VOL.13 NO.8 AUGUST 2008

香港醫訊
THE HONG KONG MEDICAL DIARY

OFFICIAL PUBLICATION FOR THE FEDERATION OF MEDICAL SOCIETIES OF HONG KONG

www.fmshk.org

ISSN 1812 - 1691

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INDICATIONS : TYKERB is indicated in combination with capecitabine for the treatment of patients with advanced or metastatic breast cancer whose tumours overexpress HER2 and who have received prior therapy including an anthracycline, a taxane and trastuzumab. **DOSAGE AND ADMINISTRATION :** The recommended dose is 1,250 mg (5 tablets) given orally once daily on Days 1-21 continuously in combination with capecitabine 2,000 mg/m2/day (administered orally in 2 doses approximately 12 hrs apart) on Days 1-14 in a repeating 21 day cycle. TYKERB should be taken at least 1 hr before or 1 hr after a meal and the dose should be once daily; dividing the daily dose is not recommended. Capecitabine should be taken with food or within 30 minutes after food. If a day's dose is missed, the patient should not double the dose the next day. Treatment should be continued until disease progression or unacceptable toxicity occurs. Prior to the initiation of treatment and during treatment with TYKERB, left ventricular ejection fraction (LVEF) must be evaluated and monitored to ensure that LVEF is within the institutional limits of normal. Modify dose of TYKERB for cardiac and other toxicities, hepatic impairment, concomitant use of strong CYP3A4 inhibitors or inducers, and interstitial lung disease/pneumonitis. **CONTRAINDICATIONS :** None. **WARNINGS AND PRECAUTIONS :** TYKERB has been reported to decrease LVEF. Caution should be taken if TYKERB is to be administered to patients with conditions that could impair left ventricular function. LVEF should be evaluated in all patients prior to initiation of treatment and during treatment. TYKERB has been associated with reports of interstitial lung disease and pneumonitis. Patients should be monitored for pulmonary symptoms indicative of interstitial lung disease/pneumonitis. Caution is warranted if prescribed to patients with moderate or severe hepatic impairment. Diarrhoea, including severe diarrhoea, has been reported. Proactive management of diarrhoea with anti-diarrhoeal agents is important. Severe cases of diarrhoea may require administration of oral or intravenous electrolytes and fluids, and interruption or discontinuation of TYKERB. Concomitant treatment with inhibitors or inducers of CYP3A4 should proceed with caution due to risk of increased or decreased exposure to TYKERB, respectively. Coadministration of TYKERB with medications with narrow therapeutic windows that are substrates of CYP3A4 or CYP2C8 should be avoided. **INTERACTIONS :** TYKERB is predominantly metabolised by CYP3A. Therefore, inhibitors or inducers of these enzymes may alter the pharmacokinetics of TYKERB. Coadministration of TYKERB with known inhibitors or inducers of CYP3A4 should proceed with caution and clinical response and adverse events should be carefully monitored. If patients must be coadministered a strong CYP3A4 inhibitor, a dose reduction to 500 mg/day of TYKERB is predicted to adjust the TYKERB AUC to the range observed without inhibitors and should be considered. However, there are no clinical data with this dose adjustment in patients receiving strong CYP3A4 inhibitors. If the strong inhibitor is discontinued, a washout period of approximately 1 week should be allowed before the TYKERB dose is adjusted upward to the indicated dose. If patients must be coadministered a strong CYP3A4 inducer, the dose of TYKERB should be titrated gradually from 1,250 mg/day up to 4,500 mg/day based on tolerability. This dose of TYKERB is predicted to adjust the TYKERB AUC to the range observed without inducers and should be considered. However, there are no clinical data with this dose adjustment in patients receiving strong CYP3A4 inducers. If the strong inducer is discontinued the TYKERB dose should be reduced over approximately 2 weeks to the indicated dose. TYKERB inhibits CYP3A4 and CYP2C8 in vitro at clinically relevant concentrations. Caution should be exercised when dosing TYKERB concurrently with medications with narrow therapeutic windows that are substrates of CYP3A4 or CYP2C8. TYKERB is a substrate for the transport proteins Pgp and BCRP. Inhibitors and inducers of these proteins may alter the exposure and/or distribution of TYKERB. TYKERB inhibits the transport proteins Pgp, BCRP and OATP1B1 in vitro. The clinical relevance of this effect has not been evaluated. It cannot be excluded that TYKERB will affect the pharmacokinetics of substrates of Pgp (e.g. digoxin), BCRP (e.g. topotecan) and OATP1B1 (e.g. rosuvastatin). Concomitant administration of TYKERB with capecitabine or trastuzumab did not meaningfully alter the pharmacokinetics of these agents (or the metabolites of capecitabine) or TYKERB. The bioavailability of TYKERB is affected by food. **PREGNANCY AND LACTATION :** TYKERB can cause fetal harm when administered to a pregnant woman. There are no adequate and well-controlled studies in pregnant women. Women should be advised not to become pregnant when taking TYKERB. TYKERB was not teratogenic when studied in pregnant rats and rabbits but caused minor abnormalities at doses which were maternally toxic. It is not known whether TYKERB is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for adverse reactions in breast-feeding infants from TYKERB, a decision should be made whether to discontinue nursing or to discontinue the drug. it is recommended that breast-feeding be discontinued in women who are receiving therapy with TYKERB. **ADVERSE REACTIONS :** Decreased LVEF. Diarrhoea. Anorexia. Interstitial lung disease/pneumonitis. Nausea. Vomiting. Hyperbilirubinaemia. Rash. Fatigue. Dyspepsia. Dry skin. Stomatitis, constipation, abdominal pain. Palmar-plantar erythrodysaesthesia. Mucosal inflammation. Pain in extremity, back pain. Headache. Insomnia. **OVERDOSE :** There is no known antidote for overdoses of TYKERB. The maximum oral dose of TYKERB that has been administered in clinical trials is 1800 mg once daily. More frequent ingestion of TYKERB could result in serum concentrations exceeding those observed in clinical trials, therefore missed doses should not be replaced, and dosing should resume with the next scheduled daily dose. There has been a report of one patient who took an overdose of 3000 mg of TYKERB for 10 days and suffered grade 3 diarrhoea and vomiting on day 10. The symptoms resolved following IV hydration and interruption of treatment with TYKERB and letrozole. TYKERB is not significantly renally excreted and is highly bound to plasma proteins, therefore haemodialysis would not be expected to be an effective method to enhance the elimination of TYKERB.

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Demethylation Therapy in Haemic Cancer

Dr. James CS Chim

Editor

Dr. James CS Chim

Major advances have been made in the last decade on the molecular pathogenesis of cancers. Activation of oncogenes and inactivation of tumour suppressor genes have been elucidated in many forms of cancers, opening up a map of molecular pathways leading to unchecked cellular proliferation, impaired apoptosis and failure of cellular differentiation, and hence cancer formation. Oncogenes are usually activated by a gain-of-function mutation, while tumour suppressor genes are inactivated by a loss-of-function mutation. (Figure 1)

For instance, some haematological cancers are initiated by chromosomal translocation leading to activation of oncogenes. An example is the constitutive activation of cytosolic tyrosine kinase ABL by a chromosomal translocation t(9;22) in chronic myeloid leukaemia (CML), which is the basis of success of tyrosine kinase inhibitors in CML. On the other hand, Epidermal Growth Factor (EGF) (the ligand) and its cognate receptor, EGF Receptor (EGFR), together with the receptor-associated tyrosine kinase, constitute a system of utmost importance in the pathogenesis of most cancers of epithelial origin. Moreover, while haematological cancers naturally spread by the bloodstream, solid cancers spread by local lymphatics to regional lymph nodes before invasion of the blood stream and hence distant metastasis. Therefore, while there are similarities between haemic and solid cancers, there are also genetic alterations that are specific to solid or haematological cancers.

Recently aberrant gene promoter methylation has been shown to result in gene silencing, and hence serves as an alternative mode of gene inactivation. Indeed, some tumour suppressor genes involved in the regulation of the cell cycle (CDKN2A and B), genes protecting cells from oncogenic transformation (P14, DAP kinase) and genes important in cellular differentiation (soluble Wnt inhibitors) have been shown to be inactivated by gene promoter hypermethylation. (Figure 2) In MDS, CDKN2B (alias p15) is hypermethylated and silenced. Interestingly, unlike gene mutation, which is irreversible, gene hypermethylation can be reversed with hypomethylating agents such as Vidaza or Decitabine. Indeed, both Vidaza and Decitabine have been shown to be effective in MDS.

With the knowledge of these molecular pathways, one will envisage that either therapeutic antibodies or small molecules that target the EGFR or the receptor-associated tyrosine kinase will lead to downregulation of growth and survival signals in the cancer cell, and hence apoptosis of the cancer cells. After the first success from rituximab in B-cell lymphomas and imatinib in CML, there is a massive explosion of both therapeutic antibodies and small molecules in solid cancers. The antibodies include bevacizumab (Avastin) in both breast and colon cancer, trastuzumab (Herceptin) in breast cancer and Cetuximab (Erbitux) in colon cancer targeting VEGF, HER2 and EGFR respectively. Therefore, these antibodies target angiogenesis or cellular proliferation associated with growth

receptor-mediated cell signaling. On the other hand, small molecules targeting receptor-associated tyrosine kinase or multiple kinases are also found to be effective in multiple solid cancers, which include Gefitinib (Iressa) and Erlotinib (Tarceva) in bronchogenic cacrcinoma, sorafenib in renal cell and recently hepatocellular carcinoma, and sunitinib in renal cell cancers. In particular, synergistic effect may be derived when conventional chemotherapy is combined with some of these targeted therapies. Therefore, advances in cancer therapy is evolving with high-speed in recent years.

On the other hand, another important advance is made in the advent of more potent anti-fungal therapeutic agents. Treatment of acute leukaemia is often complicated with prolonged neutropenia leading to invasive fungal infections such as pulmonary aspergillosis or invasive candidiasis. The development of these fungal infections poses major difficulty to further intensive chemotherapy, leading to suboptimal treatment. Conventional treatment with amphotericin B is effective, but is associated with frequent side-effects like infusion toxicities and renal impairment. The advent of new anti-fungal agents including liposomal amphotericin B, caspofungin, voriconazole and recently posaconazole is important as they have a broad-spectrum of anti-fungal activity and can be used even in the presence of renal impairment in contrast to conventional amphotericin B, in which the dose has to be reduced.

Therefore, in the field of solid and haematological cancers, major advances have been made. In this issue of the Medical Diary, the advances of targeted therapy in breast, lung and liver cancers, the use of hypomethylating agents in MDS, and new anti-fungal agents are discussed.

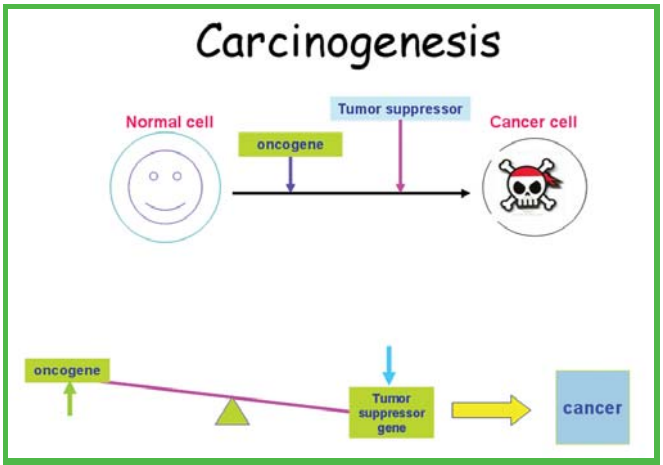


Figure 1 illustrated the mechanism of carcinogenesis. Normally tumour suppressor genes will be activated if oncogenic transformation is detected in the cell. (Upper panel) Therefore, cancer formation usually results from activation of oncogenes together with inactivation of tumour suppressor genes.

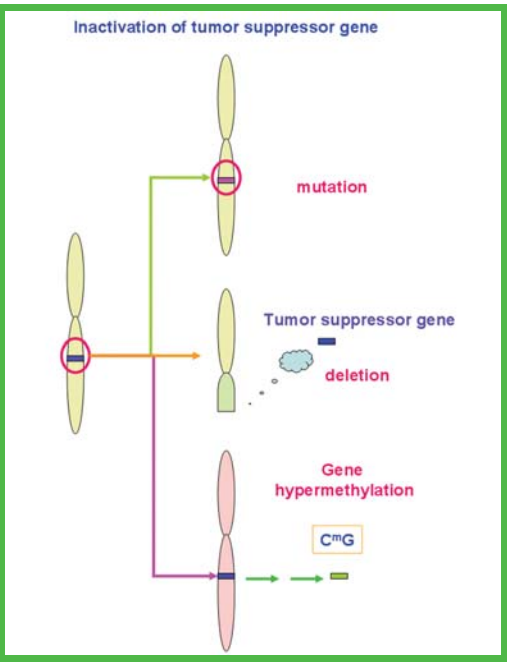
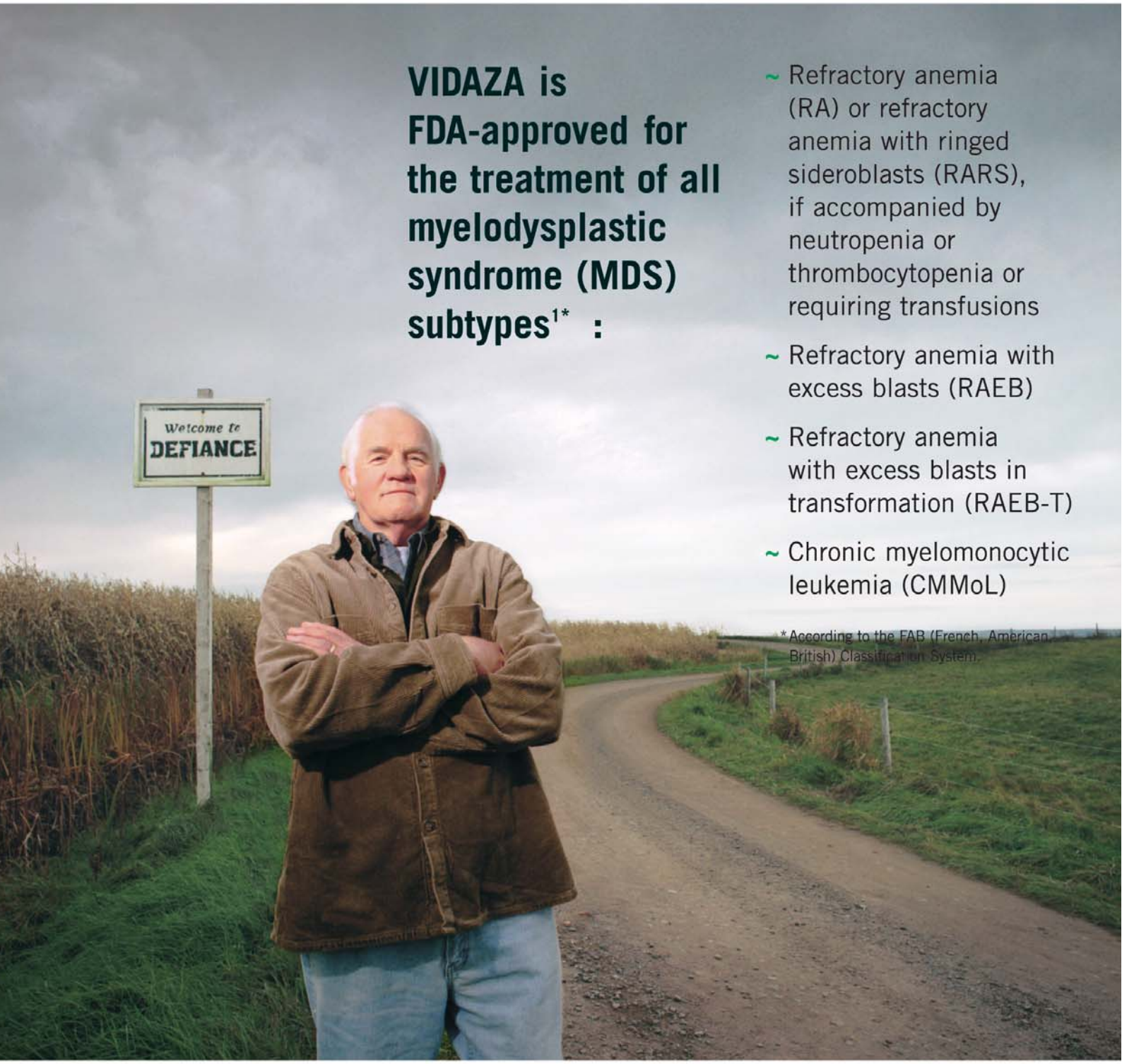


Figure 1 illustrated the mechanism of carcinogenesis. Normally tumour suppressor genes will be activated if oncogenic transformation is detected in the cell. (Upper panel) Therefore, cancer formation usually results from activation of oncogenes together with inactivation of tumour suppressor genes.

The First and Only Treatment Proven to Fight MDS



VIDAZA is FDA-approved for the treatment of all myelodysplastic syndrome (MDS) subtypes[1*] :

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- Refractory anemia with excess blasts in transformation (RAEB-T)
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*According to the FAB (French, American, British) Classification System.

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Epigenetic Therapy Comes of Age: Waking Up Silenced Tumour Suppressor Genes in Myelodysplastic Syndrome

Dr. James CS Chim

MB.Ch.B., MD, Ph.D., MRCP(UK), FRCP(London, Edinburgh, Glasgow), FRCPath, FACP, FHKCP, FHKAM
Associate Professor, Department of Medicine, Queen Mary Hospital, The University of Hong Kong

Dr. James CS Chim

This article has been selected by the Editorial Board of the Hong Kong Medical Diary for participants in the CME programme of the Medical Council of Hong Kong (MCHK) to complete the following self-assessment questions in order to be awarded one CME credit under the programme upon returning the completed answer sheet to the Federation Secretariat on or before 31 August 2008.

Myelodysplastic Syndrome

Myelodysplastic Syndrome (MDS) is a group of clonal stem cell disorders with ineffective haematopoiesis of the bone marrow.[1-2] Clinically MDS is characterised by peripheral cytopenia with a hypercellular and dysplastic bone marrow. Patients usually presents with complications of cytopenia including symptomatic anaemia, bleeding from thrombocytopenia or infections from neutropenia. MDS comprises a group of disorders with variable cytopenia and a variable amount of myeloblasts, and hence a variable risk of leukaemic transformation. In French-American-British (FAB) classification,[3] MDS comprises 5 disorders based on the severity of cellular dysplasia, the nature of erythroid dysplasia, the amount of blast cells and presence of monocytes including refractory anaemia (RA), refractory anaemia with ringed sideroblasts (RARS), chronic myelomonocytic anaemia (CMML), refractory anaemia with excess blasts (RAEB) and refractory anaemia with excess blasts in transformation (RAEB-t).[3] Frequent karyotypic aberrations include chromosomal loss such del(5q) or 5q-, del(7q) 7q- or chromosomal gain such as trisomy 8. In general, normal karyotype or 5q- are associated with good prognosis while complex karyotypic abnormality and chromosomal loss of 7q- with poor prognosis. Moreover, based on the amount of blasts, severity of cytopenia and the type of chromosomal aberration, patients with MDS can be stratified into different risk groups by the International Prognostic Scoring System (**Table 1**).[4] In general, based on the median survivals, MDS can be classified into high-risk or low-risk with median survivals <5 or >5 years. High-risk MDS include RAEB and RAEB-t and low-risk MDS includes RA or RARS. (Figure 1)

Treatment may be directed towards killing the blasts by conventional chemotherapy (such as cytarabine and daunorubicin used in acute myeloid leukaemia) or ameliorating the pancytopenia by cytokine therapy such G-CSF or erythropoietin. However, the only modality of treatment that may render a cure is bone marrow transplantation (BMT) in the form of high-dose therapy with allogeneic haematopoietic stem cell rescue (allo-BMT). Recently, the advent of non-myeloablative allogeneic BMT or mini-allo-BMT has allowed more elderly MDS patients to receive BMT.[5] On the other hand, certain MDS subtypes may benefit from other therapies. For instance, patients with sideroblastic anaemia may respond to high-dose of pyridoxine and patients with hypoplastic MDS may respond to immunosuppressive therapy such as cyclosporine A or anti-thymocyte globulin (ATG.).[5] A special syndrome of MDS, 5q- syndrome, in which 5q- is the sole cytogenetic aberration, is characterised by refractory anaemia with thrombocytosis in a middle or old-aged female.[6] Interestingly, patients with 5q- syndrome respond favourably to an immunomodulatory agent, lenalidomide, which is a derivative of thalidomide. However, 5q- syndrome is an uncommon subtype amongst MDS. Despite the large number of treatment options, the majority including conventional chemotherapy are largely palliative, and do not lead to a cure. Indeed, the majority of the current treatments may result in improvement in blood counts but do not alter the natural history of the disease especially leukaemic transformation. Moreover, while allogeneic BMT is potentially curative, only young patients with an HLA-identical sibling can be considered because of the inherent risk of graft-versus-host disease and infective complications, and hence is not applicable to the majority of elderly MDS patients.[7] Therefore, an alternative treatment strategy especially one that may reduce the risk of leukaemic transformation is urgently needed.

DNA Methylation

DNA methylation, catalysed by DNA methyltransferase, involves the addition of a methyl group to the carbon 5 position of the cytosine ring in the CpG dinucleotide and results in the generation of methylcytosine.[8,9] (Figure 2) Methylation of cytosine to methylcytosine in DNA is a heritable genetic alteration during cell replication in the absence of any change in the genetic sequence. In the normal mammalian genome, CpG rich regions (CpG islands) exist and these are often found within the promoter of genes. These promoter-associated CpG islands that serve as gene promoters in about 40%-50% of human genes are protected from methylation, rendering these genes a transcription-ready state.[8,9] The only exceptions are the promoters of selectively silenced alleles in imprinted autosomal genes, and the gene promoters of the inactivated X-chromosome of females. By contrast, CpG islands of various genes have been shown to be

aberrantly methylated (***hypermethylated***) in cancer. Importantly, hypermethylation of gene promoters has been shown to result in repression of gene transcription and gene silencing, thus serving as an alternative mechanism of gene inactivation. The mechanism of gene silencing has recently been shown to be related to the recruitment of repressor protein complex containing histone deacetylase and other repressor proteins such as methyl-cytosine binding protein (MBP), resulting in de-acetylation of histone covered by the hypermethylated promoter DNA. This results in a closed chromatin structure that precludes access of the active transcription complex and hence ***gene silencing***. However, the mechanism of these de novo gene promoter hypermethylation is largely unknown, and is the topic of intensive research.

Promoter Hypermethylation in Haemic Malignancies

In haemic malignancies, methylation of tumour suppressor genes including CDKN2B (alisas P15), CDKN2A (alias, P16), P73, DAP kinase, SHP1 has been reported in various haematological malignancies.[9-19] These genes either regulate progression of the cell cycle (CDKN2A and B), and hence cellular proliferation, the induction of apoptosis upon detection of oncogeneic transformation (P14, P73 and DAP kinase) or intracellular JAK/STAT signalling such as SHP1.[9-19] For instance, P15 but not P16 is frequently methylated in acute leukaemia but both P15 and P16 are frequently methylated in NHL, MM and CLL. SHP1 is frequently methylated in literally all types of haemic cancers but p73 only methylated in Burkitts' lymphoma. Therefore, there is heterogeneity in the profile of gene methylation in different types of haemic malignancies. Importantly, re-expression of these genes has been shown in vitro by 5-AzaCytidine treatment to result in growth inhibition and/or apoptosis. Moreover, the high frequency of methylation of certain genes in some haemic malignancies suggests that gene hypermethylations are probably early events in the pathogenesis of these cancers. For instance, P15 is methylated in >70% of acute leukaemia including APL, which carries the PML-RARA fusion gene, suggesting p15 gene methylation might collaborate with t(15;17) in leukaemogenesis.[15] Similarly, in mantle cell lymphoma with upregulation of cyclin D1, SHP1 has been shown to be methylated in >80% of cases, suggesting that SHP1 methylation might be an early event collaboration with cyclin D1 dysregulation in lymphomogenesis. On the other hand, methylation of some genes is associated with disease progression, e.g. P16 methylation at relapse but not diagnosis in acute leukaemia,[16] and Abl methylation during progression to accelerated phase or blastic transformation in CML. Furthermore, certain methylated genes are associated with prognosis and survival. For instance, P15 methylation was shown to confer an inferior DFS in APL.[13,15,18] Therefore, aberrant gene promoter methylation is potentially important in either pathogenesis, progression and prognosis. Therefore, treatments which may reverse these methylation alterations are potentially beneficial in haematological cancers.

Therapeutic DNA Methyltransferase Inhibitors

In clinical practice, two cytidine analogues, azacytidine (5-azacytidine; ***Vidaza*** Pharmion, USA) and Decitabine (5-aza-2'-deoxycytidine; DCB, ***Decogen***, SuperGen, USA), have been shown to carry hypomethylating properties by inhibiting DNA methyltransferase.[20] In cancers, inhibition of DNA methylation reactivates the expression of tumour suppressor genes that have undergone epigenetic silencing, and leads to apoptosis of cancer cells.

In MDS, CDKN2B (alias, P15), a cyclin-dependent kinase inhibitor that negatively regulates the cell cycle and hence cellular proliferation, has been shown to be hypermethylated in marrow stem (CD34+) cells in patients with MDS,[21] and is potentially important in its pathogenesis. Therefore, clinical trials have been conducted to test the efficacy of these DNA methyltransferase (DNMT) inhibitors in MDS, and hence the concept of hypomethylating therapy. At present both Vidaza and Decitabine are approved for the treatment of MDS.

Vidaza in MDS

After promising results from 2 phase II studies by the CALGB in patients with RAEB, RAEB-T and CMML, a phase III study using Vidaza in the treatment of MDS has been published in 2002.[22] Recently, data from a phase III Cancer and Leukaemia Group B (CALGB) 9221 study led to the approval of Vidaza by the US Food & Drug Administration (FDA). In the study, MDS patients were randomised to receive Vidaza and best supportive care. Vidaza was given subcutaneously at the dose of 75mg/d x 7 days at 28-day cycles. Moreover, patients in the BSC arm in whom the disease progressed might cross-over to receive Vidaza after 4 months. Responses (complete, partial or haematological improvement) were assessed after 4 cycles of treatment. Patients in complete remission would receive 3 further cycles of Vidaza treatment. 191 patients were recruited. There was a significant improvement in overall response in the Vidaza arm compared with the BSC arm (ORR 60% Vidaza arm versus 5% BSC arm, $p<0.001$). Complete and partial remissions occurred only in the Vidaza but not the BSC arm. The frequency of leukaemic transformation was also significantly reduced in the Vidaza arm (15% versus 38%). Because of the cross-over nature of the study, a landmark study was conducted to assess the impact of Vidaza treatment on survival, which showed median survival of 18 and 6 months in the Vidaza and BSC arms ($p=0.03$). Moreover, the improved survival was associated with an improvement in the quality of life.

Decitabine in MDS

On the other hand, phase I/II studies of decitabine (DCB) in high-grade MDS has also been conducted.[23] O'Brien et al showed that in 52 patients with high-grade MDS, an overall response was observed in 81% of patients with 35% CR rate. Wijermans et al showed that in 66 patients with intermediate- to high-grade MDS,

DCB (at 45mg/m²/d x 3 days every 6 weeks), overall response rate was 49% with 20% being CR.[23] These encouraging data confirmed the efficacy of DCB in MDS, which accumulated to a phase III study where 170 patients with MDS were randomised to receive low-dose DCB (15mg/m² every 8 hourly x 3 days, repeated every 6 weeks) or best supportive care (BSC).[24] The study showed a superior overall response rate of 30% (with 9% CR) in the decitabine arm compared with 7% (no CR or PR) in the BSC arm (p<.001). There was a non-significant delay in leukaemic transformation (time to leukaemia was 12 months in the decitabine arm and 8 months in the BCS arm) but a significant delay in those with high-risk MDS. Moreover, patients treated with decitabine had improved quality of life, and cytogenetic remission was shown in some cases. However, there was no difference in overall survival.[24] On the other hand, comparison with a historical control group of high-grade MDS patients treated with conventional chemotherapy, who were matched in age, sex, cytogenetic findings and international prognostic scoring system with 115 MDS patients treated with low-dose decitabine, showed that there was an obvious overall survival advantage in high-grade MDS patients receiving decitabine (median overall survival: 22 months versus 12 months, p<0.001).[25] Therefore, possible survival advantages may be detected in future prospective trials. Moreover, there are recent data that patients who progressed or failed to respond to Vidaza did respond to decitabine.[26]

Common Features in Both DNMT Inhibitor Trials

First, a response was only demonstrated after several cycles of treatment. Therefore, had the patients been considered non-responding and taken off study after 2 cycles, the response would not have been captured. For instance, the median time to response was > 3 cycles in the CALGB9221 trial, and >2 cycles in the Decitabine trial. Only CR or PR occurred in the DNMT inhibitor arm while only soft end-point such as haematological improvement could occur in the best supportive care arm. Both studies were associated with improved QOL in patients receiving DNMT inhibitors. Moreover, delay in leukaemia transformation was observed in the Vidaza trial,[22] and in the subgroup of high-risk MDS in the Decitabine trial.[24] Major side-effects from these DNMT inhibitors (Vidaza & decitabine) were worsening cytopenia.

Future

Vidaza can be administered in an out-patient setting, and has been shown to be effective in all MDS subtypes, and results in delay of leukaemic transformation, and likely improvement in overall survival. Decitabine is an alternative to Vidaza but impact on survival remains to be seen in further analysis of the phase III study.

On the other hand, from the mechanistic point of view, gene silencing from promoter hypermethylation is enhanced by further modification of histone molecules, primarily deacetylation of the regional histone molecules, where the stretch of hypermethylated promoter DNA covers. Therefore, one would anticipate a synergistic effect if histone decaetylase inhibitors are added to these DNMT inhibitors so that both DNA methylation and histone deacetylation are reversed, and hence render an open chromatin in the promoter concerned, and allow access of transcription complex to the gene promoter. Indeed, clinical trials incorporating both DNMT inhibitors and histone deacetylase inhibitors are on-going, and the results are eagerly awaited.

The advent of the hypomethylating treatment in MDS is important in the following ways. First, MDS is a disease of the elderly who generally cannot tolerate intensive chemotherapy, and hence demethylating therapy is particularly appealing as they do not mediate their activity by cytotoxicity. Second, unlike mutations in cancers, which are irreversible, gene promoter hypermethylation is a reversible process, and hence is an important modality of therapy to the treatment of cancers.

Table 1.

International Prognostic Scoring System (IPSS)

	Score Value				
Prognostic Variable	0	0.5	1.0	1.5	2.0
BM blasts (%)	<5	5-10	—	11-20	21-30
Karyotype*	Good	Interm.	Poor		
Cytopenias	0/1	2/3			

Good:	Normal - y del (5q) del (20q)
Poor:	Complex (≥ 3 abn) Chr. 7 abn
Int.:	Other

Low :	0
Int-1 :	0.5 - 1.0
Int-2 :	1.5 - 2.0
High :	≥ 2.5

Greenberg et al. Blood '97

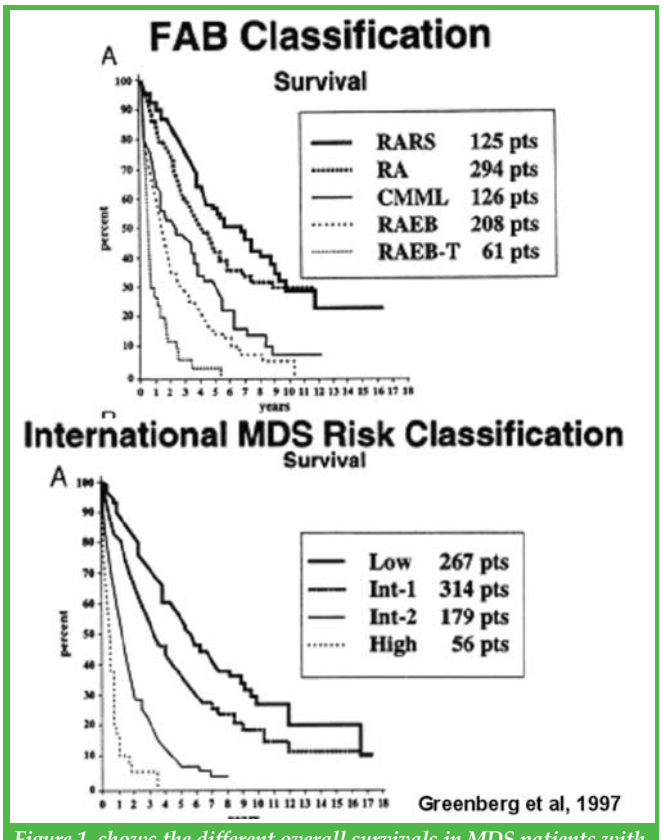

Figure 1. shows the different overall survivals in MDS patients with different FAB subtypes (upper panel), and IPSS risk-groups (lower panel). The figure is adapted from the paper by Greenberg et al, Blood, 1998.

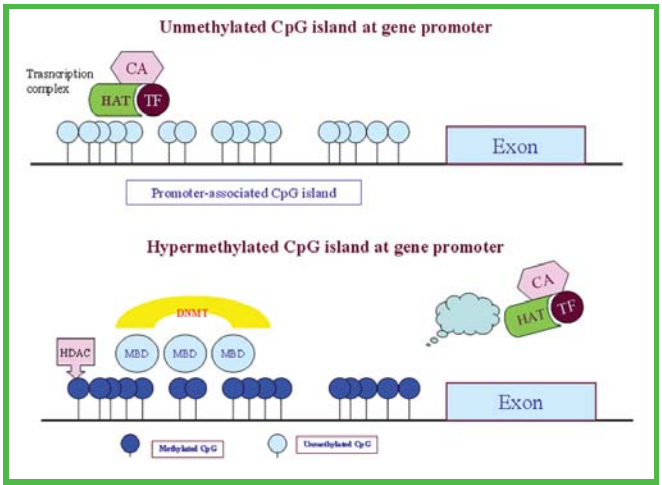

Figure 2. shows the binding of the promoter-asociated CpG island by a transcription complex in unmethylated promoter, but the exclusion of transcription complex in a promoter that is aberrantly methylated

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MCHK CME Programme Self-assessment Questions

Please read the article entitled "Epigenetic Therapy Comes of Age: Waking Up Silenced Tumour Suppressor Genes in Myelodysplastic Syndrome" 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 August 2008. 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. MDS is characterised by peripheral cytopenia with a hypercellular bone marrow

2. There are 5 disorders under the FAB classification

3. The risk of lung cancer is increased in patients with MDS

4. The risk of leukaemia is NOT increased in MDS

5. Allogeneic bone marrow transplantation is the only form of curative treatment in MDS
6. Promoter-associated CpG islands are usually unmethylated, and hence render the gene transcriptional ready status
7. Hypomethylating treatment refers to the reversal of aberrant methylation of promoter-associated CpG islands of tumour suppressor gene
8. Azacytidine (Vidaza) is a hypomethylating agent
9. Azacytidine (Vidaza) is usually given by subcutaneous injection
10. Decitabine is usually administered by the intravenous route

ANSWER SHEET FOR AUGUST 2008

Please return the completed answer sheet to the Federation Secretariat on or before 31 August 2008 for documentation. 1 CME point will be awarded for answering the MCHK CME programme (for non-specialists) self-assessment questions.

Epigenetic Therapy Comes of Age: Waking Up Silenced Tumour Suppressor Genes in Myelodysplastic Syndrome

Dr. James CS Chim

MB.Ch.B., MD, Ph.D., MRCP(UK), FRCP(London, Edinburgh, Glasgow), FRCPath, FACP, FHKCP, FHKAM

Associate Professor, Department of Medicine, Queen Mary Hospital, The University of Hong Kong

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

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Contact Tel No.:_____ CDSHK No.: _____

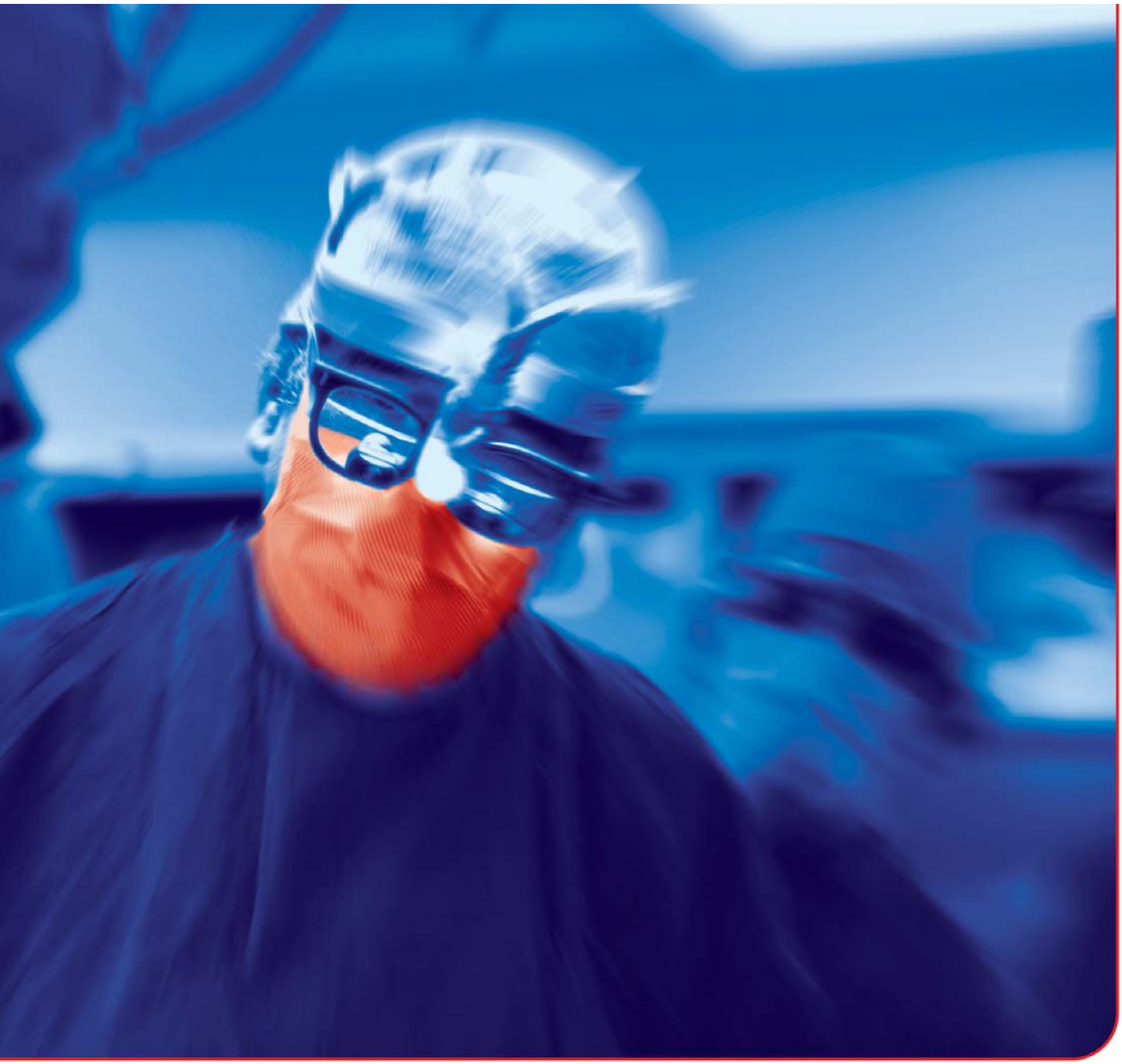
Answers to July 2008 issue

Skin Cancer Management

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

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

Date	Course No	Course Name	Co-organiser	Target Participants
5 Aug - 16 Sep 2008	C132	Common Psychiatric Problems	The Hong Kong College of Psychiatrists	General Practitioners & Healthcare Professionals
4 Sep - 25 Sep 2008	C134	Clinical Management of Vertigo	NIL	General Practitioners & Paramedic
20 Sep 2008	C135	Current Management of Common Problems in Orthopaedics & Traumatology	The Hong Kong Orthopaedics Association	General Practitioners & Healthcare Professionals
14 Oct - 18 Nov 2008	C133	Certificate Course on Respiratory Medicine 2008	The Hong Kong Thoracic Society & American College of Chest Physicians (HK and Macau Chapter)	Nurses and Allied Health Professions



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Update on Antifungal Treatment in Neutropenic Patients

Dr. Ivan FN Hung

MB ChB, MRCP, FHKAM, FHKCP

Specialist (Infectious Disease), Department of Medicine, The University of Hong Kong, Queen Mary Hospital, Hong Kong

Dr. Ivan FN Hung

Introduction

Fungal infections in neutropenic patients have always posed a great challenge even to the most experienced clinician. Patients are immunocompromised in dismal situations with high mortality (invasive aspergillosis 58-87%, systemic candidiasis 40-60%)[1], and only prompt diagnosis with effective antifungal treatment will salvage these patients. Despite advances in methods of early diagnosis of invasive aspergillosis, such as serial measurement of peripheral blood galactomannan antigen or circulating *Aspergillus* DNA[2], clinical presentations are often late and diagnosis is delayed. With the introduction of the new echinocandins class of antifungal agent and the new triazoles including voriconazole and posaconazole, successful treatment is more likely with less toxic effects. In this article, we will discuss the different classes of antifungal agents and their applications in different clinical scenarios.

Antifungal Agents

Triazoles

The triazole antifungals target the fungal cytochrome P-450 dependent 14α -sterol demethylase[3-5]. This enzyme converts the lanosterol to ergosterol, a vital component of the cellular membrane of fungi. As a result, ergosterol synthesis is disrupted leading to increased cell membrane permeability, cell lysis and death. The triazoles are fungistatic against Candida species and only voriconazole possesses fungicidal activity against *Aspergillus* species[6]. The triazoles include fluconazole, itraconazole, voriconazole and posaconazole. Triazoles are associated with abnormal hepatic function, ranging from asymptomatic mild liver function derangement to fulminant hepatic failure. Regular monitoring of the liver function during antifungal treatment with the triazoles is recommended.

Fluconazole

Fluconazole is very hydrophilic with an excellent bioavailability of around 90%. It is available in both oral and intravenous preparations. Once it is absorbed in the stomach, it is widely distributed in body fluids and tissues. It also penetrates well into the cerebral spinal fluid (CSF), achieving about 80% of the serum level[7]. It has potent activity against most of the *Candida* species; apart from *C glabrata* that demonstrates significant resistance to fluconazole. It has no activity to *C norvogenesis, C ciferrii and C krusei.* It is active against *Cryptococcus neoformans, Trichosporon,* histoplasmosis and coccidioidomycosis. It has no activity against *Aspergillus, Fusarium* and other moulds.

Itraconazole

Comparing to fluconazole, the bioavailability of itraconazole is much reduced. It varies with different formulations, ranging from 30% in the solution formulation to 55% in the capsule formulation. It also requires an acidic environment for solubilisation in the capsule form and absorption is increased with food and acidic drinks[8]. Proton pump inhibitors that reduce the gastric pH should be avoided. It is lipophilic and cannot penetrate the blood brain barrier. In addition to the *Candida* species, itraconazole is a second-line agent for the treatment of aspergillosis.

Voriconazole

It is available in both the oral and intravenous formulations. Similar to fluconazole, it has an excellent bioavailability of over 90%. It is widely distributed in body fluid and tissues including the CSF. It is metabolised by the cytochrome P450 enzyme[9]. It is active against the *C glabrata, C norvogenesis, C ciferrii and C krusei* that fluconazole has no action against. It possesses an enhanced activity against *Aspergillus* and *Fusarium* species.

Posaconazole

Currently, it is only available in the oral formulation. Similar to fluconazole and voriconazole, it has an excellent bioavailability. It undergoes hepatic metabolism and is eliminated in the faeces[10]. In addition to its activity against *Aspergillus* and *Fusarium*, it is also active against the *Zygomycetes*.

Polyenes

The polyenes interact with fungi membrane ergosterols to produce an aggregate that forms a transmembrane channel, allowing the cytoplasmic contents to leak out and subsequent fungal cell death[11].

Amphotericin B

This is a polyene originally extracted from *Streptomyces nodosus*. It is insoluble in water and all preparation of amphotericin B must be infused in 5% dextrose. It is fungicidal against all *Candida* and *Aspergillus* species, *Coccidioides immitis, Histoplasma capsulatum, Blastomyces dermatitidis, Cryptococcus neoformans* and *Sporothrix schenckii*. It has no activity against *Fusarium* and *Trichosporon*[12]. Synergistic activity of amphotericin B with flucytosine has been demonstrated against

serious *Cryptococcal* infection, especially in immunocompromised patients. Nevertheless, serum flucytosine level should be monitored if patients develop amphotericin B related nephrotoxicity.

As previously mentioned, the main side effect of amphotericin B is nephrotoxicity that manifests initially by kaliuresis and hypokalaemia, then fall in serum bicarbonate. Renal injury can be reduced by pre infusion hydration with 500ml saline and avoidance of other nephrotoxins. Infusion related adverse reactions like fever, chills and headache could be minimised by premedication with anti-histamine, corticosteroid or paracetamol. Prolonging the infusion time to 12 hours or continuous intravenous infusion over 24 hours may prevent these reactions[13].

Liposomal Amphotericin B

Liposomal formulation of amphotericin B reduces its nephrotoxicity side effect and improves its tolerance, without reducing its efficacy. Nevertheless, use of liposomal amphotericin B is hindered by its cost.

Echinocandin

Echinocandin inhibits synthesis of β -(1,3)-D-glucan, a critical component of fungal cell walls via noncompetitive inhibition of the enzyme 1,3- β synthetase[14,15]. It is fungicidal against most *Candida* species and fungistatic against *Aspergillus* species, with minimal activity against the dimorphic fungi. It also demonstrates modest activity against the spore form of *Pneumocystis carinii*. It is not active against *Fusarium* and *Rhizopus.* The echinocandins are embryotoxic (category C) and should not be used in pregnancy. Patients with chronic liver disease need dosage adjustment. Other minor side effects include nausea, vomiting, diarrhoea, headache and hypersensitivity related rash and pruritis.

Caspofungin

The first approved echinocandins. It has low oral bioavailability and thus must be given intravenously only. The drug is well tolerated and non-nephrotoxic. It interacts with cyclosporine, causing deranged hepatic parenchymal enzyme. Concomitant use of the two drugs is not recommended. Dosage reduction in patients with moderately deranged liver function is recommended.

Micafungin

Another echinocandin, indicated for the treatment of candidaemia, disseminated candidiasis and *Candida* peritonitis. It was recently approved for the prophylaxis of Candida infections in patients undergoing haematopoietic stem cell transplantation.

Anidulafungin

The third echinocandin, indicated for invasive *Candida* and *Aspergillus* infection. It differs from other echinocandins in that it undergoes chemical degradation to inactive forms at body pH and temperature. It does not rely on hepatic or renal excretion and thus does not require dosage reduction.

Clinical Scenario Requiring Systemic Antifungal Agents

Empirical Treatment for Neutropenic Fever

Neutropenic fever in a patient is defined as a sustained temperature of >38ºC for more than one hour with an absolute neutrophil count (ANC) < 500 cells/mL[16]. Threshold for initiation of empirical antifungal treatment for neutropenic fever varies from centre to centre. In general, if fever persists after five days of antibiotics therapy and no microbiological pathogen is isolated, previous guidelines recommended to add amphotericin B to the antibiotics that the patient is already receiving[16]. Recent trials however have demonstrated that caspofungin was associated with a significantly higher survival rate at seven days after the completion of therapy and a superior safety profile than amphotericin B[17]. The primary choice is caspofungin as first-line empirical therapy in patients with suspected fungal infections. Voriconazole and liposomal amphotericin B are effective alternates[18]. It is important to bear in mind that echinocandins are inactive to *Fusarium* and *Cryptococcus neoformans* that were previously mentioned. Besides antifungal treatment, all catheter in-situ should be replaced[19].

Invasive Aspergillosis

The diagnosis of invasive aspergillosis is based on culture and histology, aided by new tests includes galactomannan[20] and PCR testing[21]. The Infectious Diseases Society of America (IDSA) has recommended voriconazole as the initial treatment of choice for invasive aspergillosis[22]. Trials have shown that voriconazole is superior to standard amphotericin B in the treatment of invasive aspergillosis in terms of both partial and complete response, lower mortality rate, better tolerance and severe adverse reactions[23]. Similar efficacy and safety profile is expected from posaconazole[24]. Itraconazole is considered a second-line treatment when compared to voriconazole, based on its inferior intrinsic activity against aspergillosis. Echinocandins are also active against invasive aspergillosis with a good tolerance[25]. However, due to the lack of data on echinocandins for the treatment of invasive aspergillosis, voriconazole is the treatment of choice. Antifungal combination has great potential to improve outcome based on observational study. In vitro results have shown additive effect with combination therapy with caspofungin and voriconazole[26], whereas combinations of caspofungin and amphotericin B have a synergistic effect[27]. Most of the in vivo data showed that the use of voriconazole and caspofungin combination therapy for the treatment of invasive aspergillosis showed improved clinical outcomes and reduced mortality. Combination therapy with caspofungin and amphotericin B showed similar results. However, combination therapy with the azoles and amphotericin B is not recommended based on the fact that azole inhibits the ergosterol biosynthetic pathway thereby reducing the amphotericin B binding to the fungal membrane[28]. Nevertheless, spontaneous recovery of bone marrow function with or without the assistance of granulocyte colony-stimulating factor (G-CSF) is the utmost important factor to recovery of invasive aspergillosis.

Candidaemia

Candidaemia is defined as the presence of *Candida* species in blood. Patients are at risk of developing candidaemia if they are immunocompromised or under intensive care, especially if they have a central venous catheters in-situ, on broad-spectrum antibiotics and on haemodialysis. Diagnosis of candidaemia is based on blood culture with the BACTEC system[29]. Other methods of diagnosis include tissue biopsy and antigen testing with beta-D-glucan assay[30]. All intravenous catheters should be removed and replaced. Amphotericin B deoxycholate was previously the antifungal of choice, with rapid fungicidal action against the *Candida* species. Unfortunately, its usage is limited by its nephrotoxicity. The less toxic lipid formulation of amphotericin B however, is much more expensive. The azoles are still active against the *C albicans*. However, *C krusei* is intrinsically resistant to fluconazole due to an altered cytochrome P-450 isoenzyme[31] but remains susceptible to voriconazole and posaconazole. *C glabrata* isolates are resistant to the azoles secondary to drug efflux and cross-resistance among the azoles is common[32]. Echinocandins however, remains a potent antifungal against most Candida species including *C krusei* and *C glabrata* with an excellent safety profile. Trials have compared caspofungin against amphotericin B[33] and micafungin against liposomal amphotericin B[34] for the treatment of invasive candidasis. All trials showed similar efficacy between the two antifungals but the echinocandins are associated with less drug toxicity. In general, echinocandins are the drug of choice for unstable neutropenic patients who have evidence of invasive *Candida* infection, previously exposed to fluconazole and in institutions where *C glabrata* or *C krusei* is a common isolate. Echinocandins are superior to amphotericin B in terms of safety profile and cost effectiveness when compared to liposomal amphotericin B. Voriconazole and liposomal amphotericin B are second choice. However, cross-resistance with fluconazole may affect voriconazole efficacy[35].

Hepatosplenic Candidiasis

This occurs in patients with haematological malignancies who have recovered from an episode of neutropenia after chemotherapy. Discrete microabscesses of *Candida* are found in the liver, spleen and kidneys. The 2004 IDSA guidelines suggested that fluconazole is the first line drug of choice[36]. Amphotericin B or liposomal amphotericin B may also be used as initial therapy for the first two weeks, follow by long-term therapy with oral fluconazole. Caspofungin is another choice.

Zygomycosis (Mucormycosis)

Combination of surgical debridement and antifungal therapy with lipid formulation of amphotericin B[37] or posaconazole[38] is the treatment of choice for zygomycosis. Underlying diseases including hyperglycemias, metabolic acidosis and deferoxamine administration should also be treated.

Fursarium Infection

This filamentous fungus has become an important infection in the immunocompromised. Amphotericin B is the most commonly used antifungal for *Fusarium*[39]. With the emergence of voriconazole[40] that is fungicidal against filamentous fungi with much fewer adverse effects, it is an alternate to amphotericin B. Posaconazole[39] is also active against *Fusarium*. In view of the high mortality with disseminated *Fusarium* infection, a combination therapy of voriconazole and lipid formulation of amphotericin B is a good salvage therapy.

Conclusions

For immunocompromised patients, treatment with antifungal agents not only suppresses the fungal growth but also buys time to allow patients to recover from neutropenia. Clinical suspicion, prompt diagnosis and early treatment are the keys to success in eradication of fungal infection. Supportive therapy with G-CSF may hasten neutrophil recovery and functions. New antifungal agents including echinocandins and the new triazoles will overcome resistant strains with greater efficacy and less toxicity.

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In patients with CML

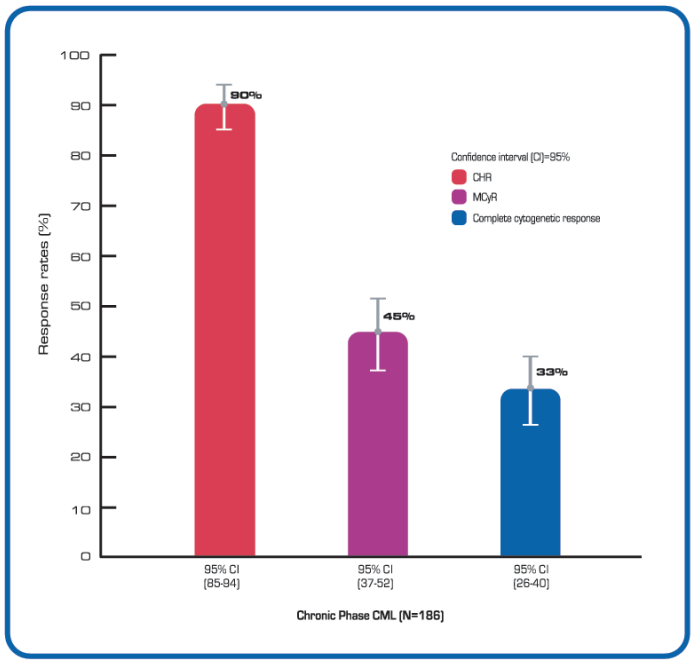
I was

resistant or intolerant to prior therapy including imatinib

Efficacy in SPRYCEL™ Clinical Studies in Chronic Phase CML Patients Resistant or Intolerant to Imatinib

SPRYCEL™ (dasatinib): Hematologic and Cytogenetic Response Rates in Chronic Phase CML[1]

SPRYCEL™ Hematologic and Cytogenetic Response Rates in Chronic Phase CML Patients Resistant or Intolerant to Prior Therapy,Including Imatinib[1]



Major hematologic response was not reported in chronic phase CML patients.

- Imatinib resistance was defined as failure to achieve a CHR (within 3-6 months) or MCyR (by month 12) or progression of disease after a previous cytogenetic or hematologic response[1]
- Imatinib intolerance was defined as inability to tolerate 400 mg or more of imatinib per day or discontinuation of imatinib because of toxicity[1]
- Hematologic and cytogenetic responses were stable during the 6-month follow-up of patients with chronic phase CML[1]
- Most cytogenetic responses occurred after 12 weeks of treatment, when the first cytogenetic analyses were performed[1]
- There were no age- or gender-related response differences[1]

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SP-AD-HK0804-011

Targeted Therapy for Non-small Cell Lung Cancer

Dr. James CM Ho

M.B., B.S.(HK), M.D.(HK), MRCP(UK), FHKCP, FHKAM(Medicine), FRCP (Glas)
Clinical Assistant Professor, University Department of Medicine, Queen Mary Hospital, The University of Hong Kong, Hong Kong

Dr. James CM Ho

Introduction

Lung cancer has been a major health problem worldwide, accounting for a global incidence of 1.2 million new cases yearly and a staggering mortality of 1.1 million deaths in 2001.[1] In Hong Kong, lung cancer has remained the commonest malignancy in men and the third commonest in women, with a total of 4,135 new cases in 2005. Being the commonest cancer killer in both sexes, there were 3,686 deaths in the same year (Hong Kong Cancer Registry). The majority (>80%) of lung cancers are non-small cell carcinomas (NSCLC), which are predominantly in advanced or metastatic stages upon presentation. The high mortality is mainly ascribed to disease recurrence after curative lung resection and the lack of effective treatment for advanced disease. The overall treatment plan for NSCLC largely depends on clinical staging: curative lung resection for early stages (mainly stage I and II), combined chemoradiotherapy for locally advanced stages (mainly stage III), and systemic platinum-based chemotherapy for advanced metastatic stages (mainly stage IIIB and IV). Prior to our understanding of molecular tumour biology of NSCLC, the use of systemic chemotherapy has been targeting at rapidly growing tumour cells in a rather non-specific fashion. In principle, a more specific approach that works on salient molecular pathways for tumourigenesis, i.e. targeted therapy, may help to enhance clinical efficacy while minimising toxicities related to damage of normal tissues. This review serves to summarise the current state-of-the-art targeted approach in the treatment of NSCLC.

Anti-angiogenesis

The majority of patients with NSCLC presented with unresectable diseases, due to regional involvement of mediastinal lymph nodes, pleural or pericardial malignant effusion, or distant metastases. In the past decade, systemic chemotherapy has become the standard first-line treatment for those with malignant effusion or distant metastases.[2] In such patients with good performance status, a combination of platinum (cisplatin or carboplatin) and a newer generation chemotherapeutic agent (e.g. paclitaxel, docetaxel or gemcitabine) has been well-documented to improve overall survival, disease-free survival and quality of life compared to best supportive care alone or older generation chemotherapy combinations.[3] However, the improvement in survival is considered modest (on average 2 months prolongation of median survival compared to best supportive care alone) and the time to disease progression is usually within a few months since commencement of chemotherapy.[4]

In general, malignant tumours cannot grow beyond 2mm in size without developing a vascular supply.[5] 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.[6,7] Angiogenesis, whether physiological or pathological, is controlled by the balance between proangiogenic and antiangiogenic factors[8] (Table 1). The most important proangiogenic factor involved in tumour angiogenesis is vascular endothelial growth factor (VEGF), which has become the target for antiangiogenic therapy in NSCLC.[9] The VEGF pathway can be inhibited by agents that target VEGF or VEGF receptors. In particular, bevacizumab (Avastin™) 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.[10]

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 chemonaive non-squamous NSCLC.[11] 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 interim results suggesting favourable progression-free survival in the bevacizumab arm compared to chemotherapy alone arm.

Epidermal Growth Factor Receptor (EGFR) Inhibition

Upon disease progression after first-line chemotherapy treatment, docetaxel as monotherapy has been shown to be superior to best supportive care alone or alternative chemotherapy in survival.[12,13] The newer chemotherapeutic agent, pemetrexed, has also been shown to have similar efficacy as docetaxel with lesser degree of adverse effects especially myelosuppression in the second-line setting.[14] However, this is still limited by the very modest improvement in median survival and also the toxicity profile in the second-line setting especially for those patients with poor performance status.

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 (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.[15, 16] It was based on two large phase II trials (IDEAL 1 and 2) of gefitinib monotherapy in previously treated patients with advanced NSCLC that was approved as second-line treatment.[17, 18] 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 patients who were refractory or intolerant to chemotherapy.[19] 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 benefit among never smokers and patients of Asian descent. The commonest toxicities were skin rash (37%) and diarrhoea (27%). On the other hand, the preliminary results of a more recent 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 (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.[20] A recent randomised, placebo-controlled, phase III trial of erlotinib versus placebo in treatment of advanced NSCLC after failure to previous chemotherapy was reported.[21] 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 the studies of gefitinib and erlotinib in treatment of advanced NSCLC, several clinical and molecular predicting factors for response to treatment were identified.[22] (Table 2) 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. Therefore this class of novel agents is particularly effective in NSCLC patients with favourable characteristics (female, Asian descent, never smokers, adenocarcinoma, specific EGFR mutations), which often serve as the selection criteria for treatment. However, there are still controversies about the best molecular markers (either single or multiple) for response and survival outcome, and there is still lack of good predictors of the group with disease stabilisation after treatment.

Future Directions of Targeted Therapy in NSCLC

Targeting specific molecular signalling pathways remains a promising approach in the management of NSCLC. However there are still several issues that need to be addressed. First, there is a clear need of better characterisation of "targeted" patient subpopulation that may potentially benefit from a particular targeted approach. Future research in identifying biomarkers that reliably predict clinical treatment outcomes is warranted. Second, the potential use of EGFR TKI in clinical settings other than second or third-line in advanced NSCLC needs to better defined, especially in the adjuvant treatment for early-stage disease after curative lung resection or the first-line treatment for advanced disease.

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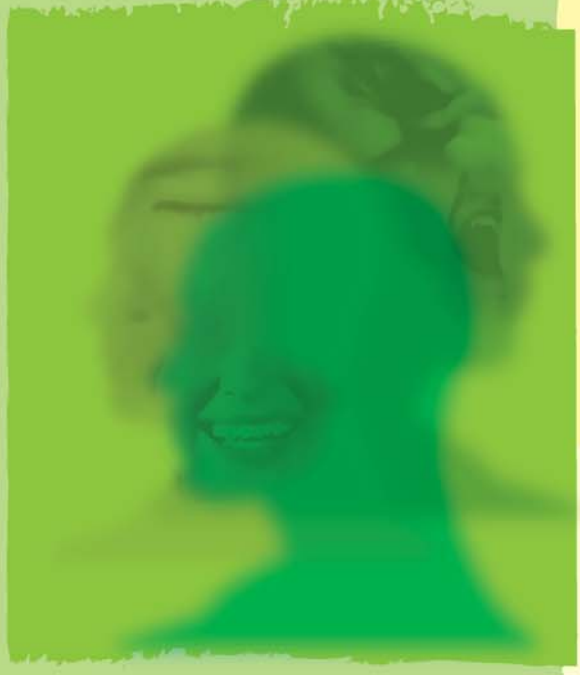

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Third, the problem of acquired resistance to EGFR TKI (mostly related to a new mutation in EGFR) requires further research. In fact, there have been some newer generations of EGFR TKI that are currently under investigations for overcoming drug resistance to gefitinib or erlotinib. Last, as there has been better understanding about the potential interactions or cross-talks between different signalling pathways, it becomes logical to simultaneously target different molecular pathways in order to achieve better tumour control. As a result, there have been quite a number of multi-targeted tyrosine kinase inhibitors (e.g. inhibiting both VEGF and EGFR) that are currently undergoing clinical trials in the treatment of NSCLC.

Conclusion

Although lung cancer, predominantly NSCLC, is still considered to be a devastating malignancy with 5-year survival less than 15%, there has been major advancement in the overall treatment especially in the era of targeted therapy. With our continuing efforts in research along the targeted approach, lung cancer will hopefully become a chronic condition like hypertension or diabetes in the near future.

*Table 1 Common endogenous proangiogenic and antiangiogenic factors**

Proangiogenic factors	Antiangiogenic factors
Acidic and basic fibroblast growth factor	Angiostatin
Angiogenin	Endostatin
Hepatocyte growth factor	Interferon-α-β
Interleukin-8	Interferon inducible protein-10
Placenta growth factor Platelet-derived endothelial cell growth factor	Platelet factor 4 Prolactin fragment
Transforming growth factor-α-β	Thrombospondin
Tumour necrosis factor-α	Tissue inhibitor of metalloproteinase
Vascular endothelial growth factor	Tumstatin Vasculostatin

** Adapted from reference no. 8*

*Table 2 Predictors for response to EGFR TKI in patients with advanced NSCLC**

Clinical	Molecular
East Asian descent	EGFR TK domain-sensitizing mutations
Female gender	EGFR polymorphisms
Nonsmokers	EGFR amplification
Adenocarcinoma histology	ErbB3 expression
Skin rash	

** Adapted from reference no. 22*

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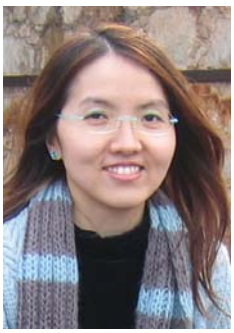
Recent Medical Advances in Breast Cancer



Dr. Janice WH Tsang

MBBS, MRCP(UK), FHKCP, FHKAM(Medicine)
Specialist in Medical Oncology
Assistant Professor, Department of Clinical Oncology, University of Hong Kong
Honorary Clinical Assistant Professor, Department of Medicine, University of Hong Kong

Dr. Janice WH Tsang

Introduction

Breast cancer is the most common female cancer in the world.[1] It is also the most common female cancer in Hong Kong with 1 in 22 cumulative life-time risk.[2]

Over the last two decades, there have been remarkable advances in the screening, diagnosis and treatment of breast cancer. Surgical resection of the primary tumour remains the basis for cure of early breast cancer. Adjuvant radiotherapy is given according to the tumour risk to help prevent local recurrence. Adjuvant chemotherapy and/or endocrine therapy help to prevent disease relapse by targeting occult micrometastasis. Through understanding new pathways, pharmacogenomics and predictors of response, the outcome of breast cancer has improved dramatically in recent years with the advent of targeted therapy while the choice of therapy depends not only on risk assessment incorporating both patient and tumour-related prognostic factors, but also biomarkers and drug toxicity profile.

Adjuvant therapy has proven to be effective in preventing both local and distant relapses.[3] Traditionally, the selection of adjuvant systemic therapy has relied on both patient and tumour-related factors. Patient factors include age at presentation, menopausal status and comorbidities. Tumour-related factors include tumour size, tumour grade, lymph node involvement, the presence or absence of oestrogen receptors (ER), progesterone receptors (PgR) and the HER-2 receptor status.

Evolution of Chemotherapy for Breast Cancer

Indications for Adjuvant Chemotherapy

Randomised trials have shown improved survival with the use of adjuvant chemotherapy after breast cancer surgery.[3] 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 are indications for adjuvant chemotherapy.[4] However, adjuvant treatment should be tailored to individuals, taking into account patients' comorbidities and preferences.

Adjuvant Chemotherapy - Past and Present

In the 1970s, CMF (Cyclphosphamide, Methotrexate and 5-FU) was the backbone of adjuvant chemotherapy for breast cancer.[3,5] The Milan research group decided in the early 1980s to challenge CMF by introducing anthracycline-based regimens in the adjuvant setting. Compared with standard CMF, anthracyclin-containing regimens reduced the annual risk of recurrence by 12% and the annual risk of death by 11%.[3] This difference was seen with regimens such as FAC (5-FU, Adriamycin, Cyclophosphamide) and FEC (5-FU, Epirubicin, Cyclophosphamide), whereas 4 cycles of AC (Adriamycin, Cyclophosphamide) appears to be equivalent to 6 cycles of CMF and has become a standard adjuvant regimen.[6,7] The taxanes were introduced into clinical practice in the 1990s, and have emerged as powerful compounds in breast cancer in several adjuvant clinical trials. The addition of four cycles of paclitaxel (Taxol®) after a standard course of AC was shown to improve the disease-free survival (DFS) and overall survival (OS) of patients with node-positive primary breast cancer.[8] The Breast Cancer International Research Group (BCIRG) 001 study showed similar enhancement of DFS and OS with the use of adjuvant docetaxel (Taxotere®). Significant improvement of DFS was seen in 6 cycles of TAC (Docetaxel, Adriamycin, Cyclophosphamide) compared to 6 cycles of FAC (82% vs 74%).[9] In a recent randomised phase III study, 4 cycles of TC (Docetaxel, Cyclophosphamide) were shown to be superior to AC, in terms of improved DFS. TC is associated with more peripheral neuropathy, myalgia and arthralgia and febrile neutropenia while AC is associated with more nausea and vomiting and cardiotoxicity. Currently, TC is considered as an alternative to AC especially in patients with background of significant heart disease.[10]

Discovering the Optimal Dose and Schedule

Duration and the most optimal schedule of adjuvant chemotherapy are also being critically reappraised. Recent study has shown that treatment with AC followed by weekly paclitaxel is associated with improved DFS and OS in comparison with treatment with AC followed by 3-weekly paclitaxel regardless of hormone receptor expression.[11] On the other hand, dose-dense regimens, i.e. giving the same type of chemotherapy with same dosage every 2 weeks instead of every 3 weeks with continuous recombinant granulocyte colony-stimulating factor (G-CSF) support, have been shown to improve both the DFS and

OS with lower incidence of febrile neutropenia in the dose-dense group.[12]

HER-2 Targeted Therapy

Targeting HER-2 with Trastuzumab

Up to 25% of women with breast cancer have human-epidermal growth factor receptor 2 (cerbB-2 / HER-2) positive disease, which is associated with aggressive disease, a higher risk of relapse and a poorer prognosis.[13,14] Trastuzumab (Herceptin®), a monoclonal antibody directed against the extracellular domain of HER-2, improves survival and quality of life when given in combination with taxanes as first-line therapy in women with metastatic breast cancer.[15, 16] It could be either given as monotherapy or as a chemosensitiser in combination with cytotoxics such as taxanes or vinorelbine, and has demonstrated activity in heavily pretreated patients[17]. Four major international adjuvant trials - Herceptin® Adjuvant (HERA), National Surgical Adjuvant Breast and Bowel Project (NSABP) B-31, North Central Cancer Treatment Group (NCCTG) N9831, and Breast Cancer International Research Group (BCIRG) 006 - including >13, 000 women with HER-2 positive breast cancer, have shown that one-year treatment of trastuzumab after adjuvant chemotherapy significantly improves DFS and OS among women with HER-2 positive breast cancer.[18] A small Finnish trial, FinHer, investigating another regimen of trastuzumab, has also shown similarly positive results.[19] Meta-analysis of these five randomised trials further supported the above benefits in terms of disease-free and overall survival.[18, 20]

Trastuzumab is not associated with the adverse events that occur typically with chemotherapy such as alopecia, myelosuppression or vomiting. It is generally well tolerated, but occasionally associated with hypersensitivity or acute reaction which is seen mainly with the first infusion. Cardiotoxicity such as congestive heart failure remained at an acceptable level with reported overall incidence of about 0.6-4.1%.[19] This is usually reversible when the drug is suspended. Therefore, close monitoring of the cardiac function with baseline and 3-monthly echocardiogram or MUGA scan is recommended.

Lapatinib - A Dual Tyrosine Kinase Inhibitor

Another novel targeted therapy, Lapatinib, is an oral dual small molecule tyrosine kinase inhibitor targeting both ErbB-2 (HER-2 / neu) and ErbB-1 (EGFR) receptors. It is active in combination with capecitabine (Xeloda®) in women with HER2-positive metastatic breast cancer that has progressed after anthracycline, taxanes and trastuzumab-based therapy, leading to significantly longer median time to progression and progression-free survival.[21] Lapatinib is active in refractory metastatic breast cancer with potential benefit in patients with brain metastases. It has very low incidence of cardiotoxicity and is well tolerated.[22] Results from the phase III randomised, double-blind, multicentre, placebo-controlled trials of lapatinib in the adjuvant setting such as the TEACH (Tykerb® Evaluation After Chemotherapy) trial are eagerly awaited to determine the role of lapatinib in the adjuvant setting.

Adjuvant Hormonal Therapy with Aromatase Inhibitors

The Advent of Aromatase Inhibitors

About two-thirds of women with breast cancer have positive oestrogen receptors and/or progesterone receptors and are candidates for adjuvant endocrine therapy. Five years of Tamoxifen, the selective oestrogen receptor modulator, has been the standard adjuvant hormonal therapy for women with hormone-positive disease since the 1970s.[23] Aromatase inhibitors are inhibitors of oestrogen biosynthesis, blocking aromatase, the enzyme responsible for converting androgens to oestrogens, thus suppressing oestrogen levels with no partial agonist activity. The third-generation aromatase inhibitors (AIs) which were introduced in the late 1990s, have expanded the adjuvant endocrine treatment options for postmenopausal women with hormone-receptor positive breast cancer and were shown to be superior to tamoxifen in improving the disease-free survival in several large, randomised controlled clinical trials.[23] The currently available AIs include the nonsteroidal compounds anastrozole (Arimidex®) and letrozole (Femara®), and the steroidal AI exemestane (Aromasin®).

Tamoxifen Remains the Gold-standard for Pre-menopausal Women

To date, tamoxifen remains the gold-standard for hormone-receptor positive disease in pre-menopausal women. Other options of ovarian function suppression include ovarian ablation by surgery or radiation, and the use of gonadotropin-releasing hormone (GnRH) agonists in the case of persistent ovarian activity after chemotherapy. Aromatase inhibitors are inactive in pre-menopausal patients and should not be used because in these women, AIs induce an increase in gonadotropin secretion secondary to the reduced negative feedback of oestrogen to the pituitary, leading to ovarian stimulation and a potential increase in ovarian size and function.[1]

Different Adjuvant Strategies with Aromatase Inhibitors

Recent large, randomised controlled clinical trials have shown consistently the superiority of AIs over tamoxifen in postmenopausal women with early breast cancer and AIs are recommended to form part of the adjuvant endocrine therapy.[1] Three different strategies for integrating the use of AIs with tamoxifen as adjuvant therapy for hormone-responsive breast cancer include: (1) upfront 5-year use of an AI as an alternative to tamoxifen in the initial adjuvant setting ("primary upfront approach")[24,25]; (2) "switching approach" whereby giving the patient 2-3 years of AI instead of tamoxifen after the patient survives disease free for 2-3 years of tamoxifen ("unplanned switching strategy") or planned from the time of surgery ("planned sequence strategy")[25-28]; and (3) as an extended adjuvant therapy, whereby the patient receives further 5-year AI therapy following completion of the recommended 5-year course of tamoxifen.[29, 30]

However, it is unclear whether one of these AI strategies is superior to the other ones. The overall therapeutic index of AIs appears superior to that of

tamoxifen with proven improved efficacy and a better toxicity profile. AIs are less toxic than tamoxifen in terms of thromboembolic disease and endometrial carcinoma, while myalgia, arthralgia, increased tendency of osteoporosis and bone fracture are more frequently observed with AIs.

Bisphosphonates: Benefits Beyond Bones

Breast cancer patients with bony metastases experience fewer skeletal-related events[31] and require less radiation therapy.[32] The use of adjunct bisphosphonate therapy with adjuvant aromatase inhibitors has been proven to reduce treatment-related osteoporosis.[33] In the recent American Society of Clinical Oncology (ASCO) 2008 annual meeting, it was reported that the addition of zoledronic acid every 6 months to adjuvant endocrine therapy with tamoxifen or aromatase inhibitors have led to significantly prolonged DFS and OS in breast cancer women compared endocrine treatment alone group. This large clinical trial has demonstrated that anti-tumour activity of adjuvant bisphosphonate improves outcome beyond the effect of endocrine therapy alone.[34]

Tailoring Treatment for Individuals

With understanding of the biology of breast cancer in the era of targeted therapy and tailored management of cancer patients, the hormone receptors and the HER-2 receptor remain the two main targets in breast cancer management. The selection of the most optimal management plan depends not only on the patient and tumour-related factors, but also the stage of the disease, and the predicted responsiveness of the tumour by molecular profiling while respecting patient's wish.

Neoadjuvant Systemic Therapy

Neoadjvuant, or pre-operative systemic therapy is increasingly used for patients with clinical stages II and III breast cancer to improve surgical outcomes. This application is not confined to inoperable or locally advanced breast cancer, but in the setting of operable disease with more aggressive curative intent and the aim of downstaging and downsizing the tumour, increasing the chance of breast-conserving surgery and assessing the drug sensitivity and treatment response. Patients who achieved a complete pathological response after neoadjvuant chemotherapy have demonstrated significantly superior DFS and OS compared to those who did not. Updated results also showed trends in favour of neoadjuvant chemotherapy for DFS and OS in women younger than 50 year-old.[35] Postmenopausal women with clinical stages II and III oestrogen receptor-positive breast cancer who are downstaged to pathological stage I disease with neoadjuvant endocrine therapy such as aromatase inhibitors have demonstrated favourable long-term outcome.

Improving Tolerability of Palliative Treatment and Directing at New Targets

Due to recent multiple advances in the treatment of breast cancer, more women with early breast cancer have become cancer survivors, while many women with aggressive disease or advanced disease at presentation live with their breast cancer for significant period of time. Newer anti-cancer drugs have emerged with excellent potency but minimal toxicity. These include the better tolerated chemotherapy such as vinorelbine, gemcitabine and oral fluoropyrimidines (capecitabine) with minimal hair-thinning and vomiting. On top of targeted therapy such as trastuzumab and lapatinib, there is another new wave of monoclonal antibodies and tyrosine kinase inhibitors emerging. The combination of bevacizumab, monoclonal antibody against the vascular endothelial growth factor receptor (VEGF) and taxanes has shown activity in patients with metastatic breast cancer with increased progression-free survival.[36] Again, selection of palliative therapy should be based upon both the patient and tumour characteristics. Elderly patients with multiple comorbidities who have hormone-positive disease with bony metastasis only but no visceral disease may do well with hormonal therapy with AI but not necessarily chemotherapy, and all these new combinations of treatment have further improve the quality of life of breast cancer patients. Another new class of hormonal agent, Fulvestrant, an oestrogen receptor antagonist has shown clinical efficacy in postmenopausal breast cancer women with hormone-positive tumour who progress after second-line aromatase inhibitors.

Potential Molecular Markers

It is observed that clinical activity of a given drug may vary between different patients. Different breast cancer sub-types are now being identified with early preclinical data suggesting that in the future some molecular markers might have practical value in predicting treatment response. Topoisomerase II (TopoII) alpha gene aberrations are the most promising molecular predictors of anthrcycline response.[37] HER-2/topoII co-amplified tumours are shown to be most sensitive to anthracyclines.

Triple Negative Breast Cancer

Although there are emerging potential targets for breast cancer, there is a distinct entity of breast cancer, which is associated with aggressive behaviour and poor prognosis, and typically do not express hormone receptors or HER-2 ("triple-negative" phenotype). Triple-negative breast cancer with a basal-like phenotype is characterised by high proliferation rate and BRCA1 gene dysfunction. Currently patients with this type of tumour cannot be managed with existing targeted treatments (trastuzumab and hormonal therapy) effectively but is associated with better response with platinum-based chemotherapy.[38] Further study on this particular subtype is recommended.

Conclusion

There is increasing hope for breast cancer patients. The hormone receptors and HER-2 receptor remain the two main targets for treatment. Through better understanding of breast cancer biology, identifying more new molecular markers and conducting quality randomised controlled clinical trials, we have achieved better outcome of breast cancer. At the same time, there remain many unexplored avenues for optimising the role of each target and new advances. The era of personalised medicine will become more complex in the future and the embracement of multidisciplinary and evidence-based medicine should continue be the standard of care for our breast cancer patients.

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Feb 2008

Latest Update in the Management of Pancreatic Cancer

Dr. Thomas Yau

Dr. Thomas Yau

MBBS (HK), MRCP(UK), FHKCP(Med Onc), FHKAM (Medicine)
Specialist in Medical Oncology, Departments of Medicine, Medical Centre, Queen Mary Hospital, Hong Kong

Introduction

Worldwide, pancreatic cancer poses a significant health hazard with more than 200,000 cases diagnosed annually and the majority of cases are in the developed countries.[1] It is the eighth most common cause of cancer-related deaths and the number of deaths is nearly equivalent to the number of newly diagnosed pancreatic cancer. This reflects the typical dismal prognosis associated with pancreatic cancer. When the disease is diagnosed at early stages, the overall 5-year survival rate is 20 % for patients with localised disease and 8% for patients with locally advanced disease.[2] Unfortunately, most patients with pancreatic cancer have advanced or metastatic disease upon presentation. The prognosis of this group of advanced pancreatic cancer patients is disappointing. In general, the median survival of untreated advanced pancreatic cancer is only three to four months. Even in treated patients, their median overall survival is only approximately 6 months with chemotherapy.

Patients suffered from pancreatic cancer often present with disease-related symptoms out of proportion to their tumour burden. The typical symptoms, such as pain and cachexia severely impact on the quality-of-life of the patients. Also, due to the poor performance status of the patients, they are more prone to develop treatment-related complications, especially after chemotherapy. It is a challenging disease for the oncologists to deal with and there is an urgent need to develop effective systemic therapy to improve the outcome of the patients.

In recent years, a better understanding of the molecular signalling pathways in cancer cells has led to the identification of new therapeutic targets for intervention and the discovery of promising targeted therapy for the treatment of otherwise chemo-resistant tumours, such as renal cell carcinoma.[3] Similar to other solid malignancies, progresses have also been made in the management of pancreatic cancer patients. This article will concisely summarise the latest development in the systemic therapy of pancreatic cancer.

Early Stage Disease And the Role of Neo-adjuvant And Adjuvant Therapy

Patients with localised pancreatic cancer, usually involving the head of the pancreas are candidates for surgery if the tumour is resectable as defined by the absence of vascular involvement. Notably, complete surgical resection is the only curative choice. However, despite recent advances in staging and surgical techniques, the outcome of patients treated with primary resection remains poor with a median survival of 13 months and the 5-year survival of 15-20% only.[4] As a result, oncologists are keen to use adjuvant and neoadjuvant therapy to improve the prognosis of patients with resectable pancreatic cancer.

The main purpose of the adjuvant therapy is to reduce the chance of local and distant recurrence in good performance patients after resection for localised pancreatic cancer. Previously, post-operative chemo-irradiation was often employed as two trials from the Gastrointestinal Tumour Study Group had demonstrated better survival in using adjuvant chemo-irradiation than surgery alone in treating resectable pancreatic cancer patients.[5,6] These trials had been criticised for their small sample size and poor accrual, albeit post-operative chemo-irradiation was still adopted as the standard treatment. More recently, a large randomised adjuvant phase III trial-- European Study Group for Pancreatic Cancer 1(ESPAC-1) trial conducted mainly in Europe had challenged the role of adjuvant chemo-irradiation.[7,8] In this randomised phase III trial with a 2x2 factorial design, the data suggested significant survival benefit of using adjuvant chemotherapy consisted of intravenous fluorouracil (5-FU) and folinic acid (overall survival of 20.1 versus 15.5 months in the chemotherapy and non-chemotherapy arm, respectively). Interestingly, patients who received chemo-irradiation had a detrimental effect on overall survival (15.9 and 17.9 months in the chemo-irradiation arm and no chemo-irradiation arm, respectively). Furthermore, another pivotal phase III trial-CONKO-001[9] demonstrated that patients who had received gemcitabine as adjuvant therapy had a significant longer disease-free survival than patients without adjuvant therapy (13.4 versus 6.9 months, $p<0.001$). Moreover, the overall survival also favoured the use of gemcitabine as adjuvant (22.1 versus 20.2, $p=0.06$). However, the US Gastrointestinal Intergroup trial[10] had shown no statistically significant difference in overall or disease-free survival in patients received gemcitabine or 5-FU as systemic chemotherapy before and after 5-FU-based chemo-irradiation as adjuvant therapy for patients with resectable pancreatic cancer. However, oncologists nowadays still prefer to use gemcitabine as adjuvant therapy for patients with resectable pancreatic cancer due to its easy tolerability. In the near future, with optimal patient selection, improved operation techniques and peri-operative care,

more patients who undergo pancreatic resection will recover adequately to receive postoperative adjuvant therapy. Therefore, it is important to develop more effective adjuvant therapy, especially by incorporation of biologics to improve the overall survival of resectable pancreatic cancer.

With respect to the role of neo-adjuvant therapy in down-staging the advanced pancreatic cancer for potential curative resection, it is still unclear. Treatment with 5-FU based chemo-irradiation or gemcitabine only downstage the disease in a minority of patients with locally advanced disease. In daily practice, oncologists tend to treat locally advanced pancreatic cancer patients with chemo-irradiation with 5/FU as radiosensitiser followed by palliative chemotherapy. However, two recent meta-analyses did not show that chemo-irradiation was better than chemotherapy alone in patients with locally advanced pancreatic cancer.[11,12] In contrast, the addition of radiotherapy to chemotherapy increased treatment-related toxicity. Hopefully, all the on-going neo-adjuvant trials can better define the role of radiotherapy, chemotherapy and other biologics in down-staging locally advanced pancreatic cancer.

Management of Metastatic Pancreatic Cancer

Only a few patients (10-15%) diagnosed to have pancreatic cancer and have limited stage disease are amenable to surgical resection. However, even with surgery, disease recurrence will occur in the majority of patients despite adjuvant therapy. Therefore, systemic therapy for patients with advanced pancreatic cancer is a pressing issue nowadays. Systemic chemotherapy has its established role in the management of metastatic pancreatic cancer patients. It is usually only offered to carefully selected patients with good performance status. In the treated patients, they usually have a significantly better median overall survival with better quality of life as well.[13,14] However, despite active treatment, less than 5% of patients are alive at 5 years.

First-line Treatment of Metastatic Pancreatic Cancer

In the past, 5-FU was first used as palliative chemotherapy for patients with metastatic pancreatic cancer.[15] Subsequently, gemcitabine became the standard of care for advanced pancreatic cancer for the past decade as in a phase III trial of patients with advanced pancreatic cancer, gemcitabine was found to be better than 5-FU in alleviating the symptoms and associated with a significant longer median survival.[16] Therefore, the US Food and Drug Administration (FDA) approved the use of gemcitabine in the treatment of advanced pancreatic cancer. The approved schedule of administration is 1000 mg/m2 over 30 mins once weekly for up to 7 weeks followed by a week of rest. Subsequent cycles consist of 30-min intravenous infusions for 3 consecutive weeks out of 4. Side effects associated with single agent gemcitabine include myelosupression, lethargy, an influenza-like syndrome, nausea and vomiting and peripheral oedema. Interestingly, the recent clinical trial results suggested that the efficacy of gemcitabine treatment may be enhanced by giving gemcitabine as a fixed-dose rate infusion of 10mg/m2/min, but at the cost of increased toxicities.[17,18] However, it has not yet been shown to improve overall survival when compared with the standard administration regimes.[19]

Although the efficacy of single agent gemcitbine is superior to bolus 5-FU, its efficacy is modest, with a median survival of only 6 months in most randomised trials and a 12-months survival of < 20%. Therefore, in the past decade, numerous attempts were made to improve the efficacy of gemcitabine treatment by adding other chemotherapeutic or biological agents. Unfortunately, a lot of gemcitabine-based doublets or triplets have been done with very disappointing results. Recently, against a background of numerous negative randomised trials of gemcitabine-based treatment, two trials have reported significant survival improvements with the use of combination treatment: the United Kingdom National Cancer Research Institute GEMCAP trial and the National Cancer Institute of Canada Clinical Trials Group PA.3 trial.

The results of the GEMCAP trial are the first in the literature which show that combination chemotherapy is better than gemcitabine alone for the treatment of advanced pancreatic cancer.[20] In this randomised phase III trial, 533 patients were randomised to receive either single agent gemcitabine (n=266) or gemcitabine and capecitabine. In patients who received gemcitabine and capecitabine combination, the median OS was 7.4 months, compared with 6.0 months for gemcitabine alone (hazard ratio 0.8, 95% confidence interval 0.65-0.98;p=0.026) and absolute 1-year survival improvement of 7%. The combination regime was well-tolerated with a similar incidence of grade 3 /4 toxicities in both treatment arms, except more neutropenia in the combination arm.

On the other hand, the PA.3 trial demonstrated the survival benefit in combining erlotinib and gemcitabine for the treatment of advanced pancreatic cancer patients. Erlotinib is a small-molecule tyrosine kinase inhibitor (TKI) of the human epidermal growth factor receptor (EGFR), which has been approved for the treatment of non-small cell lung cancer.[21] EGFR is dysregulated in many tumour types, including 40-65% of pancreatic tumours.[22] PA.3 was a multi-centre, randomised, double-blind, placebo-controlled phase III clinical study of erlotinib in combination with gemcitabine in patients with advanced pancreatic cancer. A significant survival improvement in median PFS was observed in the gemcitabine and erlotinib arm when compared with gemcitabine single agent (3.8 versus 3.5 months, p=0.006). Moreover, the treatment was well-tolerated with incidence of adverse events similar in both arms of PA.3. However, patients who received erlotinib and gemcitabine complained of more rashes, diarrhoea, infection and stomatitis. Although the survival improvement is only modest--14 days in this study, this is still a significant step forward in the management of patients with this notorious malignancy.

Second-line Therapy

Thus far, there is no standard second-line treatment for patients with metastatic pancreatic cancer and only 30-50% of patients will have a chance to receive second-line treatment. It is mainly attributed to the fact that many patients who progress with first-line treatment have suboptimal organ function and poor performance status. Therefore, they may not be able to tolerate the second-line chemotherapy well and many clinicians are quite reluctant to offer systemic chemotherapy in this setting. Lately, the results of CONKO-3 just released in the American Society of Clinical Oncology 2008 Annual meeting.[23] In this pivotal phase III trial, patients who received combination of oxaliplatin plus 5-FU and leucovorin as second-line regime had significant improvement in overall survival than patients on 5-FU and leucovorin alone (26 versus 13 weeks, p=0.014). Other second-line pancreatic trials using similar regimes or other combinations are on-going and their results will better define the role of second-line therapy in the treatment of gemcitabine-refractory patients.

Role of Biologics in the Management of Metastatic Pancreatic Cancer

Two pathways play a significant role in pathogenesis of advanced pancreatic cancer: EGFR and vascular endothelial growth factors (VEGF).

Blockade of the EGFR pathway with TKI-erlotinib has demonstrated encouraging results in the PA. 3 trial. Moreover, another TKI-lapatinib also showed encouraging activity in combining with gemcitabine-based treatment in the management of advanced pancreatic cancer patients.[24] However, blocking the EGFR pathway with monoclonal antibody-cetuximab instead showed disappointing results. In the US Southwest Oncology Group study, the addition of cetuximab to gemcitabine had failed to show survival benefit than gemcitabine alone.[25] It is interesting to note the phenomenon that there is benefit in using TKI but not monocloncal antibody in the management of pancreatic cancer. This phenomenon is in contrast to our experiences in using this class of drug in the treatment of other solid tumours. The exact reason is still not yet known.

Anti-VEGF therapy has shown promising results in the treatment of other solid tumours. Unfortunately, targeting VEGF therapy has not yet shown any success in the management of advanced pancreatic cancer. The interim results of the US Cancer and Leukemia Group B failed to show any survival benefits in the addition of bevacizumab to gemcitabine in the management of advanced pancreatic cancer patients.[26] More mature data from this and other on-going trials in using bevacizumab in the management of advanced pancreatic cancer will better define the benefits of addition of bevacizumab to gemcitabine-based regime.

Conclusion

Despite recent survival improvement with the addition of capecitabine and tarceva to gemcitabine-based treatment of metastatic pancreatic cancer, the benefit is only modest. Moreover, there is additional cost and risk of toxicity from combination regime, particularly the use of erlotinib. Thus, more active and new systemic regimes are desperately needed to improve the outcome of patients with advanced pancreatic cancer. Moreover, further research in the treatment of pancreatic cancer should be underpinned by an improved understanding the underlying pathogenesis of the disease at a cellular, molecular and genetic level.

Acknowledgement

I thank Dr Wong Ho Cheong for valuable advice and input in this article

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Clinical Quiz

Dr. KS Tai

Consultant, Queen Mary Hospital

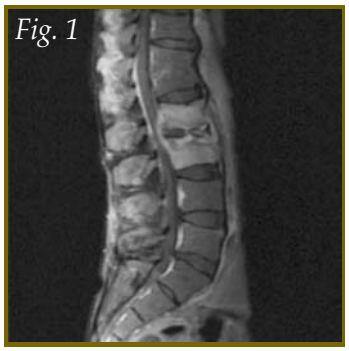


Fig. 1

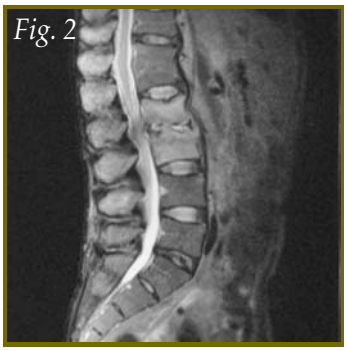


Fig. 2

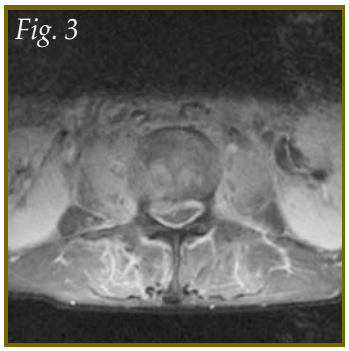


Fig. 3

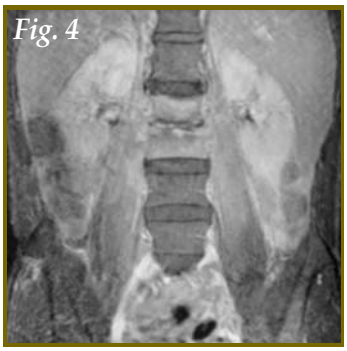


Fig. 4

Clinical history:

- M/44. Presented with low back pain.
- MRI scan of the L-S spine was performed.
- Please comment on the imaging findings and give your diagnosis.

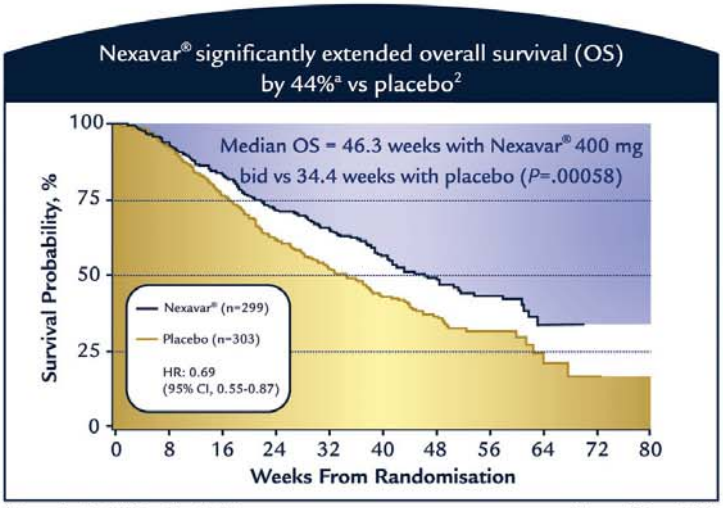
Diagnosis:

Infective spondylodiscitis of L2-3 with mild epidural extension.
Osteomyelitis of right ilium.

(See P. 37 for answers)

Nexavar® -the first and only systemic treatment approved for hepatocellular carcinoma (HCC) can...

Take Life Further



[a]Formula: (1.0/HR - 1) x 100%

Adapted from Ref.2

- Nexavar® doubled the median time to tumour progression vs placebo (24 weeks vs 12.3 weeks; *P*=.000007)[1]
- Generally well tolerated[3]

NEXAVAR® - Abbreviated Prescription Information

Qualitative and quantitative composition: 200 mg sorafenib (as tosylate). Indication: 1. Treatment of patients with advanced renal cell carcinoma. 2. Treatment of hepatocellular carcinoma. Dosage and Administration: The recommended daily dose of NEXAVAR® is 400 mg (2 x 200 mg tablets) taken twice daily, without food (at least 1 hour before or 2 hours after eating). Treatment should continue until the patient is no longer clinically benefiting from therapy or until unacceptable toxicity occurs. Contraindications: Hypersensitivity to sorafenib or to any of the excipients. Warnings and Precautions: Hand-foot skin reaction and rash, usually CTC grade 1 and 2. Increased incidence of arterial hypertension (usually mild to moderate, early in the course of treatment). Blood pressure should be monitored regularly and treated as appropriate. Increased risk of bleeding. Increased incidence of cardiac ischaemia/infarction. Levels of sorafenib may be increased in patients with severe hepatic impairment. Infrequent bleeding events or elevations in INR have been reported in some patients taking warfarin concomitantly. Patients on such kind of therapy should bemonitored. Temporary treatment interruption and/or dose modification or discontinuation maybe considered, depending on the severity of the observed adverse reactions. No formal studies on wound healing have been conducted. Temporary interruption of Nexavar® therapy is recommended in patients undergoingmajor surgical procedures. Experience of use in the elderly is limited and cases of renal failure have been reported. High risk patients according toMSKCC prognostic group were not included in the phase III study in renal cell carcinoma and benefit-risk has not been evaluated in these patients. Caution is recommended when administering Nexavar® with compounds that are metabolised/eliminated predominantly by the UGT1A1 (e.g. irinotecan) or UGT1A9 pathways. Decreased plasma concentrations of sorafenib cannot be excluded with concomitant administration of anti-acidicmedicinal products. Caution is recommended when sorafenib is co-administered with docetaxel. Undesirable effects: Very common: lymphopenia, hypophosphataemia, haemorrhage (incl. gastrointestinal, respiratory tract, cerebral), hypertension, diarrhoea, nausea, vomiting, rash, alopecia, hand-foot syndrome (palmar plantarerythrodysaesthesia syndrome), erythema, pruritus, fatigue, pain (mouth, abdominal, bone,tumour, headache), increased amylase and lipase. Common: leucopenia, neutropenia, anaemia, thrombocytopenia, anorexia, depression, peripheral sensory neuropathy, tinnitus, hoarseness, constipation, stomatitis (including dry mouth and glossodynia), dyspepsia, dysphagia, dry skin, dermatitis exfoliative, acne, skin desquamation, arthralgia,myalgia, erectile dysfunction, asthenia, fever, influenza like illness, weight decrease, transient increase in transaminases.

Reference:
1. Hong Kong Prescribing Note (Nexavar®, BHC)
2. Data on file (BHC)
3. Abou-Alfa GK, Schwartz L, Ricci S et al. Phase II study of sorafenib in patients with advanced hepatocellular carcinoma. J Clin Oncol 2006; 24: 4293-300.

Study design: A randomized, double-blind study in 602 patients with advanced measurable HCC. Patients were randomized to receive either Sorafenib 400 mg bid or placebo. Primary efficacy endpoints were overall survival and time to symptomatic progression. Secondary endpoints included time to progression and disease control rate.

Please consult the full prescribing information before prescribing.

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HK.04.2008.0011 03/04/2008

Editor's Dinner

The Hong Kong Medical Diary Editor's Dinner was held on 27 June 2008 at The Hong Kong Club. A total of 28 editors and guests joined the Dinner. The Federation took the opportunity to express our sincere gratitude to all Issue Editors and Dr. Walter King (Editor-in-Chief, 2004-2007) for their contribution for the Hong Kong Medical Diary.

Society News

News from Member Societies:

British Medical Association (Hong Kong Branch)
Updated office-bearers for the year 2008-2010 are as follows: President: Dr. Adrian WU; Vice-President: Dr. Raymond LO; Honorary Secretary: Dr. Anthony LI; Honorary Treasurer: Dr. Clarence LEUNG

Hong Kong Association of Sports Medicine & Sports Science
Updated office-bearers for the year 2008-2009 are as follows: President: Dr. Patrick Shu-hang YUNG; Honorary Secretary: Mr. Raymond Chi-hung SO; Honorary Treasurer: Dr. John Ping-shan WONG

Hong Kong Orthoptists Association
Updated office-bearers for the year 2008-2009 are as follows: Chairlady: Ms. Betty FONG; Vice-Chairman: Mr. KWOK Shing Chin; Honorary Secretary: Mr. Edmond LEUNG; Honorary Treasurer: Ms. TSANG Chi Shan

The Hong Kong Pain Society Limited
Updated office-bearers for the year 2008-2009 are as follows: President: Dr. CHEN Phoon Ping; Honorary Secretary: Ms. Rainbow Ka-yee LEUNG; Honorary Treasurer: Dr. Steven Ho-shan WONG

Hong Kong Urological Association
Updated office-bearers for the year 2008-2010 are as follows: President: Dr. Ming-kwong YIU; Honorary Secretary: Dr. Peggy Sau-kwan CHU; Honorary Treasurer: Dr. Simon Sai-man CHU

The Practising Pharmacists Association of Hong Kong
Updated office-bearers for the year 2008-2009 are as follows: President: Ms. Iris CHANG; Honorary Secretary: Ms. Rosanna WONG; Honorary Treasurer: Mr. Kevin CHEUNG

New Member Society:

Dental Society, HKUSU
Office-bearers: Chairperson: Ms. Carmen Ka-man CHAN; Vice-Chairpersons: Mr. Alvin Yue-hin KUNG, Ms. Roxy Man-ching NG; General Secretary: Mr. Angus Cheuk-hin HO; Financial Secretary: Mr. Pitar Ho-cheung CHOI

The Hong Kong Society of Cytogenetics Limited
Office-bearers: President: Mr. Wing-kwong CHAN; Honorary Secretary: Dr. Thomas Shek-kong WAN; Honorary Treasurer: Mr. Kin-wah SUEN

FMSHK would like to welcome The Hong Kong Society of Cytogenetics Limited and Dental Society, HKUSU as associate member and student member of the Federation respectively.

Society's Message

Hong Kong Midwives Association

Hong Kong Midwives Association was established in 1967, originated from The Hong Kong Nurses and Midwives Association which was founded in 1940. It is the only professional association for midwives in Hong Kong. We represent Hong Kong SAR as the Member Association of International Confederation of Midwives. All the members are registered midwives under the Midwives Registration Ordinance in Hong Kong. Up till now, our association has over 700 Full Members. We also welcome other nursing professionals to join as Associate Members.

Midwife & Baby Care in the old days

The aims of the association are as follows:
1) To protect and maintain the standards of midwifery practice in Hong Kong.
2) To explain and expound the laws and regulations of Hong Kong for the information of midwives.
3) To make representation to the Government or any of its departments on any questions or matters affecting the standards of midwifery in Hong Kong.
4) To promote and encourage unity and friendly relationship among midwives.
5) To advance and promote learning and education and to grant scholarships and prizes.

In these regards, we shall:
1. Provide training and learning opportunities to midwives.
2. Represent our profession in the Hong Kong Midwives Council to govern the development and monitor the standards of our practice.
3. Represent midwives of Hong Kong and participate as member of the International Confederation of Midwives.
4. Provide education to the public with the view to improve the public's awareness in health care during pregnancy as well as baby care and promote breast feeding.

Midwife & Parentcraft nowadays

In Year 2000, we collaborated with the Obstetrical & Gynaecological Society of Hong Kong to launch the Journal of Gynaecology, Obstetrics & Midwifery, the first of its kind in Hong Kong and worldwide. In order to further enhance the training and development of midwifery practice, as well as to focus more on standards for midwifery practice, the association intends to establish a College of Midwives to achieve the set goals in the near future.

You are cordially invited to browse our website on http://midwives.org.hk and get connected with us.

Hong Kong College of Anaesthesiologists (HKCA)

Our College is now 18 years old and now we feel that we should use our experience to help other neighbouring countries establish their own uniform training and accreditation standards. Also with the knowledge that we have gained in conference organisation with the Society of Anaesthetists of Hong Kong, we are planning to hold even larger international scientific meetings and we will be sending a delegation to bid for the World Congress of Anaesthesiologists to be held in 2016.

All the Boards and Committees have had another busy year and we have again organised clinical and basic science courses for trainees that have been very well received. Simulation is an important part of training in professions where critical incidents may occur infrequently but need to be rapidly and appropriately treated e.g. airlines, power stations. Anaesthesia has been at the forefront of such developments in medical training and our Institute of Clinical Simulation is now in the process of expansion with the appointment of a full time staff manager to coordinate the courses and manage the facility. More instructors have been recruited from other disciplines and medical specialties as well as developing overseas collaboration. Consequently a wide range of courses are now being offered not just for anaesthetists. These courses are available to both trainees and specialists who wish to refresh certain skills. As advanced human patient simulators become more widespread, it will not be surprising if they eventually become an integral part of accreditation and it is important that we support this facility.

The Board of Intensive Care Medicine has introduced a 2 year training programme that is open to both HKCA and College of Emergency Medicine trainees undergoing Higher Vocational training.

The Board of Pain Medicine will change the examination format next year to include an oral examination.

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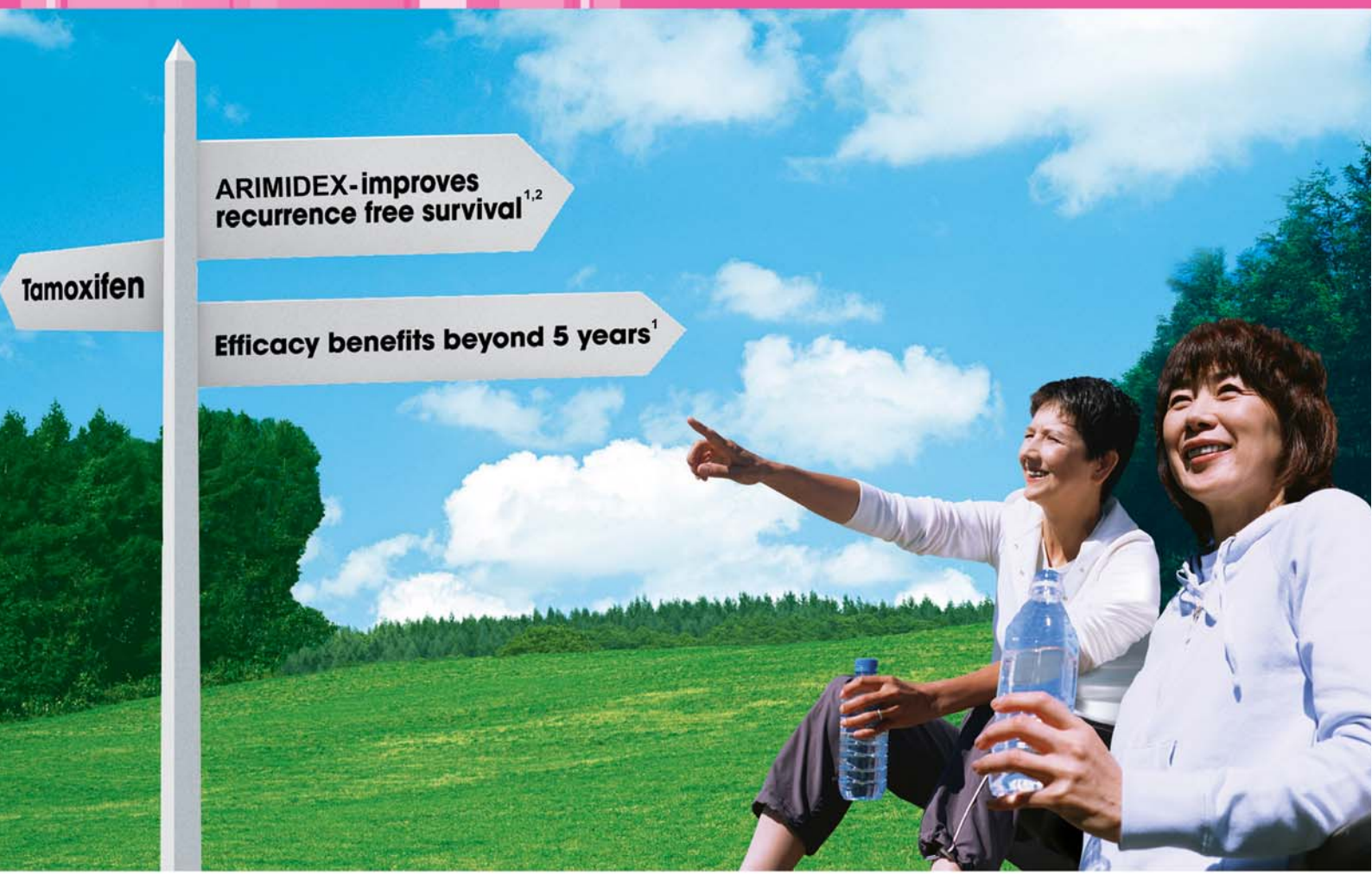

Make your decision with confidence and prevent recurrences from the start for your breast cancer patients*

ATAC
ARIMIDEX, Tamoxifen, Alone or in Combination Trialists' Group

* Breast cancer in hormone receptor positive postmenopausal women

References 1. ATAC's (Arimidex, Tamoxifen, Alone or in Combination) Trialists' Group. *Lancet.* 2005;365:60-62.
2. Houghton J. *J Clin Oncol.* 2005;23(16pt 1 Suppl S):24S, Abs 582.

ABBREVIATED PRESCRIBING INFORMATION

Presentation: Anastrozole film-coated tablet. **Indications:** 1) Adjuvant treatment of postmenopausal women with hormone receptor-positive early invasive breast cancer. 2) Adjuvant treatment of early breast cancer in hormone receptor positive postmenopausal women who has received 2 to 3 years of adjuvant tamoxifen. 3) Treatment of advanced breast cancer in postmenopausal women. **Dosage:** 1mg tab once daily. Early disease: Treat for 5 yr. **Contraindications:** Premenopausal women; pregnancy & lactation; severe renal impairment (ClCr<20mL/min); moderate or severe hepatic disease; hypersensitivity to any of its ingredients. **Precautions:** Menopausal status should be defined biochemically if there is doubt; children; osteoporosis; treatment with LHRH analogues; patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take Arimidex. **Interactions:** Oestrogen-containing therapies, tamoxifen. **Undesirable effects:** Hot flushes, asthenia, joint pain/stiffness, vaginal dryness, hair thinning, rash, nausea, diarrhea, headache. **Full local prescribing information is available upon request. API.HK.ARI.0706**

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Sunday	Monday	Tuesday	Wednesday	Thursday	Friday	Saturday
					1	2
★ HKMA Structured CME Programme at Queen Elizabeth Hospital Year 08/09 (V) - O&G and X-ray 3	4	★ Common Psychiatric Problems ★ FMSHK Officers' Meeting 5	6	★ HKMA Council Meeting 7	8	★ Colposcopy Workshop 2008 ★ Refresher Course for Health Care Providers 2007/2008 (XII) - Handling Demented Patients in Primary Care 9
★ HKMA Trailwalker Training Session III (Stage 4 - 5) 10	★ HKMA - Shatin Community Network CME Lecture on Advances and Use of Psychiatric Drugs in Primary Care 11	★ HKMA CME - Hepatitis B - Treatment Goals 12	★ Hong Kong Neurosurgical Society Monthly Academic Meeting - "Neuronavigation: The GPS of Neurosurgery" 13	★ HKMA Structured CME Programme with Hong Kong Sanatorium & Hospital Year 2008 (VIII) 14	15	16
17	18	★ Common Psychiatric Problems 19	20	★ FMSHK Executive Committee Meeting & Council Meeting 21	22	★ HKMA Trailwalker Training Session IV (Stage 6 - 8) 23
24		★ Common Psychiatric Problems				
31	25	26	27	28	29	30

Medical Diary of August

Date / Time	Function	Enquiry / Remarks
3 SUN 2:00 pm	**HKMA Structured CME Programme at Queen Elizabeth Hospital Year 08/09 (V) - O&G and X-ray** Organised by: The Hong Kong Medical Association & Queen Elizabeth Hospital Speaker: Dr. MA Wei Ling Teresa, Dr. LEE Chung Nin & Dr. WAI Man Wah Andrew # Lecture Theatre, G/F., Block D, Queen Elizabeth Hospital, Kowloon	Miss Viviane LAM Tel: 2527 8452 (Registration Fee is required) 3 CME Points
5 TUE 7:00 pm - 8:30 pm *(19, 26)*	**Common Psychiatric Problems** Organised by: The Federation of Medical Societies of Hong Kong & The Hong Kong College of Psychiatrists Speaker: Various # 4/F, Duke of Windsor Social Service Building, Wanchai, Hong Kong	Ms. June TSANG Tel: 2527 8898 Fax: 2865 0345
8:00 pm - 10:00pm	**FMSHK Officers' Meeting** Organised by: The Federation of Medical Societies of Hong Kong # Gallop, 2/F., Hong Kong Jockey Club Club House, Shan Kwong Road, Happy Valley, Hong Kong	Ms. Paulina TANG Tel: 2527 8898 Fax: 2865 0345
7 THU 8:00 pm	**HKMA Council Meeting** Organised by: The Hong Kong Medical Association Chairman: Dr. H.H. TSE # HKMA Head Office, 5/F., Duke of Windsor Social Service Building, 15 Hennessy Road, Hong Kong	Ms. Christine WONG Tel: 2527 8285
9 SAT 9:00 am - 1:00pm	**Colposcopy Workshop 2008** Organised by: The Hong Kong Society for Colposcopy & Cervical Pathology, Department of O&G, Tuen Mun Hospital Chairman: Dr. S.M. CHAN Speaker: Various # The Auditorium, 8/F, Southern Centre, 130 Hennessy Road, Wanchai, Hong Kong	Ms. Phyllis KWOK Fax: 2855 0947 3.5 CME Points
2:30 pm	**Refresher Course for Health Care Providers 2007/2008 (XII) - Handling Demented Patients in Primary Care** Organised by: The Hong Kong Medical Association & Our Lady of Maryknoll Hospital # Training Room II, 1/F., OPD Block, Our Lady of Maryknoll Hospital, 118 Shatin Pass Road, Wong Tai Sin, Kowloon, Hong Kong	Ms. Clara TSANG Tel: 2354 2440
10 SUN 8:00 pm	**HKMA Trailwalker Training Session III (Stage 4 - 5)** Organised by: The Hong Kong Medical Association	Ms. Dora HO Tel: 2527 8285
11 MON 1:45 pm	**HKMA - Shatin Community Network CME Lecture on Advances and Use of Psychiatric Drugs in Primary Care** Organised by: HKMA - Shatin Community Network Chairman: Dr. Augustine LAM Speaker: Dr. LAM Ho Bun # Royal Park Hotel, Shatin	Miss Viviane LAM Tel: 2527 8452 1 CME Point
12 TUE 1:00 pm	**HKMA CME - Hepatitis B - Treatment Goals** Organised by: The Hong Kong Medical Association Speaker: Dr. HU Hsing Cheng Wayne # Metropolitan Restaurant, 438 King's Road, North Point, Hong Kong	Miss Viviane LAM Tel: 2527 8452 1 CME Point
13 WED 7:30 am	**Hong Kong Neurosurgical Society Monthly Academic Meeting - "Neuronavigation: The GPS of Neurosurgery"** Organised by: Hong Kong Neurosurgical Society Chairman: Dr. TAN Tze Ching Speaker: Dr. LAU Chi Yan Jane # Seminar Room, G/F, Block A, Queen Elizabeth Hospital, Kowloon	Dr. Y.C. PO Tel: 2990 3788 Fax: 2990 3789 2 CME Points
14 THU 2:00 pm	**HKMA Structured CME Programme with Hong Kong Sanatorium & Hospital Year 2008 (VIII)** Organised by: The Hong Kong Medical Association & Hong Kong Sanatorium & Hospital Speaker: Dr. CHAN On On Annie # HKMA Dr. LI Shu Pui Professional Education Centre, 2/F., Chinese Club Building, 21-22 Connaught Road Central, Hong Kong	Miss Viviane LAM Tel: 2527 8452 (Registration Fee is required) 1 CME Point
21 THU 7:00 pm - 10:00 pm	**FMSHK Executive Committee Meeting & Council Meeting** Organised by: The Federation of Medical Societies of Hong Kong # Council Chambers, 4/F., Duke of Windsor Social Service Building, 15 Hennessy Road, Wanchai, Hong Kong	Ms. Paulina TANG Tel: 2527 8898 Fax: 2865 0345
23 SAT 3:00 pm	**HKMA Trailwalker Training Session IV (Stage 6 - 8)** Organised by: The Hong Kong Medical Association	Ms. Dora HO Tel: 2527 8285

Calendar of Events

Meetings

26 - 28 /9/2008	**3rd Regional Conference in Dermatological Laser and Facial Cosmetic Surgery 2008** Organised by: The Hong Kong Association of Specialists in Dermatology and The Hong Kong Society of Dermatology and Venerology & Hong Kong Society of Plastic, Reconstructive and Aesthetic Surgeons # Hong Kong Convention and Exhibition Centre, Wanchai, Hong Kong Enquiry: Ms. Ruby LUI Tel: 3151 8813 Fax: 2590 0099 Website: www.dlfcs2008.com

Meetings

22-25/11/2008	**2nd Asian Preventive Cardiology & Cardiac Rehabilitation Conference cum 7th Certificate Course in Cardiac Rehabilitation** Organised by: Hong Kong College of Cardiology Co-Chairman: Prof. LAU Chu Pak & Dr. LAU Suet Ting Speaker: Various # Hong Kong Convention & Exhibition Centre, 1 Expo Drive, Wanchai, Hong Kong Enquiry: Secretariat Tel: 2527 8285 Fax: 2865 0943 Email: dorahkma@hkma.org Website: http://www.apccrc.com
27-30/11/2008	**Human Dignity in Modern Medicine & 14th Congress of Asian Federation of Catholic Medical Associations** Organised by: The Guild of St. Luke, St. Cosmas and St. Damian Hong Kong Chairman: Dr. Peter AU YEUNG Speaker: Prof. Fr Louis Aldrich SJ & Prof. Luke Gormally # Catholic Disease Centre Enquiry: Congress Secretariat Tel: 2363 0598 Fax: 3764 0579
20-22/2/2009	**CardioRhythm 2009** Organised by: Hong Kong College of Cardiology & Chinese Society of Pacing and Electrophysiology Co-Chairman: Prof. LAU Chu Pak Enquiry: Secretariat Tel: 2899 2035 Fax: 2899 2045 Email: info@cardiorhythm.com Website: http://www.cardiorhythm.com

Courses

1/9/2008 - 3/11/08 (Every Mon)	**Certificate Course in "Health Promotion and Health Counselling" (Code No. TC-HPC-0801)** Organised by: College of Nursing, Hong Kong Enquiry: Secretariat Tel: 2572 9255 Fax: 2838 6280 CNE Accreditation: 24 Points
1/9/2008 - 3/11/08 (Every Mon)	**Certificate Course in "Update in Orthopaedic Nursing" (Code No. TC-ON-0801)** Organised by: College of Nursing, Hong Kong Enquiry: Secretariat Tel: 2572 9255 Fax: 2838 6280 CNE Accreditation: 24 Points
5/9/2008 - 31/10/2008 (Every Fri)	**Certificate Course in "Interpretation of Electrocardiography" (Code No. TC-ECG-0801)** Organised by: College of Nursing, Hong Kong Enquiry: Secretariat Tel: 2572 9255 Fax: 2838 6280 CNE Accreditation: 24 Points
5/9/2008 - 31/10/2008 (Every Fri)	**Certificate Course in "Quality Management in Healthcare" (Code No. TC-QM-0801)** Organised by: College of Nursing, Hong Kong Enquiry: Secretariat Tel: 2572 9255 Fax: 2838 6280 CNE Accreditation: 24 Points

Answer to Clinical Quiz

MRI findings:

1. TIW hypointense and T2W hyperintense areas were seen at the L2-3 vertebrae. The L2-3 disc and adjacent end plates were also involved with T2W hyperintense signal and loss of L2-3 disc height. Mild pre-, para- and epidural extension of lesion were also present. Mild focal spinal stenosis was noted at L2-3 level with crowding of nerve roots. Areas of contrast enhancement were seen at these lesions, indicating active disease.
2. Fusion of T12-Ll vertebral bodies seen with mild anterior wedge deformity. Mild posterior bulge with associated area of T2W hyperintense signal was seen at mid posterior portion of the fused T12-Ll vertebral bodies mildly indenting the thecal sac. No significant compression of the conus medullaris detected. Mild heterogeneous enhancement was seen at this region might represent residual inflammatory changes from previous episode of spondylitis.
3. Bilateral psoas muscles were also involved which were swollen with contrast enhancement and T2W hyperintense signals. No obvious drainable paraspinal abscess was detected.
4. Enhancing T2W hyperintense areas were also seen at the right ilium suggestive of active infection as well.

Operative/histological findings:

Fluroscopic guided percutaneous bone biopsy of L2-3 vertebrae was performed. Histological examination of the tissue obtained showed acute inflammatory changes. Culture revealed staphylococcus aureus. Patient was given appropriate antibiotic therapy.

Discussion:

Pyogenic infections of the spine involve primarily the disc space in children and the vertebral bodies in adults. Men are affected twice as often as women and adults in the sixth and seventh decades are more commonly affected. The lumbar spine is most frequently involved. Predisposing factors include diabetes, use of steroid or chemotherapy for cancer, immunological disease and IV drug abuse. Staphylococcus aureus accounts for 60% of adult infections, while Escherichia coli, Pseudomonas aeruginosa and Klebsiella account for another 30%.
The patient's symptoms often precede the radiographic findings by several weeks. Culture of the disc material obtained by needle biopsy are negative in 50-70% of patients.

The MRI findings of discitis and osteomyelitis closely match the pathological findings. The signal alternations reflect the early inflammatory response characterised by infiltration of polymorphonuclear leukocytes and fibrin deposition in the adjacent end plates. Bony destruction secondary to lytic enzymes and the associated increased water content are reflected by the increase T2W signal intensity and the decreased signal intensity on TIW images. MRI is the most sensitive imaging technique to make the diagnosis. However the MRI findings may lag behind the clinical symptoms of back pain. If the diagnosis is uncertain, a follow up MRI in a week may show the evolution of the early changes. Similarly the MRI findings may lag behind the healing phase of vertebral osteomyelitis. Thus in the early stages of treatment, laboratory findings such as ESR and white cell count are more helpful in monitoring the response to treatment than the MRI findings.

MRI is helpful in the detection of epidural extension of infective spondylodiscitis. The complete extent of involvement and the degree of cord compression are both clearly delineated by MRI. Gadolinium is useful to distinguish epidural granulation tissue from a frank abscess. Epidural granulation tissue enhances homogeneously while an epidural abscess will be enhanced at its periphery and contains non-enhancing pus in its centre. This differentiation may be helpful in surgical planning.

The findings of healing osteomyelitis include persistent disc space narrowing, decreased T2W signal intensity of the disc consistent with disc degeneration, fusion of adjacent vertebral bodies, and resolution of the high T2W signal intensity in the adjacent end plates corresponding to resolution of the oedema. If an epidural abscess was present, the epidural space also returns to normal.

Dr. KS Tai
Consultant, Queen Mary Hospital

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References: 1. Herbrecht R, Denning DW, Patterson TF, et al, for the Invasive Fungal Infections Group of the European Organisation for Research and Treatment of Cancer and the Global *Aspergillus* Study Group. Voriconazole versus amphotericin B for primary therapy of invasive aspergillosis. *N Engl J Med*. 2002;347:408-415. **2.** Kullberg BJ, Sobel JD, Ruhnke M, et al. Voriconazole versus a regimen of amphotericin B followed by fluconazole for candidaemia in non-neutropenic patients: a randomised non-inferiority trial. *Lancet*.2005;366:1435-1442. **3.** Data on file. Pfizer Inc, New York, NY. **4.** Elter T, Sieniawski M, Gossmann A, et al. Voriconazole brain tissue levels in rhinocerebral aspergillosis in a successfully treated young woman. *Int J Antimicrob Agents*. 2006;28:262-265. **5.** Capitano B, Potoski BA, Husain S, et al. Intrapulmonary penetration of voriconazole in patients receiving an oral prophylactic regimen. *Antimicrob Agents Chemother*. 2006;50:1878-1880.

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