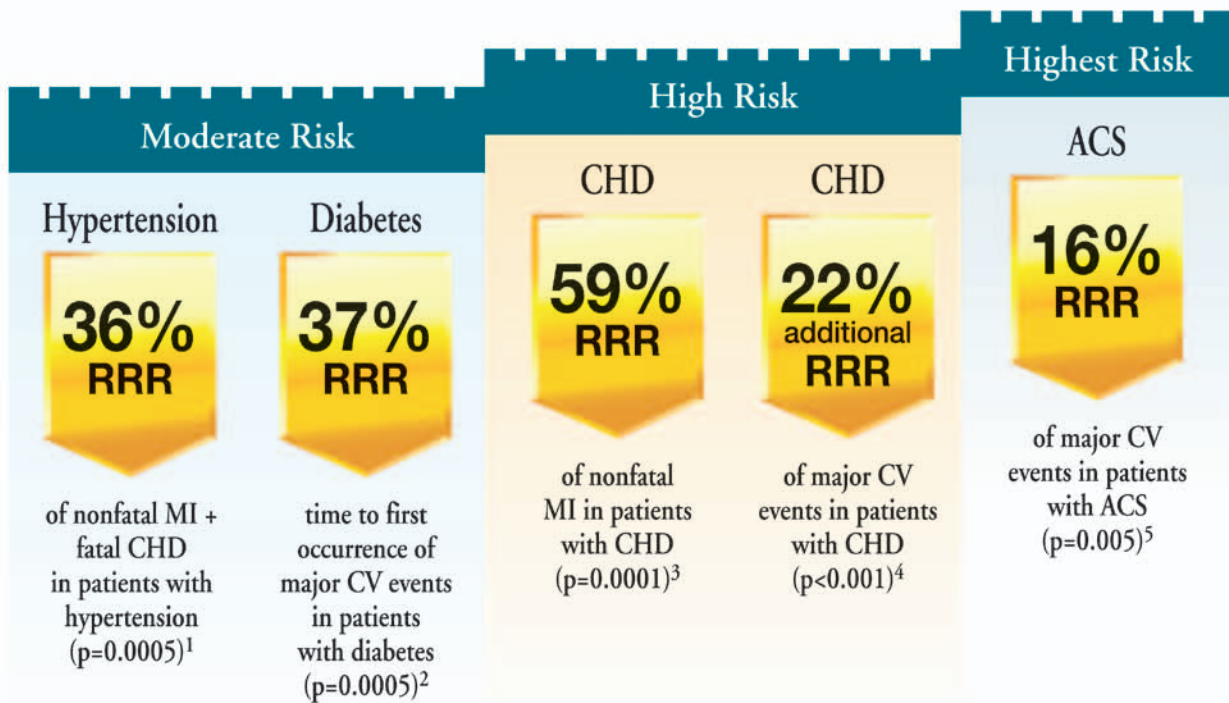




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Targeted Therapy for Non-small Cell Lung Cancer

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Introduction

Lung cancer, predominantly non-small cell carcinoma (NSCLC), has remained the top cancer killer in Hong Kong, with more than 4,000 new cases every year and the 5-year survival around 15% only. The poor prognosis is mainly due to rather late presentation with metastatic diseases in the majority and the propensity of occult distant metastases even for early resectable stages. Systemic platinum-based chemotherapy has been the cornerstone treatment for advanced diseases over the past two decades. Because of the non-specific killing of rapidly proliferating cells, systemic chemotherapy is notoriously associated with a wide spectrum of adverse effects, often limiting the use in elderly subjects with multiple co-morbidities and poor performance status. At the turn of the century, with better understanding of lung cancer biology, the concept of targeted therapy has emerged from bench to bedside, with more specific killing of cancer cells. The most promising targeted approaches include anti-angiogenesis, anti-epidermal growth factor receptor (EGFR), and more recently the inhibition of anaplastic lymphoma kinase (ALK). This review serves to highlight the important advances in targeted therapy for NSCLC.

Anti-angiogenesis

In general, malignant tumours cannot grow beyond 2mm in size without developing a vascular supply.¹ The process of neovascularisation also provides a channel for tumour cells to migrate to the systemic circulation and subsequent development of distant metastases. In fact, tumours remain dormant and unable to metastasise in the absence of a functional vascular supply.^{2,3} Angiogenesis, whether physiological or pathological, is controlled by the balance between proangiogenic and antiangiogenic factors.⁴ The most important proangiogenic factor involved in tumour angiogenesis is the vascular endothelial growth factor (VEGF), which has become the target for antiangiogenic therapy in NSCLC.⁵ The VEGF pathway can be inhibited by agents that target VEGF or VEGF receptors. In particular, bevacizumab is an anti-VEGF recombinant humanised monoclonal antibody, which contains the human immunoglobulin G1 framework (93%) and murine VEGF-binding complementarity-determining regions (7%) blocking the binding of VEGF to its receptors and subsequent downstream biologic activities. A randomised phase II study of bevacizumab in combination with carboplatin and paclitaxel or same chemotherapy alone as first-line treatment in patients

with stage IIIB or IV NSCLC has demonstrated superior response rate, time to progression and survival in the bevacizumab combination arm, with increased risk of life-threatening haemoptysis in squamous cell carcinoma.⁶

In view of these promising results, a recent randomised phase III study (E4599) was conducted comparing the combination of bevacizumab with chemotherapy (carboplatin and paclitaxel) versus chemotherapy alone in the treatment of advanced chemo-naïve non-squamous NSCLC.⁷ There was a statistically significant survival advantage that favoured the bevacizumab combination arm (median survival 12.3 months vs 10.3 months in bevacizumab vs chemotherapy alone arms, hazard ratio for death 0.79, p=0.003). The major reported toxicities in bevacizumab versus chemotherapy alone arms were grade 3/4 neutropenia (25.5% vs 16.8%), grade 3/4 hypertension (7% vs 0.7%), grade 3/4 proteinuria (3.1% vs 0%) and grade 3/4 haemorrhage (4.4% vs 0.7%). Out of the 17 treatment-related deaths, 15 were in bevacizumab arm and 2 in chemotherapy alone arm, in which the 5 deaths related to haemoptysis were exclusively from the bevacizumab arm. This is the first landmark study to demonstrate superiority in combination of targeted therapy and chemotherapy compared to chemotherapy alone (standard-of-care) in the first-line treatment of patients with advanced NSCLC. In addition, another similar study has been conducted with the combination of bevacizumab and gemcitabine and cisplatin in advanced NSCLC (AVAiL study), with favourable progression-free survival in the bevacizumab arm compared to chemotherapy alone arm.⁸

Anti-epidermal Growth Factor Receptor (EGFR)

With advancement in molecular research, it becomes logical to target specific and crucial pathways involved in carcinogenesis to achieve better control of tumour growth while minimising the detrimental effects on normal body tissues. This concept of molecularly targeted therapy has been best exemplified by the inhibition of EGFR pathway in the treatment of NSCLC. The EGFR forms part of the signalling pathway that regulates tumour cell proliferation, invasion, angiogenesis, metastasis, and apoptosis. Since overexpression of EGFR is commonly found in NSCLC, various novel agents that inhibit EGFR pathway have been developed for treatment of this neoplasm. Apart from the use of monoclonal antibody that targets the EGFR extracellular binding site, small molecules that



target the intracellular adenosine triphosphate (ATP) binding site of EGFR tyrosine kinase have been studied extensively.

Gefitinib (or Iressa) was the first EGFR tyrosine kinase inhibitor (TKI) used in the treatment of advanced NSCLC. Previous large-scale phase III trials (INTACT 1 and 2) failed to show clinical benefit by combining gefitinib with platinum-based chemotherapy in first-line treatment of advanced NSCLC.^{9,10} It was based on two large phase II trials (IDEAL 1 and 2) of gefitinib monotherapy in previously treated patients with advanced NSCLC that it was approved as second-line treatment.^{11,12} From these trials, the objective response rate was up to 18% with encouraging median survival of 7-8 months, without the inclusion of a placebo arm. The most common toxicities were skin rash and diarrhoea, with rare occurrence of interstitial pneumonitis. Later a randomised, placebo-controlled, phase III study (ISEL) was reported on gefitinib versus placebo in treatment of advanced NSCLC who were refractory or intolerant to chemotherapy.¹³ It was shown that gefitinib (250mg daily) was not associated with significant improvement in survival compared to placebo (median survival 5.6 vs 5.1 months in gefitinib vs placebo), despite some benefits among never smokers and patients of Asian descent. The commonest toxicities were skin rash (37%) and diarrhoea (27%). On the other hand, a subsequent phase III study of gefitinib versus docetaxel as second-line treatment for advanced NSCLC (INTEREST trial) suggested similar clinical efficacy between gefitinib and docetaxel.

Erlotinib (or Tarceva) is a later developed EGFR TKI that has also been extensively studied in treatment of NSCLC. Similar to gefitinib, large-scale phase III trials (TALENT and TRIBUTE) showed no clinical benefit in adding erlotinib to standard platinum-based chemotherapy as first-line treatment of advanced NSCLC.¹⁴ A randomised, placebo-controlled, phase III trial of erlotinib versus placebo in treatment of advanced NSCLC after failure to previous chemotherapy was reported.¹⁵ The erlotinib treatment arm was found to be superior in response rate (8.9% vs 1%), progression-free survival (2.2 vs 1.8 months) and overall survival (6.7 vs 4.7 months) compared to placebo arm. The more frequent adverse effects associated with erlotinib treatment were skin rash (76% vs 17%), anorexia (69% vs 56%), stomatitis (19% vs 3%), diarrhoea (55% vs 19%), ocular toxic effect (28% vs 9%) and infection (34% vs 21%) compared to placebo.

From earlier studies of gefitinib and erlotinib in treatment of advanced NSCLC, several clinical and molecular predicting factors for response to treatment were identified.¹⁶ Specific mutations in the EGFR tyrosine kinase domain (exons 18-21) have been shown to be associated with treatment response, while other mutations might predict drug resistance. Interestingly, activating EGFR mutations that predict sensitivity to EGFR TKI are more prevalent among females, Asians, never smokers, and adenocarcinoma, in which these predictive clinico-epidemiological factors have previously served as the selection criteria for treatment. Undoubtedly, the more exciting development derives from the recent reports of several first-line clinical trials of EGFR TKI in NSCLC carrying activating EGFR

mutations.^{17,18} The first of such landmark phase III clinical trial (IPASS study) was conducted to investigate the clinical efficacy of first-line gefitinib compared with standard chemotherapy (paclitaxel and carboplatin) in an epidemiologically enriched population of advanced NSCLC (adenocarcinoma, never-smokers or former light smokers, Asians).¹⁷ It was found that only around 60% of tumours carried EGFR mutations, despite selection based on favourable clinico-epidemiological factors predicting response to EGFR TKI. Among the subgroup of tumours with activating EGFR mutations, gefitinib demonstrated superior objective response rate (71.2% vs 47.3%) and progression-free survival (hazard ratio 0.48, 95% CI 0.36-0.64) compared with standard chemotherapy. On the contrary, among tumours without EGFR mutations, gefitinib fared worse in terms of objective response rate (1.1% vs 23.5%) and progression-free survival (hazard ratio 2.85, 95% CI 2.05-3.98) compared with standard chemotherapy. The findings were subsequently confirmed with a Japanese study comparing first-line gefitinib versus paclitaxel/carboplatin in advanced adenocarcinomas of lung carrying EGFR mutations.¹⁸ Recently, the preliminary findings of a first-line study comparing erlotinib with standard chemotherapy (gemcitabine and carboplatin) in NSCLC with EGFR mutations (OPTIMA study) were also reported with very promising improvement in progression-free survival in the erlotinib arm. Based on these recent confirmatory data, the need for sufficient tumour tissues at diagnosis for EGFR mutation testing has been widely recognised and the first-line treatment with EGFR TKI in advanced NSCLC carrying activating EGFR mutations is now the standard-of-care.

Emerging Approaches of Targeted Therapy

Very similar to the evolution of EGFR targeting approach, it has been recently found that a novel oncogene (anaplastic lymphoma kinase (ALK) rearrangements, commonly EML4-ALK fusion) could account for lung carcinogenesis in around 5%.¹⁹ Interestingly, the occurrence of ALK rearrangements is particularly more prevalent among those with high chances of EGFR mutations (i.e. never-smokers, adenocarcinoma) and yet confirmed to be EGFR wild-type (i.e. lack of mutations). A recent phase I study has provided very promising evidence that a specific ALK inhibitor (Crizotinib) could result in significant tumour response among those NSCLC carrying the ALK rearrangements.²⁰ Ongoing phase II and III clinical trials on Crizotinib are underway to establish its role in management of this subgroup of NSCLC.

As the majority of advanced NSCLC would progress shortly after completion of first-line systemic chemotherapy, the role of EGFR TKI as a maintenance treatment has recently been investigated and shown to offer survival benefits than the conventional approach (i.e. observation after completion of first-line chemotherapy).²¹ Since EGFR TKI is mostly well-tolerated even for years, this approach of maintenance treatment is considered a feasible treatment option after standard first-line systemic chemotherapy.



Conclusions

The era of targeted approach in the management of advanced NSCLC has certainly begun over the past few years and the field is expected to be evolving rapidly in the near future. Lung cancer is no longer considered a homogeneous disease. Despite the traditional classification based on histology, there is increasing clinical demand of tumour molecular profiling to allow logical choice of specific targeted treatment. Second-generation targeted agents and multi-targeted agents are currently tested in clinical trials, which will help to expand the existing armamentaria in the battle against lung cancers.

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Personalised Management for Breast Cancer – “One-Size-Fits-All” Approach is Over, But What Next?

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Dr. Janice WH TSANG

Introduction

With research and development, there have been increasing advances in the field of oncology, leading to better outcome of all cancer patients. Recommendation of systemic adjuvant therapy and choice of optimal agents for early-stage breast cancers remain a challenge.

Breast cancer has been the most common female cancer worldwide and is still the most common female cancer in Hong Kong with 1 in 21 cumulative life-time risk^{1,2}. It is indeed a major public health concern. The incidence of breast cancer is increasing.

Thanks to our scientists and dedicated oncologists who have made great successes in translational research, as breast cancer patients of all types and all stages are now living longer with much better quality of life, especially those with metastatic disease. While breast cancer patients are managed in a personalised manner in the context of the new evolving breast cancer molecular classification, the rapid development of all new cancer treatments has put a new challenge everyday for the physicians who are caring for cancer patients in terms of the high expectation of the patients and the general public and the relatively high costs of the new targeted therapy and prognostic tests. This requires the most optimal communication skills to discuss openly about different treatment options available with the patients. This article aims at giving an update of personalised management of breast cancer with particular references to adjuvant therapy and the challenges ahead with this new approach of practice.

Overview of Major Breakthroughs – Higher Hopes?

From Conventional Adjuvant Regimen to Newer Generations

Adjuvant therapy after definitive surgical resection of the breast tumour has been shown to increase the overall outcome of high-risk breast cancer patients, in terms of prevention of local recurrence and distant metastasis¹. For example, adjuvant radiotherapy is given according to the tumour risk to help prevent local recurrence while the benefits of adjuvant chemotherapy has become the standard of care for selected high-risk patients since the data published more than 30 years ago by Bonadonna³. Since then, there have been many more international clinical trials showing further benefits with different chemotherapy regimens, such as

the anthracycline-based chemotherapy was associated with further risk reduction when compared with the conventional cyclophosphamide, methotrexate and fluorouracil (CMF) regimen¹; followed by the added value of taxanes (T: paclitaxel, docetaxel) being included in many newer third generation regimens (ACx4 followed by Tx4) in the 1990s⁴. The BCIRG 001 trial further showed 6 cycles of taxotere, anthracycline and cyclophosphamide (TAC) was superior to 6 cycles of fluorouracil, anthracycline and cyclophosphamide (FAC), but the TAC regimen was indeed associated with more significant myelosuppression including grade 4 neutropenia and even febrile neutropenia⁵. The recent US Oncology Research Network trial has suggested superiority of replacing anthracycline (doxorubicin) with taxanes (taxotere) (i.e. TC replacing AC)⁶. Up till now, there is indeed no recipe for adjuvant chemotherapy as individual assessment of all prognostic and predictive factors are all taken into account while open discussion with patients and the carers is of paramount importance before any final treatment decision could be made.

From Risk Assessment to Target Determinant

In the past, the final histopathology report of the definitive surgery for breast cancer has been crucial in terms of the decision on indication of adjuvant chemotherapy. Clinico-pathological features such as young age at presentation, pathological tumour size of more than 2 cm, high grade of tumour, presence of peritumoural vascular invasion, positive axillary lymph nodes, hormone-negative tumours and over-expression or amplification of the HER2/neu gene have been the indications for adjuvant chemotherapy⁷. However, with our better understanding of new pathways and breast cancer molecular biology, and the advent of trastuzumab which has now become the standard of care for HER-2 over-expressed disease as supported by the pivotal trial of the HERA trial, showing an 8.4% absolute benefit in disease-free survival after a total of 1-year adjuvant trastuzumab⁸, the “target” of the breast tumour has become the main determinant for adjuvant therapy decision. With the added value of aromatase inhibitors in terms of adjuvant hormonal therapy for the post-menopausal hormone receptor positive breast cancer patients, the hormone receptors (oestrogen receptor and progesterone receptor) and the HER-2 receptor status have become important predictive factors of treatment response.

Therefore, there is a shift of paradigm of management and decision making on the most optimal adjuvant management for breast cancer patients, from the analysis of just the clinico-pathological features of the



breast tumour to the taking into account of predictive factors for treatment response and also potential prognostic indicators. This has further led to our better understanding of all the primary breast cancers in the context of different molecular subtypes. In the old days, systemic adjuvant therapy was indicated on the assumption of existing residual microscopic disease, with estimation of risk based entirely on extrapolation of data from previous clinical trials. It was further assumed that biological characteristics and treatment responsiveness are consistent between micrometastases and the primary tumour.

From "One-Size-Fits All" Approach to Tailored Made Management

Breast cancer is a heterogeneous disease. Molecular profiling identifies at least five breast cancer subtypes: luminal-A, luminal-B, HER2-enriched, basal-like and normal breast-like⁹. An immunohistochemical profile based on the degree of expression of oestrogen receptor (ER), progesterone receptor (PgR), HER-2 and Ki-67 similarly identifies breast cancer subtypes which have diverse disease biology, behaviours, relapse risks and treatment responses¹⁰. Though current evidence-based adjuvant treatment options include chemotherapy, endocrine therapy and anti-HER-2 targeted therapy, there is still an observational phenomenon where individuals at low risks who develop disease recurrence despite standard systemic treatment while some patients with high-risk disease remain relapse free for a long time without adjuvant intervention. On the other hand, promising novel agents that are being explored include therapies that target angiogenesis, DNA damage repair, apoptosis and immunity; but the evidence for the efficacy of these agents is lacking in the adjuvant setting. Therefore, the recommendation of the most appropriate adjuvant therapy for an individual diagnosed with early-stage breast cancer remains a difficult task¹¹. The more we know, the more we know how much we do not know. With the "one-size-fits all approach" being over in the management of breast cancer patients, there has been introduction of various decision making tools such as different multi-gene signatures to better tailor our management plan for individual patients.

Breast Cancer Assessment Tools

As decisions about adjuvant therapy must be made on an individual basis while there is no recipe for adjuvant therapy for breast cancer patients, there comes various prognostic and predictive assessment tools with the aim to assist breast oncologists to decide on the most appropriate treatment for each breast cancer patients, namely the computer-based model, Adjuvant! Online, international guidelines and consensus and other models using multi-gene signatures.

Adjuvant! Online

This is a validated computer-based model (<https://www.adjuvantonline.com>) which has been a popular breast cancer assessment tool among most breast oncologists giving an approximate risk evaluation in terms of 10-year breast cancer outcome based on selected prognostic features. This prognostic model was created using 10-year overall survival data from the Surveillance, Epidemiology, and End-Results (SEER) registry data for

women aged between 36 and 69 years diagnosed with unilateral, unicentric, invasive breast adenocarcinoma between 1988 and 1992¹². However, this prognostic tool is limited as it does not incorporate important prognostic factors such as oestrogen receptor (ER), progesterone receptor (PgR), HER-2 receptor status or any proliferative markers such as Ki-67 level. The potential benefits of using third-line chemotherapy may sometimes be over-estimated, especially in those early-stage disease when available data are being extrapolated¹³.

International Guidelines and Consensus

The St. Gallen Consensus which is one of the major international guidelines with regard to the most appropriate breast cancer adjuvant management with revision made every two-yearly at the St. Gallen Breast Cancer Conference during March every other year, has incorporated both risk assessment and therapy recommendation in its latest version in 2009. It has incorporated the standard cut-off levels for ER, PgR, HER-2 and Ki-67¹⁴. The consensus recommends that tumours with ER staining $\geq 1\%$ are classified as hormone receptor positive¹⁵. The St Gallen Consensus recommends that patients with small primary tumours (pT1aN0) with no vascular invasion may be spared chemotherapy. Patients with triple-negative (ER negative, PgR negative and HER-2 negative) tumours, have no systemic alternatives to chemotherapy. For patients with HER2-positive tumours, chemotherapy is indicated with anti-HER-2 targeted therapy with a total of 1-year adjuvant trastuzumab. For HER2-positive, small (<1 cm) node-negative tumours, the St Gallen Panel acknowledged emerging evidence of poor prognosis despite small tumour size. However, the lack of robust prospective evidence did not allow a definitive recommendation regarding anti-HER2 therapy in this cohort at this moment.

Multi-gene Signatures Assessment Tools

Over the last few years, significant effort has been made in identifying relevant molecular markers as prognostic and predictive factors to aid better decision making on adjuvant therapy for breast cancer patients. The innate capacity of a tumour to metastasise has prompted the use of multi-gene profiling for relapse risk estimation. A potential limitation of these mRNA-based signatures is the assumption that measurable mRNA will be translated to protein. However, most mRNA is not translated. Some markers, such as HER2, have evidence of a strong correlation between gene amplification and protein over-expression.

The 21-gene Oncotype DX[®] (Genomic Health Inc., Redwood City, CA) assay was developed to assign adjuvant chemotherapy in women with ER-positive, node-negative breast cancers who would receive adjuvant endocrine therapy. Sixteen cancer genes and five reference genes are used to calculate a Recurrence Score (RS) between 0 and 100, which correlates to a specific likelihood of recurrence within 10 years of diagnosis, defined as low (RS <18), intermediate (RS 18–31) or high (RS >31). As a prognostic tool for ER-positive, node-negative women, Oncotype DX[®] is superior to patient age, tumour size or tumour grade, and to a modified 5-year outcome version of Adjuvant! Online¹⁶. However it remains to be seen whether



Oncotype DX[®] is more useful than combined assessment of ER, PgR, HER2 and Ki-67 at a high-quality laboratory. In another study, Microarray in Node-negative Disease may Avoid Chemotherapy Trial (MINDACT), the genomic profiling of a 70-gene signature (MammaPrint[®]) is studied and compared with the conventional clinical assessment to determine the indication of chemotherapy in women with node-negative breast cancers. So far, studies on the MammaPrint[®] 70-gene signature have shown that the multi-gene signatures correlate a good-risk signature with chemoresistance and a poor-risk signature with increased chemosensitivity, but they do not show that MammaPrint[®] is more clinically valuable than morphology and immunohistochemical (IHC) subtyping in predicting these responses.

What Next After All High Hopes – More Burden?

Matching Science with the Affordability

Our research and development has proven success as evidenced by the promising results of the clinical trials, leading to the many more options and avenues in the treatment for breast cancer patients. While the incidence of breast cancers is increasing and the number of breast cancer patients living with the disease is also increasing, the access to all the new regimens especially the targeted therapy and the assessment tools is not equal to all individuals. Currently, the use of adjuvant trastuzumab in the public sector is a self-financed item for patients in Hong Kong, so are some of the taxanes in the intermediate risk group. The cost of the Oncotype Dx is indeed a self-financed item if the patient and physician would like to ascertain the benefits of chemotherapy for the node-negative hormone receptor positive early breast cancer patients. The current cost of a total of 1-year adjuvant trastuzumab is about HK\$ 200,000 while the cost of the Oncotype Dx test is about HK\$ 20,000. The cost-effectiveness of the Oncotype Dx assay has been verified in the United States but not in individual countries and thus there is another challenge of whether the clinical data derived from these multi-gene signature assays could be translated into direct application in other non-US countries such as the Asian population like our Chinese population.

Open Discussion and Communication is of Paramount Importance

With the ever increasing number of new anti-cancer treatments and molecular assays, there comes the increasing high expectation from the patients and their families. While the issue of life and death, breaking bad news and dealing with complex psychoncology of cancer patients is usually not thoroughly touched during our traditional medical training, not all oncologists or cancer physicians are well equipped with the proper communication skills in terms of discussing various costs and options of anti-cancer treatments with the breast cancer patients. This has been supported by the recent cross-sectional study looking at the perceived difficulties and stress from a cancer patient consultation among 134 Australian cancer specialists, all being members of the Clinical Oncological Society of Australia, and it has shown that to the doctors, the most stressful practice being discussing the high-cost drugs during the consultation¹⁷. There is indeed a growing challenge

among the oncologists in discussing all the high-cost treatment options with the cancer patients¹⁸. Therefore, there is an unmet need to further better equip our cancer physicians and cancer carers with better communication skills so that they could provide relevant information with regard to the high-cost treatment and relevant tests to our cancer patients.

Conclusion

There has been ever increasing hopes for breast cancer patients with our better understanding of the breast cancer molecular biology, and the ever increasing avenues of different treatment options for different subtypes of patients. The “one-size-fits-all” approach is over and we have come to the new era of personalised medicine for our breast cancer patients. However, whether higher hopes mean greater burden in terms of the extra time and empathy to discuss various treatment options including the ever growing list of self-financed items with our patients, and whether we could directly translate all the clinical data from the western population to our own clinical practice, this requires the continuous effort of the multidisciplinary approach for breast cancer management, and further international multi-centre trials and investigation of biological and treatment heterogeneity within breast cancer subtypes, such as good prognosis subsets within triple-negative disease or benefit of anti-HER2 therapy in small, HER2-positive tumours, and within individuals are warranted to further advance our risk assessment. While we are planning to explore further clinical utility of promising assessment tools in future and biologically driven trials, we should also better equip our oncologists or oncologists-to-be with better communication skills which involves an appreciation of both Art and Science. There is no single recipe for adjuvant management of breast cancer patients, but there should always be an open discussion with the patient, the family and all other supporting parties before any treatment decision is made.

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The Management of Advanced Hepatocellular Carcinoma: Are We Making Progress in the Era of Targeted Therapy?

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Dr. Thomas YAU

Introduction

Hepatocellular cancer (HCC) is the sixth- and eleventh-most common cancer worldwide in men and women respectively.¹ It occurs most often in male patients over 40 years of age. It is the most common primary liver malignancy, with an annual incidence of over 500,000 new patients worldwide with more than half of the new cases occurring in China.² In the Asia-Pacific region, HCC is the third most common cancer and the second most common cause of cancer-related death. The incidence rate for HCC in the Asia-Pacific region has been rising, linked to a high hepatitis infection rate. On the other hand, the incidence of HCC in Western countries is rising due to the sequels of hepatitis C infection and alcoholic cirrhosis. In the United States, the incidence of HCC almost doubled during the last two decades.^{3,4} There will be a steady rise in the incidence of HCC worldwide due to an increasing prevalence of non-alcoholic steatohepatitis associated with the metabolic syndrome. It becomes one of the important global health problems that physicians have to face, especially in the Asia-Pacific region.

HCC is a cancer of high particular relevance in Hong Kong because of the high prevalence (10%) of hepatitis B infection. It is the second most common cancer causing death in Hong Kong.⁵ Current effective treatments for HCC include liver resection, transplantation, various local ablative and trans-arterial therapies. Nevertheless, only around 20% of patients, mostly diagnosed by regular screening, may benefit from these potentially curative surgical therapies. The majority of patients have unresectable HCCs because of advanced tumour stage and poor liver function.^{6,7} Besides, transplantation is indicated only for early small HCCs, and its application is limited by the shortage of liver graft, which is a particularly severe problem in Hong Kong.⁸

Prior to the advent of targeted therapy in HCC, most advanced HCC patients were only palliated by various systemic therapies and in fact a significant proportion of patients were treated by at best supportive care only.⁹ Historically, the prognosis of the advanced HCCs was dismal with an overall survival of 2.3-2.6 months.¹⁰ HCC is a relatively chemo-resistant tumour and is highly refractory to cytotoxic chemotherapy. There is no convincing evidence so far that systemic chemotherapy improves overall survival in advanced HCC patients.¹¹ Single-agent doxorubicin has been shown to produce a response rate of about 10-15% but with no proven survival benefits.¹² Nevertheless, significant grade 3 or 4 toxicities, especially neutropenia,

are encountered in patients treated with doxorubicin.¹³ The newer generation of chemotherapeutic agents, such as gemcitabine, irinotecan and pegylated liposomal doxorubicin, also shows disappointing results.^{14,15} The combination of cisplatin, interferon-alpha-2b, doxorubicin and fluorouracil (PIAF) caused a great deal of enthusiasm at one time. However, in the phase III study, although this combination had achieved seemingly higher response rates than other combinations, there was no demonstrable survival benefits and there were considerable toxicities.¹⁶

Emerging insights into the biology and molecular signalling pathways in cancer cells has led to the identification of potential targets for intervention and the advent of promising targeted therapy for the treatment of otherwise chemo-resistant tumours. In contrast to other solid tumours, HCC has a complex molecular and genetic pathogenesis. Chronic liver injuries, due to either viral infections or environmental toxins play a pivotal role in the carcinogenesis. Many key carcinogenic pathways play a pivotal role in the development of HCCs, and it is difficult to assess which is the driven pathway for hepato-carcinogenesis.¹⁷ Among these targets, exciting clinical results have been shown by targeting the anti-angiogenic pathway and the Raf/mitogen-activated protein kinase-extracellular signal-regulated kinase (MAPK)/extracellular signal-regulated kinase (ERK) pathways. Other signalling pathways such as epidermal growth factor receptor-1 (EGFR), and phosphatidylinositol-3-kinase (PI3K)/AKT/mammalian target of rapamycin (mTOR) have also emerged as attractive avenues for future therapeutic interventions. Notably, thus far, most of these targets mainly focus on targeting the tumour growth pathway and/or inhibiting tumour angiogenesis.

Sorafenib (Bayer 43-9006; Nexavar) is an oral multi-kinase inhibitor that blocks tumour proliferation by targeting the Raf/MAPK/ERK signalling pathway; it also has significant anti-angiogenic properties attained by targeting the tyrosine kinase VEGFR-2, VEGFR-3 and PDGF receptor β .¹⁸ Recently, two pivotal phase 3 randomised placebo-controlled trials in the West¹⁹ and Asia-Pacific region²⁰ have clearly shown the survival benefits in using single agent sorafenib in treating patients with advanced HCC: In the SHARP study, 602 patients with biopsy-proven advanced HCC who had not received any prior systemic treatment were evaluated and randomised to receive either sorafenib (400 mg twice daily, n = 299) or a placebo (n = 303). Of note in this study, only patients with Child-Pugh A cirrhosis were included, and 37 (6%) and 56 (9%)



of patients were hepatitis B and hepatitis C carriers, respectively. The results demonstrated a significant improvement in both OS (median 10.7 versus 7.9 months) and TTP (median 5.5 versus 2.8 months) in the sorafenib group versus the placebo group. These results indeed represented a 44% increase in OS (hazards ratio, 0.69; $p = 0.00058$) and 73% prolongation in the TTP (hazards ratio, 0.58; $p = 0.000007$). Sorafenib was generally well-tolerated and serious adverse events only occurred in 13% of patients. Similarly, an Oriental sorafenib study was performed to investigate the efficacy and tolerability of using single agent sorafenib in treating advanced HCC patients in hepatitis-B endemic Asian populations.²¹ In this study, a total of 226 patients were recruited and randomised in a 2:1 fashion, i.e. 150 patients on sorafenib and 76 patients on placebo. The disease control rate was 35% in the sorafenib arm. The median OS of patients on sorafenib was 6.2 months which was significantly better than 4.1 months achieved in patients on placebo ($p=0.0155$). Based on the results of these two pivotal trials, sorafenib has been approved by the U.S. Food and Drug Administration (FDA) and other regulatory authorities worldwide for the management of advanced HCC patients. Although these two pivotal studies have demonstrated good activity and tolerability in treating advanced HCC patients with sorafenib, most of the enrolled patients belonged to Child-Pugh A cirrhosis with favourable clinical parameters. Therefore, the benefits and safety profile of sorafenib in unselected advanced HCC patients, especially those with Child-Pugh B/C patients or other poor prognostic factors are still unknown. More mature results are needed before recommending the routine use of sorafenib use in Child-Pugh B patients.

The recent development of sorafenib represents a step forward in the treatment of advanced HCCs. However, it is just the beginning of a new horizon in molecular targeted therapy of HCC. It has promulgated strong interests among researchers to unravel more underlying molecular mechanisms of HCC growth and metastasis. Besides sorafenib, other targeting agents have also shown encouraging activity in the treatment of patients with advanced HCC in early clinical trials.

HCC is a highly vascular tumour with a high propensity for vascular invasion, and thus tumour angiogenesis plays a pivotal role in the pathogenesis of HCC.^{22,23} Vascular endothelial growth factor (VEGF)²³ is the most potent known angiogenic factor and its over-expression varies from 37% to 100% in HCC cells, and aberrant VEGF expression is a prominent feature in HCC.²⁴ The anti-angiogenic effect can be achieved either by using monoclonal antibodies to target the VEGF or employing anti-angiogenesis inhibitor to block various VEGF receptors. Bevacizumab as a single agent or in combination with other agents has shown modest activity in treating advanced HCCs. In the study conducted by Siegel et al., among 46 enrolled patients with advanced unresectable HCC, single agent bevacizumab achieved a 13% response rate (RR), while 65% of patients had stable disease (SD)²⁵. Nonetheless, 4% of the enrolled patients had arterial thrombosis and grade 3 or higher haemorrhage occurred in 11% of patients, including one patient who died of variceal bleeding. On the other hand, Thomas et al. had performed a non-randomised phase II study of

combination of high dose bevacizumab with erlotinib in the treatment of advanced HCC patients. Based on the results of the enrolled patients, the RR was surprisingly high with one patient having complete response, 22% PR and 55% having SD.²⁶ Moreover, the OS was 15.65 months. Nevertheless, a significant proportion of the enrolled patients discontinued from the study due to treatment-related toxicities and one patient even died from treatment-related adverse events. Sunitinib is another oral anti-angiogenic multi-targeted tyrosine kinase inhibitor with partially overlapping target inhibition with sorafenib. It inhibits VEGF receptor 1-3, PDGFR- α and β , c-kit, Flt-3, colony-stimulating factor receptor type 1 and RET kinases.²⁷ Although phase II studies employing different doses of sunitinib suggested initial activity of single-agent sunitinib in treating advanced HCCs²⁸, a recent randomised phase III sunitinib study was halted early because of concerns about efficacy and treatment-related toxicities. Thus, targeted agents with comparable kinase profiles may produce very different clinical outcomes in similar patient populations. Brivanib (BMS-582664) is a small molecule tyrosine kinase inhibitor of both VEGF and fibroblast growth factor (FGF) receptor family. Raoul et al.²⁹ reported the results of an open-label phase II study on the use of brivanib both as first-line treatment of advanced HCC patients. In this study, when brivanib was used as first-line treatment of 55 advanced HCC patients, the overall RR was 5%, while another 47% of the patients achieved SD. The TTP was 2.8 months. Currently, brivanib as a single agent is being investigated in large-scale phase III randomised studies either as first-line therapy compared with sorafenib or as second-line treatment after sorafenib failure for advanced HCC patients. Last but not least, linafinib (ABT-869) is another novel orally active, potent and selective inhibitor of the VEGF and PDGF families of receptor tyrosine kinases. Toh et al recently reported the results of a phase 2 trial of ABT-869 in advanced HCC.³⁰ In this open-label, multicentre phase II trial, oral ABT-869 was administered in patients with both Child Pugh A and B cirrhosis. The median OS of the enrolled patients was approaching one year. Based on this preliminary results, a randomised phase III trial is underway to assess the efficacy and tolerability of ABT-869 compared with sorafenib as first line treatment for patients with advanced HCC.

While sorafenib and other anti-angiogenic multi-targeted tyrosine kinase inhibitors show early promises in the management of advanced HCC patients, most of these targeted agents have demonstrated very low response rate when they are used alone. They will not induce radiological regression of the tumour but rather result in mostly disease stabilisation. Thus, the other direction in the future systemic trials of treatment of advanced HCCs is to test the potential benefits of combining sorafenib together with various systemic agents to increase the response rate and downstage the tumour for potential curative resection. By adding other systemic agents to sorafenib, there is a potential for gaining additional efficacy through possible synergistic effects. To this end, several investigators are trying to investigate the benefits of adding either novel molecular targeting agents, biological agents or chemotherapeutic agents to enhance sorafenib efficacy. In particular, there are preliminary data in the literature suggesting



potential benefits in combining sorafenib with various chemotherapy agents to enhance sorafenib activity. The results from a randomised phase II study by Abou-Alfa et al. showed encouraging activities in combining sorafenib with doxorubicin in the treatment of advanced HCC patients.³¹ This study has suggested possible synergistic actions between sorafenib and doxorubicin as sorafenib may potentially inhibit the Ras/Raf/MEK/ERK pathway, which in turn may prevent activation of the multidrug resistance pathway.³² Notably, more than one-third of the recruited patients experienced significant treatment related toxicities, such as febrile neutropenia and treatment-related death. Instead of using doxorubicin as the chemotherapy partner, our group at Queen Hospital, the University of Hong Kong has reported the results of a multi-centre phase II study of combining sorafenib with capecitabine and oxaliplatin (SECOX) in the treatment of advanced HCC patients.³³ Our results demonstrated promising activities with an overall RR of 16% and OS 11.8 months. Moreover, this regimen was well-tolerated by most enrolled patients. In view of this promising result, a large scale randomised phase III Asia-Pacific study is underway to investigate the benefits of this regime over single agent sorafenib in the treatment of advanced HCC patients. Clinical trials of combination of sorafenib with various other chemotherapeutic agents, such as fluoropyrimidine, platinum compounds and gemcitabine are still in the stage of active patient recruitment and the results will be eagerly awaited.

Conclusion

In summary, in the era of targeted therapy, there are some real progresses made in the systemic treatment for advanced HCC patients. The recent development of single agent sorafenib in the treatment of advanced HCC patients indeed represents a major milestone in the treatment of advanced HCC. It proves the concept that molecular targeted therapies, especially anti-angiogenic agents, play a pivotal role in the treatment of HCC. Nevertheless, our current understanding of the underlying pathogenesis of HCC is still very primitive. More in-depth basic and translational researches need to be done to further elucidate the underlying molecular pathogenesis in the disease. The future direction in improving the survival of advanced HCC patients will likely rely on either combining sorafenib with others to circumvent the complex signalling pathways in HCC or the development of novel targeted agents which can target the main oncogenic driving pathway in the disease.

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Adjuvant Colon Cancer in the Era of Personalised Medicine and Targeted Therapy

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Specialist in Medical Oncology



Dr. Roland LEUNG

Introduction

It has been estimated that there would be 148,000 new cases of colorectal cancers in 2008, about 2/3 from the colon and 1/3 from the rectum. The annual death figure from colorectal cancers was estimated to be 50000 in 2008 (data taken from American Cancer Society statistics). This discrepancy can be explained by the 5 year localised survival rate of 90% and 5 year overall survival rate of 64% according to the latest statistics from the American Cancer Society. The push for early detection efforts made in the past decade leading to earlier detection of limited stage colorectal cancers and the improvements made in therapeutics in metastatic colon cancers are responsible for these progresses. Due to the different approaches to the management of resected colon cancers and the current debate in how to best manage limited stage rectal cancers where pre-operative chemo-radiation may be the optimal approach for limited stage rectal disease, this article will focus on reviewing the current approaches to adjuvant therapy for resected limited stage colon cancers (LSCC) only.

6th edition. LSCC encompasses disease from Stage I to Stage III. Within Stage III disease, increasing number of positive LNs is no doubt related to worsening outcome after surgery. In fact with positive LN numbers above 15 the outcome is comparable to Stage IV disease. The focus of this paper will be on Stage I to III disease.

Development of Adjuvant Chemotherapy for Colon Cancer

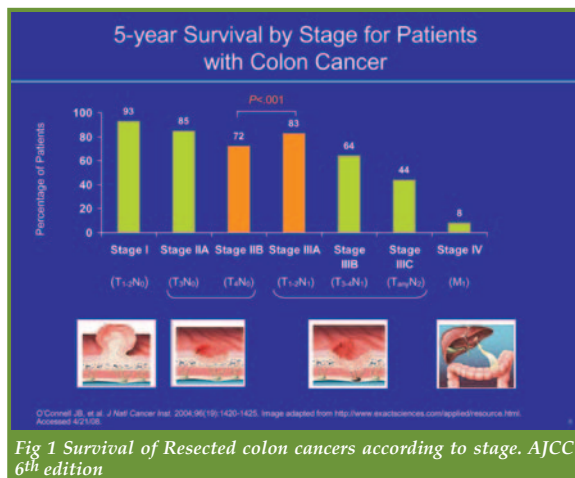
In the era of modern imaging techniques, all patients should be evaluated with CT or CT/PET scans prior to curative intent surgery after the diagnosis of colorectal cancer is made. If there is no distant metastasis detected by the chosen imaging modality, a curative procedure is performed. After surgery, treatment failure can be either local recurrence or the development of metastatic disease at distant organs. A third scenario is the development of new primary tumours which in general occur some years after the initial diagnosis. Local or peritoneal disease relapse may be attributed to suboptimal resection or seeding during the primary operation. If such events are suspected, radiation can offer excellent local disease control. New primary tumours that occur independently of the previous disease on the other hand are revealed through diligent surveillance of the remaining colon with regular examinations.

The presence of micro-metastatic tumour cells which are too small to be demonstrated by conventional imaging techniques prior to surgery is the cause of the most fatal form of recurrence. Distant metastases represent outgrowths of such disseminated cells and in general the treatment is palliative since the patient can no longer be cured.

We have information back in the 1990s that adjuvant chemotherapy with 5FU based regimens following curative intent surgery for colon cancers can deliver survival benefits.¹ However it was also noted that clinical benefits from adjuvant chemotherapy for limited stage (II and III) colon cancers can disappear with increasing clinical follow-ups.²

Current Adjuvant Therapy Recommendations for LSCC

Within LSCCs, the probability of survival is heavily influenced by the amount and degree of involvement



Staging of Colon Cancer

Currently the AJCC recommends the TNM staging system. It is based on tumour size and pathology, lymph nodes status and the extent of metastases. LSCC encompasses tumours that have not spread beyond draining regional LNs at pathological staging. The disease survival of colorectal cancers broken down by stages is summarised in Fig 1 using the recently superseded AJCC



of the cancer beyond the primary organ. It varies from the excellent prognosis of 90+ % survival of a Stage I disease at 5 years to a worrisome less than 50% survival at 5 years for Stage IIIC disease. Staging is a powerful surrogate for the likelihood of tumour dissemination. Since the target of adjuvant therapy is beyond our clinical detection limit, we use the degree of tumour spread as our guide in identifying patients at risk of disease relapse.

Due to the excellent outlook for resected Stage I patients, there is no adjuvant therapy recommended for this group of patients. There is a paucity of data investigating the role of adjuvant therapy in Stage II colon cancers alone despite the relatively poor outcome in the subgroup of Stage IIB patients. The one study which recruited an overwhelming number of Stage II patients was the QUASAR study. Whilst there was a statistically significant improvement in outcome, the difference was small and achieved with considerable mortality. Therefore, current literature does not support the routine use of adjuvant therapy for early stage colorectal cancers (Stage I and II)³⁻⁵.

In the review of CRC adjuvant therapy by de Gramont and Haller⁵, the current therapeutic standard for resected Stage III disease is oxaliplatin based regimen FOLFOX 4 or FLOX for 6 months where the absolute improvement in DFS is approximately 7% according to the most recent reports from the MOSAIC trial and NSABP C-07 when compared to the older standard of 5FU/leucovorin⁹ with an overall total risk reduction of more than 25% over observation alone.

One should also bear in mind that in the landmark studies which showed advantages of using oxaliplatin based adjuvant therapy, there was a significant enrollment of Stage II patients, yet there was no benefit seen in a retrospective non-preplanned subset analysis⁶. An exploratory analysis of high risk Stage II patients did show a benefit of 7.7% for 5 yr DFS favouring those who received FOLFOX 4⁶. It must also be noted that the trials presented were performed with the AJCC 6th edition staging system. The obstacle to a definite answer has been the lack of reliable predictor of adverse outcome in early colorectal cancers. Whilst staging is useful, there is a clear need of better prognostic markers for disease relapse. Without such markers to distinguish the heterogeneity of Stage II disease, it is a mountainous challenge to design an adjuvant trial to address this sizable group of patients which is increasing due to the early detection of disease with the widely adapted practice of population screening.

Past Limitations of TNM Staging of Colon Cancer

Currently the stage of disease at diagnosis is the best prognostic predictor for LSCCs. Although staging of colon cancers can provide excellent prognostic information for LSCC, careful inspection of Figure 2 will reveal an anomaly of prognostic prediction of TNM staging. 5 year survival of Stage IIB disease is actually worse than Stage IIIa disease. Stage IIB is defined as T4 disease but LN negative.

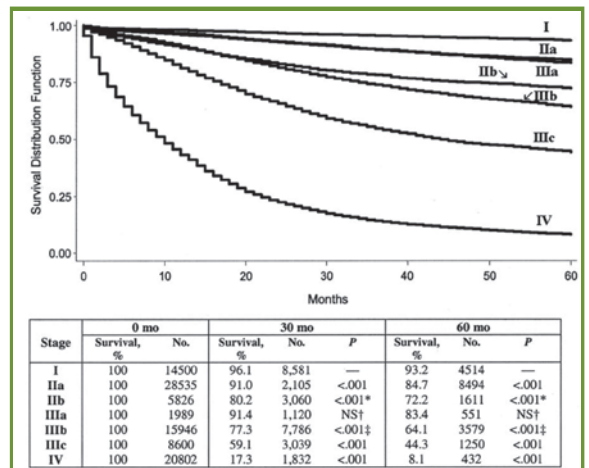


Fig 2 Survival of colorectal cancers broken down by stage according to AJCC 6th edition. Adapted from²¹

Since staging is heavily dependent on the LN status, a nagging challenge is to define a standard for LN sampling for LSCCs. A consistent LN assessment standard is key to distinguish true Stage II disease and understaged Stage III. Recently multiple work groups have addressed this concern and although slightly different in regards, the minimum number of LNs sampled in staging of colorectal cancers is agreed to be at least 12 (NCCN guidelines, www.nccn.org) and 10-14 in the AJCC 7th edition. The statistics shown in Fig 1 was prior to the formal recommendation of the minimum number of LNs sampled at surgery, it is conceivable that some of those Stage IIB disease patients were in fact understaged Stage III using the most recent recommendations. With a robust denominator in place, the accuracy of disease staging is improved when coming to design of future clinical trials for adjuvant colon cancers.

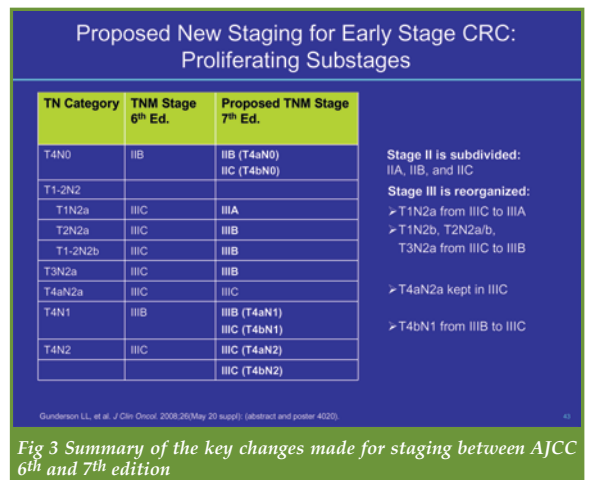


Fig 3 Summary of the key changes made for staging between AJCC 6th and 7th edition

In response to the advances made, the AJCC has published a revised staging guide in 2010. The summary of the key changes in staging is summarised in Fig 3 and the survival analysis based on the 6th and 7th edition staging system is shown in Fig 4⁷⁻⁸. The introduction of a T4 a and b stage takes into account of tumour invasion and adherence to adjacent organs which is related to worsened outcome of resected CRCs. There will be an inclusion of minimum number of LNs sampled. The

revised staging proposal was tested against the current 6th edition. The results yielded a surprising amount of changes in the prognostic outcome between the old 6th edition and the proposed 7th edition.⁹ It is estimated that up to 25% of the newly diagnosed LSCCs will have their treatment decision altered as a result of the 7th edition. As a result, the clinical trials designed using the 7th edition of AJCC staging should not be compared retrospectively to the trials based on earlier editions.

Other Risks Factors Used in LSCC Risk Stratification

Many attempts have been made to augment and improve on the accuracy of the predictive value of the TNM staging system. The aim is to find better surrogate markers to segregate the otherwise homogenous disease with equal TNM stage into those who are at different risk of disease recurrence. The most common ones used are listed below

- 1) Tumour perforation at resection
- 2) High tumour grade/ Lack of tumour differentiation
- 3) Lymphovascular invasion
- 4) Bowel obstruction
- 5) Neurovascular invasion
- 6) Inadequate LN sampling

Clinical Trial Groups have incorporated clinical characteristics listed and produced nomograms for predicting relapse risks for early CRCs. These include the nomogram by Weiser¹⁰ and the Adjuvant on line [<http://www.adjuvantonline.com>] type risk calculators. These tools are invaluable in the clinical discussion of the use of adjuvant chemotherapy in preventing disease recurrence in LSCCs.

Novel Predictive Biomarkers is an Urgent Unmet Medical Need in Colon Cancer

There is an urgent need to develop a set of prognostic markers which can give useful information regarding the likelihood of disease relapse in LSCCs. Since some of the high risk features are directly related to the time lag in making the diagnosis of colon cancer, it would be most useful to have available markers which are based on intrinsic tumour biology. Of equal importance, there also needs to be a set of predictive markers which can be utilised to select patients who are likely to respond to therapy being tested in colon cancer. The strategy of combining prognostic and predictive markers can revolutionise clinical trial designs to select enriched population for responders and select high risk patients to capitalise on the novel developments in therapeutics.

In the field of breast cancer, there are currently multiple validated molecular tests which can greatly aid physicians in making treatment decisions for adjuvant breast cancers. It would provide a much needed boost for fighting colon cancers if we have available similar tests for evaluating relapse risks for colon cancers. Molecular tests in development and testing are summarised in Table 1.

Table 1 Summary of markers undergoing evaluation in adjuvant Colon Cancers.

Molecular Marker	Material required	Method used	Prospective validated	Nature
CEA	Serum	ELISA based	Yes	Prognostic
GCC ²²	Fixed tumour tissue	PCR	Yes	Prognostic
Circulating tumour DNA ^{23,24}	Plasma	PCR based	?	Prognostic
MSI ²⁵	Fixed tumour tissue	Immuno-histochemistry	Yes	Prognostic but may also be predictive*
18q LOH	Fixed tumour tissue	PCR	Yes	Prognostic
Gene signature ¹¹	Frozen tissue	Gene expression array	No	Prognostic
LDH	Serum	ELISA	No	Predictive
k-Ras ¹⁶	Fixed tumour tissue	PCR	No	Predictive
b-Raf ²⁶	Fixed tumour tissue	PCR	No	Predictive

Table 3. SEER Colon Cancer Analysis, 5-Year Relative and Observed Survival by TN Category of Disease in Patients With Invasive Cancer and Evaluable TN Category

TN Category	No. of Patients	SEER 5-Year Relative Survival Rate (%)	SE	TNM Stage (6th edition)	Proposed TNM Stage (7th edition)*	SEER 5-Year Observed Survival Rate (%)	SE
T1N0	10,930	97.4	0.6	I	I	78.7	0.5
T2N0	12,931	96.8	0.6	I	I	74.3	0.4
T3N0	40,338	87.5	0.4	IIA	IIA	66.7	0.3
T4aN0	5,020	79.6	1.0	IIIB	IIIB	60.6	0.8
T4bN0	3,088	58.4	1.3	IIIB	IIIC	45.7	1.0
T1-2N1a	1,913	90.7	1.5	IIIA	IIIA	73.7	1.2
T1-2N1b	1,221	83.0	2.0	IIIA	IIIA	67.2	1.6
T1-2N2a†	377	79.0	3.6	IIIC	IIIA/IIIB†	64.7	3.0
T3N1a	8,759	74.2	0.8	IIIB	IIIB	58.2	0.6
T4aN1a	1,311	67.6	2.0	IIIB	IIIB	52.2	1.5
T3N1b	9,107	65.3	0.8	IIIB	IIIB	51.7	0.6
T1-2N2b	122	62.4	6.5	IIIC	IIIB	51.8	5.3
T4aN1b	1,460	54.0	1.9	IIIB	IIIB	42.1	1.5
T3N2a	5,331	53.4	1.0	IIIC	IIIB	42.8	0.8
T4aN2a‡	982	40.9	2.1	IIIC	IIIC	32.5*	1.7
T3N2b	3,235	37.3	1.2	IIIC	IIIC	30.4	0.9
T4bN1a	845	38.5	2.2	IIIB	IIIC	30.6	1.8
T4bN1b	929	31.2	2.0	IIIB	IIIC	25.4	1.6
T4bN2a	730	23.3	2.1	IIIB	IIIC	18.3	1.6
T4aN2b	671	21.8	2.2	IIIB	IIIC	17.5	1.7
T4bN2b	653	15.7	1.9	IIIC	IIIC	12.9	1.5

Abbreviation: SEER, Surveillance, Epidemiology, and End Results.
 *Proposed changes in substaging of stages II/III (bold type), based on expanded outcomes in SEER data analyses.
 †Patients with T2N2a colon lesions fared better than patients with T2N2a rectal lesions; both categories placed in stage IIIB.
 ‡Patients with T4aN2a colon lesions fared worse than patients with T4aN2a rectal lesions; both categories placed in stage IIIC.

Fig4 Survival according to Staging between AJCC 6th vs 7th



Currently there are no data to recommend the use of molecular markers in the decision making process for adjuvant therapy of CRCs. Loss of heterozygosity at chromosome 18q (LOH18q) and the lack of microsatellite instability (MSI) are potential markers for aggressive clinical disease. These markers will be tested in ECOG5202 where Stage II colon cancers are first assayed for recurrence risks based on 18q and MSI status. Those who fall in the high risk category are prospectively stratified to treatment with FOLFOX (5-fluorouracil [5-FU]/leucovorin[LV]/oxaliplatin) with or without the addition of bevacizumab. The low-risk patients are assigned to surveillance alone. This trial is a landmark in adjuvant CRC trial since it will be the first to test a molecular prognosticator for decision making in adjuvant CRC.

In constructing a trial like ECOG 5202, it is provocative to test the reliability of a novel biomarker to predict the clinical outcome. Traditional Stage II disease does not benefit from adjuvant therapy taken as a group. Subjecting the patients to risk stratification prospectively and then selecting the high risk group for therapy enriches a subset of patients who may show differential benefits from adjuvant therapy.

Tumour Biology Based Testing

The most ambitious test of all is probably the expression array or gene panel RT-PCR based assay which investigates the biology of colon cancers where certain molecular signatures are identified and their clinical outcome correlated.

The more robust test is likely to be RT-PCR based test similar to the oncotype RX 21 gene signature set used in breast cancers. This test can be done in archival materials and does not require fresh tissue preservation unlike the expression array based which requires snap frozen materials which limit the general availability of the test across a mixture of community and specialised hospitals dealing with colon cancer care. In ASCO 2009, there was a presentation of a RT-PCR based tumour recurrence score. It utilised 4 large prospective studies as the training set and an 18 gene panel was ultimately used in the validation study. The validation sample came from the QUASAR adjuvant colon cancer trial where 90% of the 3238 patients were Stage II are randomised to be treated with 5FU based chemotherapy or observation alone. The preliminary report showed that this Oncotype colon test has demonstrated a predictive role in determining relapse likelihood for resected Stage II disease¹¹. This marks a major breakthrough in risk prediction in adjuvant colon cancers since the introduction of TNM staging with revised LN sampling recommendation.

Defining the End Point for Adjuvant Studies in the Era of Biological Therapies

The goal of adjuvant therapy is to eliminate potential micrometastatic disease and ensure the patient leads a cancer free life after completion of chemotherapy. In

practice however, with the advancing age of the general population and the increasing number of elderly patients diagnosed with colon cancer, disease free survival (DFS) at 3 year is adopted as a surrogate with good supporting data¹². The ACCENT group further reported another meta-analysis incorporating the latest adjuvant trials for Stage III patients which utilised oral fluoropyrimidines, oxaliplatin, and irinotecan in ASCO 2009¹³. They concluded that 2yr DFS is an excellent surrogate for 5 yr and 6 yr OS. Incidentally, the FDA had accepted 3 yr DFS as acceptable clinical end point for trial design for future approval of adjuvant therapy for colon cancers.

NSABP C-08 is a trial that aimed to investigate the addition of bevacizumab, an anti VEGF-a antibody which has demonstrated substantial benefits in the metastatic setting to the standard of FOLFOX 6 for the treatment of Stage II and III colon cancers. The much anticipated results were published¹⁴. It was sobering to learn that there was no benefit seen at all at the accepted time point of DFS at 3 years. In the exploratory analysis, there were no differences between Stage II and III patients. Despite a very significant DFS at 1 year, as the trial matured, the DFS between the experimental arm and the standard arm gradually came together at the 3 yr mark¹⁴. This result should strike a cautionary note to clinical trial groups, whilst DFS is a reliable end point in chemotherapy based adjuvant colon cancer trials, this may not be the case in the era of targeted therapy. Bevacizumab does deliver a statistical advantage at follow ups during year 1 and 2 but negative results at 3 years. This was confirmed by a recent presentation of the AVANT trial using a similar study design but carried out in Europe¹⁵.

The superior year 1 and 2 outcome of the bevacizumab containing arm in the 2 trials tells us that the combination is effective in prolonging disease relapse by radiological measures. However, with time, microscopic tumour deposits will be triggered into a growth phase and develop into radiological apparent metastatic disease. The bevacizumab-FOLFOX combination contributes no further benefit in eradicating these microscopic deposits compared with FOLFOX. Therefore, one can consider this combination is more tumour static but not more tumouricidal. This could explain the difference in efficacy between the metastatic and adjuvant setting. This novel phenomenon needs to be taken into account when designing future clinical trials.

Therapeutic Differences Between Adjuvant and Metastatic Colon cancer

Adjuvant chemotherapy for cancer has generally been the adaptation of effective regimens used in metastatic setting and testing them for efficacy in the adjuvant setting. The adjuvant therapy for colon cancer has reached some rather unexpected conclusions. CPT11 or irinotecan, a very effective drug in the metastatic setting, failed in the adjuvant setting despite its proven role in the management of metastatic disease. Multiple trials have repeatedly failed to show additional benefits when it is combined with the older standard of 5 FU/Leucovorin¹⁷.

It is also becoming apparent in colon cancers that certain genetic mutations carry predictive power to the response to given therapy. For example, k-Ras mutants have been shown to derive no benefit from agents targeting the EGFR signalling pathway¹⁶. Furthermore, it is now known that downstream b-Raf status is also critical in predicting response to EGFR targeting agents in metastatic CRCs¹⁷.

A fraction of the NCCTG N0147 trial was reported earlier this year¹⁸. This part tested the combination of FOLFIRI alone or with the addition of Cetuximab, a highly effective combination in metastatic colon cancers¹⁹. The FOLFIRI Cetuximab combination yielded a disease free survival which is disappointingly lower than the standard of FOLFOX4 even for the k-RAS wt patients.

To further add to this confusion, the ill-fated NCCTG N0147 trial where prospectively selected k-RAS wt patients were randomised to FOLFOX with or without Cetuximab. The results were again disappointing because there was no benefit in adding Cetuximab for this group of patients²⁰. The fate of the utility of Cetuximab in adjuvant colon cancers will rest with the results of the PETACC 8 trial which has completed recruitment and results are eagerly awaited.

Conclusion

Development of adjuvant therapy for early colon cancers has hit an unfortunate road block. Whilst there was a quantum leap in terms of disease control and overall survival during the past 10 years for metastatic disease, the recent reports of multiple failed trials trying to incorporate these advances in the adjuvant setting is perplexing and disappointing. Since the target of adjuvant chemotherapy is the disseminated non-measurable tumour cells, their response to targeted therapy may not mirror that of larger macroscopic disease. Whilst the biology of micrometastases is beyond the scope of this review, factors like cell cycle status, tumour dormancy, cancer stem cell biology, pharmacodynamics and pharmacokinetics may explain some of the differences seen in efficacy.

Looking ahead, in addition to prognostic markers, response predictors are essential in guiding the appropriate selection of patients who are likely to benefit from adjuvant therapy in the future. In order to be effective, we must address the difficult problem of personalised adjuvant chemotherapy decision.

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Discovering new ways forward

Seminar: Studying in the UK

The Federation of Medical Societies of Hong Kong, British Medical Association (HK), and the British Council present a seminar on studying in UK schools and universities, with tips on how to apply. Families of our members interested in UK education are also welcome to attend.

Date: 7 March 2011, Monday

Time: 6.15 p.m. - 6.45 p.m. Session 1 and Q&A session
7.00 p.m. - 7.30 p.m. Session 2 and Q&A session

Venue: 4th floor, Lecture Hall, the Federation of Medical Societies of Hong Kong, Duke of Windsor Social Services Building, 15 Hennessy Road, Wanchai

Registration: Call 2527 8898, fax 2865 0345 or e-mail info@fmshk.org

Session 1

Hong Kong's new academic structure and pathways to studying in UK at school and university levels.

This session will look at how schools and universities in the UK are responding to the new system in Hong Kong, the optimum timing for children to study in the UK, and how to choose the right school.

By Katherine Forestier,
Director of Education and Society,
British Council Hong Kong

Session 2

Applying to universities in the UK: how to make the right choice of university and course, and how to make a winning application.

By Rob Aldridge,
Regional Manager for the Far East,
Oxford Brookes University

Rob will speak generically, with his advice applicable to any university in the UK. He is a sought-after speaker and workshop leader. His presentation on writing personal statements is both fun and invaluable in making sure a student stands out for all the right, rather than wrong, reasons.

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Date / Time	Function	Enquiry / Remarks
1 TUE 1:45 pm 8:00 pm – 10:00 pm 8:00 pm	HKMA Tai Po Community – Early Detection of Dementia in the Family and Medical Treatment Abstract Organiser: HKMA Tai Po Community Network, Speaker: Dr. David Lok-kwan DAI, Venue: Tai Po	Miss Viviane LAM Tel: 2527 8452 1 CME Point
	FMSHK Officers' Meeting Organiser: The Federation of Medical Societies of Hong Kong, Venue: Gallop, 2/F., Hong Kong Jockey Club House, Shan Kwong Road, Happy Valley, Hong Kong	Ms. Sonia CHEUNG Tel: 2527 8898 Fax: 2865 0345
	HKMA Council Meeting Organiser: The Hong Kong Medical Association, Chairman: Dr. K Choi, Venue: HKMA Head Office, 5/F., Duke of Windsor Social Service Building, 15 Hennessy Road, Hong Kong	Ms. Christine WONG Tel: 2527 8285
2 WED 6:30 pm – 9:30 pm (9,16,23,30)	Certificate Course in Urology Nursing (Code No. TC-UN-11-01) Organiser: College of Nursing, Hong Kong	Secretariat Tel: 2572 9255 25 CNE/PEM Points
3 THU 1:00 pm 6:30 pm -10:00 pm 1:00 pm 1:00 pm 1:00 pm 7:00 pm – 10:00 pm (10,17,24,31)	HKMA YTM Community Network CME- Screening and Investigation of Prostate Diseases Organiser: HKMA YTM Community Network, Chairman: Dr. Chung-ping HO, MH, JP, Speaker: Dr. Byron Bok-wai WONG, Venue: Pearl Ballroom, 2/F, Eaton Smart, Hong Kong, 380 Nathan Road, Kowloon	Ms. Candice TONG Tel: 2527 8285 1 CME Point
	Practical Considerations in the Treatment of Osteoporosis and New Findings with Bisphosphonates Organiser: Osteoporosis Society of Hong Kong, Speaker: Prof. John EISMAN (Australia), Venue: Ballroom Four, 18/F, the Mira Hong Kong	Ms. Portia LEE Tel: 2606 8426 Fax: 2506 2537 Email: portia.lee@sanoof-aventis.com Website: http://www.oshk.org.hk
	HKMA – HK East Community Network – Quadrivalent HPV Prevention – More than Cervical Cancer Prevention Organiser: HKMA – HK East Community Network, Chairman: Dr. Bernard Bun-lap WONG, Speaker: Dr. Kar-fai TAM, Venue: HKMA Head Office, 5/F., Duke of Windsor Social Service Building, 15 Hennessy Road, Hong Kong	Ms. Candice TONG Tel: 2527 8285 1 CME Point
	HKMA – KLN East Community Network; HA – UCH; HKCFP – CME Course for Health Personnel 2011 Organiser: HKMA – KLN East Community Network, Chairman: Dr. Man-wo TSANG, Speaker: Dr. Chi-sang HUNG, Venue: Lei Garden Restaurant, APM, Kwun Tong (Pending)	Ms. Gary WONG Tel: 3513 5548 1 CME Point
	HKMA NTW CME – Certificate Course on Diabetes Mellitus (Session 1 – Session 3) Organiser: HKMA NTW Community Network, Chairmen: Dr. Alvin Kwok-wai CHEUNG; Dr. Charlie Kam-sun YAN & Dr. Aaron Fook-kay LEE, Speakers: Dr. Ernest Ngai-pang WONG & Dr. Gary Tin-choi KO, Venue: Plentiful Delight Banquet (元朗喜尚嘉喜酒家)1/F, Ho Shun Tai Building, 10 Sai Ching Street, Yuen Long, New Territories (Pending)	Miss Carman WONG Tel: 2527 8285
中醫藥理論精華與中西醫結合專題療講課程 Organiser: Hong Kong Association for Integration of Chinese-Western Medicine, Chairman: Dr. Edwin Chau-leung YU, Venue: SGN, G/F., Room 08, Queen Elizabeth Hospital, 30 Gascoigne Road, Kowloon	Miss Y.C. YEUNG Tel: 3119 1858 Fax: 2301 2414 27 CNE Points	
4 FRI 8:00 am - 9:00 am	Joint Surgical Symposium - Vascular Surgery and Recurrent Disease Organiser: Department of Surgery, The University of Hong Kong & Hong Kong Sanatorium & Hospital, Chairman: Dr. Lik-Cheung CHENG, Speakers: Prof. Stephen CHENG & Dr. Yiu-Che CHAN, Venue: Hong Kong Sanatorium & Hospital	Department of Surgery, Hong Kong Sanatorium & Hospital Tel: 2835 8698 Fax: 2892 7511 1 CME Point (Active)
5 SAT 2:00 pm (12,19,23)	MPS – Mastering Professional Interactions Organiser: The Hong Kong Medical Association, Speakers: Various, Venue: Kowloon & Hong Kong	Miss Viviane LAM Tel: 2527 8452 2.5 CME Points
6 SUN 2:00 pm	HKMAPS 1st Photo Competition & Sharing Session 2011 Organiser: The Hong Kong Medical Association Photographic Society, Venue: HKMA Head Office, 5/F., Duke of Windsor Social Service Building, 15 Hennessy Road, Hong Kong	Miss Alice TANG; Miss Sharon HUNG Tel: 2527 8285
7 MON 7:30 pm - 8:00 pm 8:00 pm (14,21,28)	(1) Heal Replacement of the Ureter (2) Management of Ureteric TCC in an Elderly Male Organiser: Hong Kong Urological Association, Chairman: Dr. Ida Soo-fan MAH, Speakers: Dr. Wai-sang WONG & Dr. Ida Soo-fan MAH, Venue: Seminar Room, G/F, Block A, Queen Elizabeth Hospital, Kowloon	Dr. Hing-hoi HUNG / Ms. Tammy HUNG Tel: 2958 6006 / 9609 6064 Fax: 2958 6076 / 8344 5115 1 CME Point (for The College of Surgeons of Hong Kong)
	HKMA Choir Rehearsal Organiser: The Hong Kong Medical Association, Venue: GPI, HKCC	Ms. Candy YUEN Tel: 2527 8285
8 TUE 1:00 pm	HKMA CMS 3X Briefing Session Organiser: HKMA CMS Club, Speaker: Mobigator Technology Group, Venue: The HKMA Dr. Li Shu Pui Professional Education Centre, 2/F, Chinese Club Building, 21-22 Connaught Road Central, Hong Kong	Miss Carman WONG Tel: 2527 8285
9 WED 7:30 am 1:00 pm (23,30) 6:00 pm	Hong Kong Neurosurgical Society Monthly Academic Meeting, Special Lecture – State of the Art Technology in Stereotactic RadioSurgery and Radiotherapy Organiser: Hong Kong Neurosurgical Society, Speaker: Miss Victry WONG, Venue: Seminar Room, Ground Floor, Block A, Queen Elizabeth Hospital	Dr. Gilberto LEUNG Tel: 2255 3368 Fax: 2818 4350 1.5 CME Points (The College of Surgeons of Hong Kong)
	HKMA CW&S CME – Certificate Course on Dermatology (Session 2) Organiser: HKMA - CW&S Community Network, Chairmen: Dr. Yim-kwai LAW; Dr. Sabrina Lai-ching HO & Dr. Ping-yin YIK, Speakers: Dr. Louis Tai-cho SHIH; Dr. Kuen-kong LO & Dr. William Yuk-ming TANG, Venue: The HKMA Dr. Li Shu Pui Professional Education Centre, 2/F, Chinese Club Building, 21-22 Connaught Road Central, Hong Kong	Miss Carman WONG Tel: 2527 8285 1 CME Point
	MPS – Mastering Your Risk Workshop Organiser: The Hong Kong Medical Association, Dr. Ka-lam HAU, Venue: Hong Kong	Miss Viviane LAM Tel: 2527 8452 2.5 CME Points
10 THU 2:00 pm	HKMA Structured CME Programme with Hong Kong Sanatorium & Hospital Year 2011 – Common Knee Injuries Organiser: The Hong Kong Medical Association, Chairman: Dr. Bun-lap WONG, Speaker: Dr. Jimmy Wai-kwok WONG, Venue: The 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 1 CME Point
11 FRI 1:00 pm	HKMA Shatin Doctors Network CME – Advances in the Management of Allergic Rhinitis Organiser: HKMA Shatin Doctors Network, Chairman: Wilson Yee-leung FUNG, Speaker: Prof. Gary Wing-kin WONG, Venue: 2/F, Jasmine Room, Royal Park Hotel, Shatin, NT	Miss Candice TONG Tel: 2527 8285



Date / Time	Function	Enquiry / Remarks
12 SAT 2:30 pm	Refresher Course for Health Care Providers 2010/2011 Organiser: The Hong Kong Medical Association, Dr. Tin-sik CHENG, Venue: OLMH	Miss Viviane LAM Tel: 2527 8452 2 CME Points
13 SUN 2:00 pm	MPS – Mastering Adverse Outcomes Workshop Organiser: The Hong Kong Medical Association, Speaker: Dr. Ares LEUNG, Venue: Kowloon	Miss Viviane LAM Tel: 2527 8452 2.5 CME Points
2:00 pm	HKMA Certificate Course on Family Medicine 2011 Organiser: The Hong Kong Medical Association, Speakers: Dr. Yee-shing CHAN & Dr. Hung-hing TSE, Venue: Queen Elizabeth Hospital, Kowloon	Miss Viviane LAM Tel: 2527 8452 3 CME Points
9:00 am	HKMA Photographic Society – The Magic of Migration (Photo Shooting Tour) Organiser: The Hong Kong Medical Association Photographic Society, Venue: Mai Po	Ms. Dorothy KWOK Tel: 2527 8285
15 TUE 8:00 pm – 10:00 pm	FMSHK Executive Committee Meeting Organiser: The Federation of Medical Societies of Hong Kong, Venue: Council Chambers, 4/F., Duke of Windsor Social Service Building, 15 Hennessy Road, Wanchai, Hong Kong	Ms. Sonia CHEUNG Tel: 2527 8898 Fax: 2865 0345
18 FRI 1:30 pm	HKMA Shatin Doctors Network CME – Common Eye Disease in GP Practice and Management Organiser: HKMA Shatin Doctors Network, Chairman: Dr. Wilson Yee-leung FUNG, Speaker: Dr. Albert WONG, Venue: 3/F, Jasmine Room, Royal Park Hotel, Shatin, NT	Ms. Candice TONG Tel: 2527 8285 1 CME Point
20 SUN 12:00 pm	HKMA Football Day 2011 Organiser: The Hong Kong Medical Association, Venue: CUHK	Ms. Dorothy KWOK Tel: 2527 8285
21 MON (28) 6:30 pm – 9:30 pm	Workshop of Touch & Infant Massage for Nursing Professionals (Code No. WS-TIM-11-01) Organiser: College of Nursing, Hong Kong	Secretariat Tel: 2572 9255 12 CNE/PEM Points
31 THU 8:00 pm	HKMA Choir Family Concert Organiser: The Hong Kong Medical Association, Venue: Theatre, Sheung Wan Civic Centre	Ms. Candy YUEN Tel: 2527 8285

Course / Meeting

12-14/5/2011

18th Asian Congress of Surgery & 37th Philippine College of Surgeons Mid-year Convention

Organiser: Asian Surgical Association, Venue: Waterfront Cebu City Hotel & Casino, Lahug, Cebu City, Philippines, Enquiry: Congress Secretariat, Tel: (632) 9274973-74; (632) 9281083; (632) 9292359, Fax: (632) 9292297, E-mail: secretariat@acs2011.org, Website: <http://www.acs2011.org>

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

Date	Course No	Course Name	Target Participants	CME/CNE
01/04/2011 - 13/05/2011	C173	Certificate Course on Management of Common Psychiatric Disorders 2011	Medical and Health Professionals	9 CNE Points; CME/CPD Accreditation in application
06/04/2011 - 11/05/2011	C176	Certificate Course on Paediatric Nephrology 2011	General Practitioners, Health Care Providers and Public Who Are Interested in Common Kidney Problems in Children	9 CNE Points; CME/CPD Accreditation in application



Society News

News from Member Societies

- Hong Kong Society of Cytology**
Updated office-bearers for the year 2010-2011 are as follows: President: Dr. Yue CHENG; Honorary Secretary: Ms. Kit-ye LEE; Honorary Treasurer: Ms. Yin-ye SO
- The Hong Kong College of Family Physicians**
Updated office-bearers for the year 2010-2011 are as follows: President: Dr. Ruby LEE; Honorary Secretary: Dr. Tung-chi LAW; Honorary Treasurer: Dr. Ho-lim LAU
- The Hong Kong College of Psychiatrists**
Updated office-bearers for the year 2010-2012 are as follows: President: Prof. Linds LAM; Honorary Secretary: Dr. W. H. CHEUNG; Honorary Treasurer: Dr. Victoria TANG

The FMSHK would like to send its congratulations to the new office-bearers and look forward to working together with the societies.



Answer to Dermatological Quiz

1. Isotretinoin-induced pyogenic granuloma-like lesions
2. The main differential diagnosis is acne fulminans. Other possibilities include gram-negative folliculitis and pyoderma, although these usually do not give rise to the haemorrhagic lesions.
3. This uncommon side-effect of oral isotretinoin was more frequently seen in patients receiving high dose regimen in the past. In fact, it is much less seen in recent years as low-dose regimen of oral isotretinoin is more frequently used now in the treatment of acne. To minimise the chance of these exuberant granulation tissues, one can use a lower starting dose in patients presented with markedly inflammatory acne, together with the cover of an oral macrolide during the first month of treatment. Once the condition is stable, the dosage of oral isotretinoin can then be increased if necessary. In acne fulminans, concomitant use of prednisolone is often needed, especially in the initial phase.
4. Strong teratogenicity, hepatic dysfunction like elevated liver enzymes, hyperlipidaemia, skeletal abnormalities like DISH (diffuse idiopathic skeletal hyperostosis) or rarely benign intracranial hypertension (pseudotumor cerebri) should be watched out. In recent years, anecdotal reports suggested a causal association between oral isotretinoin and severe depression has led to new blackbox warning and medicolegal implications of this drug. However, this has not been proven by subsequent more evidence-based researches. A systemic review of studies comparing depression before and after treatment with isotretinoin did not find a statistically significant increase in this morbidity.¹ In addition, a large population-based cohort study did not show evidence for a causal link between isotretinoin exposure and an increased risk of newly diagnosed depression, suicidal behaviour, psychosis or other psychiatric disorders.² In practice, psychiatric morbidities are far more common in patients with uncontrolled or severe acne than those treated with oral isotretinoin.

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Certificate Course on Current Management of Common Head & Neck Cancers

Course No. C172

CME/CNE Course

Jointly organised by



The Federation of
Medical Societies of
Hong Kong



Hong Kong
Head and Neck Society

Objectives:

State of art cancer treatment nowadays involves a multi-disciplinary approach. The management of Head and Neck cancer requires a collaboration of surgeons, clinical oncologist and radiologists. With the advances in surgical and radiotherapy technique and technology, survival of patients has improved across time and at same time, organ preservation is achieved for selected patients. The aim of this course has brought together local leading experts to share their experiences in combined modality management of malignancies of common head and neck cancer and we look forward to an exciting and invigorating meeting for the audiences.

Date	Topics	Speakers
5 May 2011	Understanding the Challenges in the Fight against Nasopharyngeal Cancer Diagnosis & Salvage of Nasopharyngeal Carcinoma: role of ENT Head and Neck surgeon	Dr. Anne Wing-mui LEE Chief of Service, Department of Clinical Oncology, Pamela Youde Nethersole Eastern Hospital Prof. William I. WEI Head, Department of Surgery and Director, Li Shu Pui ENT Head & Neck Surgery Centre, Hong Kong Sanatorium & Hospital; Li Shu Pui Professor of Surgery, Chair in Otorhinolaryngology, Department of Surgery, Queen Mary Hospital, The University of Hong Kong
12 May 2011	Post operative Management and Monitoring of well differentiated Thyroid Cancer Carcinoma of Thyroid	Dr. Sin-ming CHOW Private Practice, Specialist in Clinical Oncology Dr. Chung-yau LO Private Practice, Specialist in Surgery Honorary Professor, Department of Surgery and Honorary Consultant, Hong Kong West Cluster, Department of Surgery, Queen Mary Hospital
19 May 2011	Radiotherapy for Tongue Cancers Management of Tongue Cancer	Dr. Roger Kai-cheong NGAN Consultant, Department of Clinical Oncology, Queen Elizabeth Hospital Prof. Po-wing YUEN Private Practice, Specialist in ENT Surgery
26 May 2011	Updates on Management of Salivary Gland Carcinoma Surgical Aspects on Carcinoma of Salivary Gland	Dr. Kwok-hung AU Associate Consultant, Department of Clinical Oncology, Queen Elizabeth Hospital Dr. Chiu-ming HO Private Practice, Specialist in Plastic Surgery Consultant (part-time), Department of Surgery, Tuen Mun Hospital
2 June 2011	Update on Non-surgical Management of Larynx Cancer Management of Cancer of the Larynx: an ENT surgeon's perspective	Dr. Kwok-hung YU Consultant, Department of Clinical Oncology, Prince of Wales Hospital Dr. Kwong-hon MA Cluster Chief of Service, Department of ENT, Yan Chai Hospital
9 June 2011	Surgical Treatment of Facial Skin Cancers Management of Head & Neck Skin Cancer by Radiotherapy	Dr. Wing-yung CHEUNG President (HK-INS), Chairman (Plastic Surgery Board), Consultant (Plastic and HN Surgery), Kwong Wah Hospital Dr. Anthony Chi-ho YING Private Practice, Specialist in Clinical Oncology

Time : 7:00 p.m. – 8:30 p.m.

Venue : Lecture Hall, 4/F., Duke of Windsor Social Service Building,
15 Hennessy Road, Wanchai, Hong Kong

Language Media : English (Supplemented with Cantonese)

Course Fee : HK\$750 (6 sessions)

Certificate : Awarded to participants with a minimum attendance of 70%

Enquiry : The Secretariat of The Federation of Medical Societies of Hong Kong
Tel.: 2527 8898 Fax: 2865 0345 Email: info@fmshk.org

CME / CPD Accreditation in application

A total of **9 CNE** points for the whole course and the points will be awarded according to the number of hours attended.

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