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  Dr. James CS Chim

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Demethylation Therapy in Haemic Cancer

Dr. James CS Chim

Editor

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 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 Receptor (EGFR) (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 associated with 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 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 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.

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 ABL by a chromosomal translocation leading to activation of oncogenes. An example is the constitutive activation of cytosolic tyrosine kinase 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 Receptor (EGFR) (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.

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On the other hand, another important advance is made in the advent of more potent anti-fungal therapeutics. 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.
VIDAZA is FDA-approved for the treatment of all myelodysplastic syndrome (MDS) subtypes*: 

~ Refractory anemia (RA) or refractory anemia with ringed sideroblasts (RARS), if accompanied by neutropenia or thrombocytopenia or requiring transfusions

~ Refractory anemia with excess blasts (RAEB)

~ Refractory anemia with excess blasts in transformation (RAEB-T)

~ Chronic myelomonocytic leukemia (CMMoL)

*According to the FAB (French-American-British) Classification System.
Epigenetic Therapy Comes of Age: Waking Up Silenced Tumour Suppressor Genes in Myelodysplastic Syndrome

Dr. James CS Chim

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 monocytuses 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 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 deacetylation 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 (alias P15), CDKN2A (alias P16), P73, DAP kinase, SHP1 has been reported in various haematological malignancies.\(^9\)\(^\text{—}\)\(^\text{19}\) These genes either regulate progression of the cell cycle (CDKN2A and B), and hence cellular proliferation, the induction of apoptosis upon detection of oncogenic transformation (P14, P73 and DAP kinase) or intracellular JAK/STAT signalling such as SHP1.\(^9\)\(^\text{—}\)\(^\text{19}\) 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.\(^13\)\(^\text{—}\)\(^\text{15}\)\(^\text{,}\)\(^\text{18}\) 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 reactives 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.\(^21\) 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. 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). 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<0.001). 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. 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). 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.

**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, and in the subgroup of high-risk MDS in the Decitabine trial. 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 deacetylase 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.**

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<th>Prognostic Variable</th>
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<td>Karyotype*</td>
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<td>Intern.</td>
<td>Poor</td>
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<td>Cytopenias</td>
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*Good: Normal, 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

**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, 1997.
4. The risk of leukaemia is NOT increased in MDS

2. There are 5 disorders under the FAB classification

1. MDS is characterised by peripheral cytopenia with a hypercellular bone marrow

completed answer sheets via fax (2865 0345) or by mail to the Federation Secretariat on or before 31 August 2008.

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.

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

References

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

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**Answers to July 2008 issue**

**Skin Cancer Management**


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

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<td>Certificate Course on Respiratory Medicine 2008</td>
<td>The Hong Kong Thoracic Society &amp; American College of Chest Physicians (HK and Macau Chapter)</td>
<td>Nurses and Allied Health Professions</td>
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NovoSeven® induces haemostasis rapidly with a unique mode of action.
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

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 DNA2, 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 demethylase3-5. 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 species6. 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 level7. 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 drinks8. 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 enzyme9. 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 faeces10. 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 death11.

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 Trichosporon12. Synergistic activity of amphotericin B with flucytosine has been demonstrated against
Clinical Scenario Requiring Systemic Antifungal Agents

Empirical Treatment for Neutropenic Fever
Neutropenic fever in a patient is defined as a sustained temperature of >38°C for more than one hour with an absolute neutrophil count (ANC) < 500 cells/mL. 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. Recent trials however demonstrated that caspofungin was associated with a significantly higher survival rate at seven days after the completion of therapy and a superior safety profile compared to amphotericin B. The primary choice is caspofungin as first-line empirical therapy in patients with suspected fungal infections. Voriconazole and liposomal amphotericin B are effective alternates. 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.

Invasive Aspergillosis
The diagnosis of invasive aspergillosis is based on culture and histology, aided by new tests including galactomannan and PCR testing. The Infectious Diseases Society of America (IDSA) has recommended voriconazole as the initial treatment of choice for invasive aspergillosis. 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. Similar efficacy and safety profile is expected from posaconazole. 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. 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, whereas combinations of caspofungin and amphotericin B have a synergistic effect. 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. 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.

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. 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 ciclosporine, 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.

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.

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.
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 catheter in-situ, on broad-spectrum antibiotics and on haemodialysis. Diagnosis of candidaemia is based on blood culture with the BACTEC system. Other methods of diagnosis include tissue biopsy and antigen testing with beta-D-glucan assay. 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 is more widely used.

With the emergence of voriconazole that is fungicidal against filamentous fungi with much fewer adverse effects, it is an alternate to amphotericin B. Posaconazole 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 function.

New antifungal agents including echinocandins and the new triazoles will overcome resistant strains with greater efficacy and less toxicity.

References


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

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

SPRYCEL™ is indicated for the treatment of adults with chronic, accelerated, or myeloid or lymphoid blast phase chronic myeloid leukemia with resistance or intolerance to prior therapy including imatinib.

SPRYCEL™ is also indicated for the treatment of adults with Philadelphia chromosome-positive acute lymphoblastic leukemia with resistance or intolerance to prior therapy.

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Targeted Therapy for Non-small Cell Lung Cancer

Dr. James CM Ho

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. 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. 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. 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.

In general, malignant tumours cannot grow beyond 2mm in size without developing a vascular supply. 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. Angiogenesis, whether physiological or pathological, is controlled by the balance between proangiogenic and antiangiogenic factors (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. 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.

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. 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%). 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 5%), 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 be better defined, especially in the adjuvant treatment for early-stage disease after curative lung resection or the first-line treatment for advanced disease.
Part-time Postgraduate Courses

Postgraduate Diploma in Community Psychological Medicine
社區精神醫學深造文憑

Postgraduate Diploma in Community Geriatrics
社區老年醫學深造文憑

Quotable Qualification by the Medical Council of Hong Kong

Each course comprises two Modules. Applicants can enroll in one Module, or both Modules at the same time if they prefer. The Postgraduate Diploma will be granted to students who have completed both Modules and passed the final assessment.

Postgraduate Diploma in Community Psychological Medicine:
Module I – Seminars (20 sessions)
Module II – Clinical Attachment (20 sessions of case discussion, clinical training in psychotherapy and clinical teaching by specialist clinicians)

Postgraduate Diploma in Community Geriatrics:
Module I – Distance Learning (10 weeks) & Interactive Workshops (5 sessions)
Module II – Clinical Attachment (25 sessions of rehabilitation and clinical geriatric teaching)

The Conjoint PDCG/DGM Clinical Examination enables primary care doctors enrolled in the Postgraduate Diploma in Community Geriatrics (PDCG) to attain the Diploma in Geriatric Medicine (DGM) offered by the Royal College of Physicians and Surgeons of Glasgow.

The two courses will commence in September on a part-time basis of half a day per week. Tuition fee for the whole programme of each course is HK$42,000, and that for Module I and Module II are HK$12,000 and HK$30,000 respectively, subject to adjustment in 2008/2009.

Closing date for application:
15th August 2008
Certificate Course in Clinical Dermatology

The Course, jointly organized by the Family Medicine Unit and Division of Dermatology, consists of 10 weekly seminars conducted by specialist dermatologists from 8 October to 17 December 2008 on Wednesday afternoons (no class on 19 November 2008).

Applicants can choose to attend the full Course or individual seminars. Tuition fee for the whole Course is HK$5,000, and that for spot admission is HK$700 per session. The Certificate will be awarded to candidates who have enrolled in the full Course and attended at least 80% of the sessions.

Closing date for application:
20th September 2008

Application forms for the above programmes can be downloaded from our websites:
www.hku.hk/fmunit/geriatrics
www.hku.hk/fmunit/psychiatry
www.hku.hk/fmunit/dermatology

For further information, please contact Magdalene Tang, Executive Assistant at 2518 5688 (voice mail) or 2814 7475 (fax) or email to magtang@hku.hk.

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

<table>
<thead>
<tr>
<th>Proangiogenic factors</th>
<th>Antiangiogenic factors</th>
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</thead>
<tbody>
<tr>
<td>Acidic and basic fibroblast growth factor</td>
<td>Angiostatin</td>
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<tr>
<td>Angiogenin</td>
<td>Endostatin</td>
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</tbody>
</table>
| Hepatitis C virus growth factor | Interferon-α-
| Interleukin-8 | Interferon inducible protein-10 |
| Placenta growth factor | Platelet factor 4 |
| Platelet-derived endothelial cell growth factor | Prostatin fragment |
| Transforming growth factor-α | Thrombospondin |
| Tumour necrosis factor-α | Tissue inhibitor of metalloproteinase |
| Vascular endothelial growth factor | Vascuostatin |

* Adapted from reference no. 8

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

<table>
<thead>
<tr>
<th>Clinical</th>
<th>Molecular</th>
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<tbody>
<tr>
<td>East Asian descent</td>
<td>EGFR TK domain-sensitizing mutations</td>
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<tr>
<td>Female gender</td>
<td>EGFR polymorphisms</td>
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<tr>
<td>Nonsmokers</td>
<td>EGFR amplification</td>
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<tr>
<td>Adenocarcinoma histology</td>
<td>EGR1 expression</td>
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</table>

* Adapted from reference no. 22

References

Recent Medical Advances in Breast Cancer

Dr. Janice WH Tsang

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

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. 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.

Indications for Adjuvant Chemotherapy

Randomised trials have shown improved survival with the use of adjuvant chemotherapy after breast cancer surgery. 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. However, adjuvant treatment should be tailored to individuals, taking into account patients’ comorbidities and preferences.

Adjuvant Chemotherapy - Past and Present

In the 1970s, CMF (Cyclophosphamide, Methotrexate and 5-FU) was the backbone of adjuvant chemotherapy for breast cancer. 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%. 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. 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. 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%). 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.

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. 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.\textsuperscript{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 (HerbB-2 / HER-2) positive disease, which is associated with aggressive disease, a higher risk of relapse and a poorer prognosis.\textsuperscript{13,14} Trastuzumab (Herceptin\textsuperscript{®}), 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.\textsuperscript{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\textsuperscript{17}. Four major international adjuvant trials - Herceptin\textsuperscript{®} Adjuvant (HERA), National Surgical Adjuvant Breast and Bowel Project (NSABP) B-31, North Central Cancer Treatment Group (NCCCTG) 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.\textsuperscript{18} A small Finnish trial, FinHer, investigating another regimen of trastuzumab, has also shown similarly positive results.\textsuperscript{19} Meta-analysis of these five randomised trials further supported the above benefits in terms of disease-free and overall survival.\textsuperscript{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%.\textsuperscript{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\textsuperscript{®}) 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.\textsuperscript{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.\textsuperscript{22} Results from the phase III randomised, double-blind, multicentre, placebo-controlled trials of lapatinib in the adjuvant setting such as the TEACH (Tykerb\textsuperscript{®} 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 hormonereceptor positive disease since the 1970s.\textsuperscript{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.\textsuperscript{23} The currently available AIs include the nonsteroidal compounds anastrozole (Arimidex\textsuperscript{®}) and letrozole (Femara\textsuperscript{®}), and the steroidal AI exemestane (Aromasin\textsuperscript{®}).

**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.\textsuperscript{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.\textsuperscript{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”)\textsuperscript{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”)\textsuperscript{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.\textsuperscript{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 and require less radiation therapy. The use of adjunct bisphosphonate therapy with adjuvant aromatase inhibitors has been proven to reduce treatment-related osteoporosis. 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.

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

Neoadjuvant, 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 neoadjuvant 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. 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. 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 clinical value in predicting treatment response. Topoisomerase II (TopoII) alpha gene aberrations are the most promising molecular predictors of anthracycline response. 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. 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 embrace of multidisciplinary and evidence-based medicine should continue be the standard of care for our breast cancer patients.
References

34. Grant M. Adjuvant ovarian suppression combined with tamoxifen or anastrozole, alone or in combination with zoledronic acid, in premenopausal women with endocrine-responsive, stage I and II breast cancer: First efficacy results from ABCSG-12. Journal of Clinical Oncology Supplement 2008;26:1086s.
Power to beat Hep C

Throughout the treatment journey – An enduring response lets you predict their success

- **Rapid Viral Responses (RVR)**
  - 92% of genotype 1 low viral load patients who are HCV-RNA negative at week 4 and 24 achieve an (n=235) ¹

- **Early Viral Response (EVR)**
  - 80% of genotype 1 patients achieve who achieve EVR by week 12 go on to achieve an SVR (n=110) ²

- **End Of Treatment Response (EOT)**
  - 86% of genotype 1 patients who are HCV-RNA negative at the end of treatment achieve an SVR (n=309) ³

- **Sustained Viral Response (SVR)**
  - 63% of genotype 1 patients achieve SVR with Pegintron (n=67) ⁴

References:
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THERAPEUTIC INDICATIONS:
VELCADE (bortezomib) for injection is indicated for the treatment of multiple myeloma patients who have received at least 1 prior therapy.

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POSODOSIS AND METHOD OF ADMINISTRATION:
The recommended dose of VELCADE is 1.3 mg/m²/dose administered as a 3 to 5 second bolus intravenous injection twice weekly for 2 weeks (days 1, 4, 8, and 11) followed by a 10-day rest period (days 12-21). For extended therapy of more than 8 cycles, VELCADE may be administered on the standard schedule or on a maintenance schedule of once weekly for 4 weeks (Days 1, 8, 15, and 22) followed by a 13-day rest period (Days 23 to 35). At least 72 hours should be elapsed between consecutive doses of VELCADE.

CONTRA-INDICATIONS:
Hypersensitivity to bortezomib, boron or mannitol.

PRECAUTIONS:
- Monitor complete blood counts. Gastrointestinal toxicity is common, monitor closely. If patients experience Grade 4 haematological toxicities temporarily discontinue use; treatment can be re-initiated at a reduced dose after resolution of toxicities. Patients who experience life-threatening bleeding events during treatment are at a higher risk of future bleeds. Carefully monitor for symptoms of neutropenia. Patients with peripheral neutropathy are likely to experience worsening during treatment. Special care of patients with risk factors for sepsis. Caution is advised when treating patients with a history of syncope receiving medicinal products known to be associated with hypotension, or who are dehydrated due to recurrent diarrhoea or vomiting. Monitor closely patients with cardiac risk factors. Rare reports of acute diffuse infiltrative pulmonary disease of unknown etiology eg pneumonitis, interstitial pneumonia, lung infiltration and Acute Respiratory Distress Syndrome (ARDS). In event of new or worsening pulmonary symptoms perform prompt diagnostic evaluation and treat appropriately. Development or exacerbation of congestive heart failure, Q3 prolongation, Immuno-complex-mediated reactions eg serum sickness, proliferative glomerulonephritis. Discontinue if severe. Patients with renal impairment; monitor closely. Extreme caution in patients with hepatic impairment. Patients with high tumour burden prior to treatment are at risk of tumour lysis syndrome; monitor closely. Caution in patients with amyloidosis. Monitor patients closely when given concomitant medicinal products CYP3A4 inhibitors, CYP2C19 inhibitors or CYP3A4 inducers. Exercise caution when combined with CYP3A4- or CYP2C19 substrates.

INTERACTIONS:
- No formal drug-drug interaction studies conducted. In vitro studies indicate that bortezomib is a weak inhibitor of the cytochrome P450 (CYP) isoenzymes 1A2, 2C9, 2C19, 206 and 3A4. In clinical trials, hyperglycaemia were reported in diabetic patients receiving oral hypoglycemics.

SIDE EFFECTS:

LEGAL CATEGORY: PS3

PACK SIZES: 1 vial per pack.

FURTHER INFORMATION AVAILABLE FROM: Janssen Pharmaceutica. Unit 1302-1307, Tower 1, Grand Century Plaza, 193 Prince Edward Road West, Mong Kok, Hong Kong.

Reference:

VELCADE is a registered trademark of Millennium Pharmaceuticals, Inc.
Latest Update in the Management of Pancreatic Cancer

Dr. Thomas Yau

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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. 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. 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. 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. 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. 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. 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 folic 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 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 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 chemoradiation was better than chemotherapy alone in patients with locally advanced pancreatic cancer. 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. 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. 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. 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 myelosuppression, 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. However, it has not yet been shown to improve overall survival when compared with the standard administration regimes.

Although the efficacy of single agent gemcitabine 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. 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 regimen 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. EGFR is dysregulated in many tumour types, including 40-65% of pancreatic tumours. 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 monoclonal 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 capectabine 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.

References

Clinical Quiz

Dr. KS Tai
Consultant, Queen Mary Hospital

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:
Infected spondylodiscitis of L2-3 with mild epidural extension.
Osteomyelitis of the right ilium.

(See P. 37 for answers)
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Nexavar® significantly extended overall survival (OS) by 44%* vs placebo

Nexavar® doubled the median time to tumour progression vs placebo (24 weeks vs 12.3 weeks; P=0.00007)

Generally well tolerated

NEXAVAR® - Abbreviated Prescription Information

Qualitative and quantitative composition: 200 mg sorafenib (as tartrate). 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 × 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 ischemia/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 concurrently. Patients on such kind of therapy should be monitored. Temporary treatment interruption and/or dose modification or discontinuation may be 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 undergoing major surgical procedures. Experience of use in the elderly is limited and cases of renal failure have been reported. High risk patients according to mHCC- asian prognostic score 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 metabolized/eliminated predominantly by the UGT1A1 (e.g. metoprolol) or UGT2B7 pathways. Decreased plasma concentrations of sorafenib cannot be excluded with concomitant administration of anti-acid/anti-secretory products. Caution is recommended when sorafenib is co-administered with doxercycline. Unwanted effects: Very common: Lymphopenia, hypophosphatemia, hyperglycaemia (incl. gastrointestinal, respiratory tract, central nervous system), hypertension, diabetes, nausea, vomiting, rash, alopecia, hand-foot syndrome (palmar plantar erythrodysesthesia syndrome); rhinorrhea, pruritus, fatigue, pain (musculoskeletal, bone/joint, headache); increased transaminases and lipase. Common: Incontinence, neuropathies, anemia, thrombocytopenia, dermatitis, depression, peripheral sensory neuropathy, oedema, hoarseness, constipation, stomatitis (including dry mouth and glossodynia), dyspepsia, dysphagia, dry skin, dermatitis cutaneous, acne, skin desquamation, arthralgia, myalgia, erectile dysfunction, asthma, fever, inflammatory skin disorders, weight decrease, stomatitis increase in transaminases.

Reference:
1. Hong Kong Prescribing Note (Nexavar®, BHC)
2. Data on file (BHC)

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.
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.
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.

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.

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

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**ARIMIDEX-improves recurrence free survival**

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*Breast cancer in hormone receptor positive postmenopausal women


**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 5 years of adjuvant tamoxifen. 3. Treatment of advanced breast cancer in postmenopausal women. **Dosage:** 1 mg tab once daily. Early disease: Treat for 5 yr. **Contraindications:** Premenopausal women; pregnancy & lactation; severe renal impairment (CrCl<10mL/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, diarrhoea, headache. Full local prescribing information is available upon request. APLMKARL0709

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<td><em>HKMA Trailwalker Training Session III (Stage 4 - 5)</em></td>
<td><em>HKMA CME - Hepatitis B - Treatment Goals</em></td>
<td><em>Hong Kong Neurosurgical Society Monthly Academic Meeting - &quot;Neuronavigation: The GPS of Neurosurgery&quot;</em></td>
<td><em>HKMA Structured CME Programme with Hong Kong Sanatorium &amp; Hospital Year 2008 (VIII)</em></td>
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<td><em>FMSHK Executive Committee Meeting &amp; Council Meeting</em></td>
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<td><em>HKMA Trailwalker Training Session IV (Stage 6 - 8)</em></td>
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### 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
Operative/histological findings:

MRI findings:

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.

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.

Fusion of T12-L1 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-L1 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 spondylodiscitis.

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
This is the time to choose efficacy first

VFEND® offers superior efficacy versus amphotericin B in invasive aspergillosis and proven efficacy in candidemia*, providing antifungal coverage when it matters most

*In nonneutropenic patients.

Superior efficacy in invasive aspergillosis versus amphotericin B (53% vs 32%, P<0.0001)¹
— Survival rate (71% vs 58% for amphotericin B)¹

Proven efficacy in candidemia in nonneutropenic patients
— As effective as a regimen of amphotericin B followed by fluconazole (41% vs 41%)²

Extended-spectrum efficacy
— The only agent indicated for serious infections due to Fusarium and Scedosporium spp²

Better tolerated than amphotericin B in the treatment of invasive aspergillosis³,⁴
— Fewer drug-related adverse effects, severe adverse events, and discontinuations of therapy due to adverse effects³

Patients can switch to oral therapy when clinically indicated due to available IV and oral formulations³

Extensive penetration and distribution into the central nervous system and epithelial lining of the lungs³,⁵


Detailed prescribing information is available upon request.

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16/F, St Thomas House, 738 King’s Road, North Point, Hong Kong
Tel: (852) 2811 9711 Fax: (852) 2819 1699
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(voriconazole)

EFFICACY WHEN IT MATTERS MOST