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## Editorial

### ■ Editorial

*Dr. James CS Chim*

## Medical Bulletin

### ■ Advances in the Treatment of Multiple Myeloma: Long Awaited

*Dr. James CS Chim*

### ■ Advances in Management of Lymphoma

*Dr. Raymond Liang*

### ■ Chronic Myeloid Leukaemia

**CME**

*Prof. Yok-lam Kwong*

### ■ Haemopoietic Stem Cell Transplantation for Adults with Haematological Malignancies

*Dr. Albert KW Lie*

### ■ Recent Advances in the Management of Chronic Lymphocytic Leukaemia

*Dr. Bonnie Kho  
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### ■ Papers from the Federation's Annual Scientific Meeting 2006: Stem Cells -From Bench to Bedside

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Dr. James CS Chim

## Molecular targets of therapy in haemic cancers

Haemic cancers comprise cancers arising from lymphoid (lymphoma, acute lymphoblastic leukaemia, chronic lymphocytic leukaemia and multiple myeloma) and myeloid lineage (acute myeloid leukaemias [AML] and chronic myeloid leukaemias [CML], myelodysplasia). Many either arise from progenitors or stem cells in the bone marrow or metastasise to the bone marrow (lymphoma, multiple myeloma).

In general, cancers including haematological cancers are characterised by either of the following three mechanisms: 1. activation of oncogenes; 2. loss of function of tumour suppressor genes or 3. inhibition of cellular differentiation.<sup>1,2</sup> (Figure 1) Oncogenes confer proliferative or survival advantage while tumour suppressor normally prevent development of cancer by activating apoptosis. Therefore, cancer cells often have constitutive activation of oncogenes together with inactivation of tumour suppressor genes. On the other hand, failure of proper differentiation of precursor cells may result in cancer. For instance, acute promyelocytic leukaemia (APL), which is a M3 subtype of AML, results from the failure of differentiation of promyelocytes into mature granulocytes when normal myeloid differentiation mediated by RAR is disrupted by PML/RAR (promyelocytic leukaemia/retinoic acid receptor alpha) fusion gene.

Pathogenesis depends on the type of haemic cancers. Acute and chronic leukaemias are often characterised by the presence of reciprocal chromosomal translocations, e.g. t(15;17) in AML-M3, t(8;21) in AML-M2 and t(9;22) in CML.<sup>3</sup> These translocations generate fusion genes, resulting in constitutive activation of oncogenes. For instance, activation of the ABL tyrosine kinase by virtue of t(9;22) is the primary event in chronic myeloid leukaemia. The importance of these reciprocal translocations are demonstrated by the recapitulation of leukaemic phenotype in transgenic mice over-expressing the corresponding fusion gene, e.g. APL in mice harbouring t(15;17) or CML in mice harbouring t(9;22).

Over the last decades, considerable advances have been achieved in the elucidation of the pathogenesis of haemic cancers, and hence identification of molecular targets for therapeutic intervention. Moreover, the efficacy of many of these targeted therapeutic agents has been demonstrated in clinical trials.<sup>4</sup> (Figure 1)

A major breakthrough has been achieved in chronic myeloid leukaemia (CML), in which constitutive activation of cellular tyrosine kinase, ABL, has been demonstrated to be the primary event in leukaemogenesis of CML. Constitutive activation of ABL, a tyrosine kinase mapped to chromosome 22q, results from t(9;22) where BCR/ABL fusion gene is generated. Imatinib (Glivec) or dasatinib are





tyrosine kinase inhibitors that result in very high clinical and cytogenetic response in patients with CML. It has indeed been so effective that allogeneic BMT, a curative procedure once recommended in all young CML patients with an HLA-identical sibling is now only recommended to those not responding to Glivec.

Moreover, CD20 is a pan-B cell marker expressed on the surface all B-cell lymphoma cells. Therapeutic monoclonal antibody targeting CD20 in B-cell lymphoma results in apoptosis of B-cell lymphoma cells, and improved clinical outcome by incorporating the CD20 antibody (known as rituximab or mabthera) with conventional chemotherapy have been demonstrated in clinical trials in both follicular and large B-cell non-Hodgkin's lymphomas. On the other hand, CD52, a cell surface protein expressed in leukaemic cells of B-CLL. Application of Campath, a therapeutic monoclonal antibody targeting CD52, in relapsing CLL patients has resulted in clinical response. In APL, ALL trans retinoic acid (ATRA), a vitamin A derivative, induces differentiation of promyelocytes into granulocytes, and has become the standard induction therapy in patients with APL. In MM, in which NF-kB is constitutively activated, inhibition of NF-kB by bortezomib results in apoptosis of myeloma plasma cells. Moreover, upfront use of bortezomib has resulted in a high rate of complete remission (CR) in patients with MM, a disease in which only about 5% CR rate has been achieved by conventional combination chemotherapy.

Bone marrow transplantation (BMT) comprising high-dose chemotherapy followed by stem cells rescue. The source of stem cells may come from the patient's own bone marrow (autologous bone marrow transplantation) or from a HLA-identical sibling or HLA-matched unrelated donor (allogeneic bone marrow transplantation). The source of stem cells has also been extended to cord blood which is rich in CD34+ stem cells. The impact of allogeneic BMT has been demonstrated in the impressively high rate of cure in acute leukaemias, which is uniformly fatal in the majority treated by conventional chemotherapy. Moreover, autologous BMT has become a standard rescue therapy in patients with relapsing non-Hodgkin's lymphoma.

In summary, major advances in the understanding of the pathogenesis of haemic cancers have been achieved, which is being translated into clinical benefit in various forms of haemic cancer.

### Legend

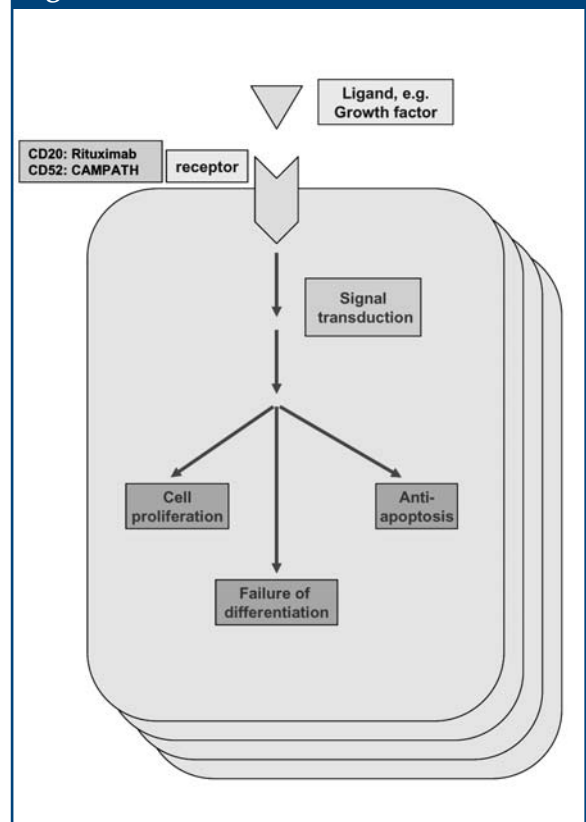
A cancer cell will proliferate into multiple cells (a clonal proliferation) carrying the same genetic information (genotype), and the same appearance (phenotype). Ligand binding to receptor triggers activation of oncogenes by signal transduction, conferring proliferative, survival (anti-apoptosis) advantage or failure of differentiation. Therefore, therapeutic agents may be devised to target the ligand, the receptor, signal transduction pathways. For

example, receptor targeting includes monoclonal antibodies against CD20 (rituximab) or CD52 antibody (Campath); signal transduction targeting include imatinib or dasatinib, tyrosine kinase inhibitors targeting the constitutively active tyrosine kinase ABL in CML; and bortezomib targeting the constitutively activated NF-kB in multiple myeloma; and all trans retinoic acid (ATRA) targeting failure of differentiation in APL.

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Figure 1





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- 4) Denning DW, et al. *Clin Infect Dis* 2002;34:563-571.

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# Advances in the Treatment of Multiple Myeloma: Long Awaited

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Dr. James CS Chim

## Pathogenesis of MM

Multiple myeloma (MM), a neoplastic proliferation of plasma cells, may evolve from monoclonal gammopathy of unknown significance (MGUS).<sup>1</sup> MGUS occurs when limited number of immortalised plasma cells home to the bone marrow, adhere to the stroma, and trigger an autocrine/paracrine IL-6 cytokine loop that confers survival advantage to the myeloma plasma cells. With time, clonal evolution in the plasma cells develops, leading to metastasis of the neoplastic plasma cells to multiple sites of the bone marrow. Interaction of the plasma cell with the marrow micro-environment leads to osteolytic bone lesions, and thus symptomatic multiple myeloma.<sup>2</sup> Therefore, MM is not only a disease of neoplastic plasma cells but also a disease where the micro-environment is of utmost importance to the development of complications and chemo-resistance. As a result, treatment of MM requires targeting of not only the neoplastic plasma cells but also the microenvironment. (Figure 1)

The most important initiation event in myeloma pathogenesis involves upregulation of D-type cyclins, majority by virtue of various chromosomal translocations involving the immunoglobulin heavy chain gene.<sup>3</sup> Deletion of chromosome 13 occurs in about half of the patients with MGUS and MM, and is an important adverse prognostic factor that defies tumour cell kill by high-dose chemo-irradiation inherent with autologous bone marrow transplantation.

## Diagnosis of MM and monitoring of disease activity

The diagnosis of MM is based on plasmacytosis (usually >10%) in the bone marrow, osteolytic bone lesions on skeletal survey, and presence of a monoclonal gammopathy in the serum. Therefore, the usual investigations in a case of suspected myeloma include serum protein electrophoresis, bone marrow aspiration and skeletal survey.<sup>1</sup> New modalities that enable detection of occult bone disease include magnetic resonance imaging of the bone marrow and PET-scan.

While the detection of a monoclonal immunoglobulin in the serum usually raises the suspicion of MM, monoclonal gammopathy may also occur in other lymphoproliferative diseases such as CLL, indolent lymphoma, or even primary amyloidosis in the absence of MM. Moreover, the most common immunoglobulin subtypes in MM, in order of prevalence, are: IgG, IgA

and then light chain disease.

Apart from clinical symptoms, disease activity is monitored by the level of monoclonal paraprotein (M-protein).<sup>1</sup> Recently, serum free light chain has been shown to correlate with M-protein and is a useful adjunct to M-protein measurement for the monitoring of myeloma disease, especially in those with light chain myeloma.

## Natural course of disease in MM

Clinically, patients with MGUS are entirely asymptomatic, which may progress to symptomatic MM at the rate of 1% per year.<sup>1</sup> On the other hand, patients with MM are usually symptomatic with hypercalcaemia, Renal impairment, Anaemia or Bone pain/fracture (abbreviated as CRAB).<sup>1</sup> Conventional treatment comprises combination of alkylators with steroid, usually in the form of melphalan + prednisolone, which induces a response rate of about 50% but complete remission in about 5% of patients. Treatment of patients with MP usually leads to plateau phase when a reduced amount of M-protein remains detectable but at stable levels. The disease inevitably progresses with escalation of M-protein and recurrence of clinical symptoms, which may be controlled with further chemotherapy. However, patients will eventually succumb due to refractory disease. Moreover, high-dose chemotherapy followed by stem cell rescue, i.e bone marrow transplantation (BMT) is only applicable to younger patients in view of its toxicity. Therefore, MM is regarded as a largely incurable disease.

## Treatment goals and cytoreduction chemotherapy

The modalities of treatment in patients with MM depend on the age of the patients. For instance, *cure* is aimed at in young myeloma patients, *prolongation of survival* in myeloma patients entitled for autologous bone marrow transplantation, and *symptomatic control* in the elderly patients. Initial cytoreduction usually involve combination chemotherapy, followed by autologous BMT (ABMT) in those eligible patients. The median survival in MM is about 3-5 years, depending on if the patient has undergone ABMT.

## Prognostic factors

1. Durie-Salmon versus International myeloma staging





(ISS): In Durie-Salmon staging system, assessment of tumour load is based on the presenting clinical parameters (haemoglobin levels, serum calcium levels, extent of osteolytic bone lesions, serum M-protein levels), in which myeloma patients with advanced Durie-Salmon stage fare worse than those with limited stage. However, recently, an ISS incorporating diagnostic parameters such as serum albumin and 2-microglobulin levels presented a better and more convenient prognostic model than Durie-Salmon system.<sup>4</sup>

2. Biological factors: role of karyotypic abnormality is an important factor predicting clinical outcome. For instance, chromosome 13 deletion is a prevalent aberration and presents in about 50% of myeloma patients.<sup>3</sup> Moreover, patients with deletion 13 have a lower response rate and a shorter survival than those without.

## Conventional chemotherapy in MM

MP (melphalan/prednisolone) has been the mainstay of treatment for decades.<sup>1</sup> Subsequent intensification of treatment with additional chemotherapeutic agents did not improve survival. In the early 1990, VAD (vincristine, adriamycin, dexamethasone) has been applied with an improvement in response rate. Importantly, VAD does not contain any alkylator, which will decrease the yield of stem cell harvest for subsequent autologous BMT. Moreover, VAD results in a rapid response and can be applied in patients with renal insufficiency.<sup>1</sup> Therefore, myeloma patients who are eligible for autologous BMT will receive VAD.

## Role of autologous BMT

In the last decade, one of the most important advances in the treatment of MM is the advent of autologous bone marrow transplantation (ABMT), which will enable increase in the rate of complete remission (CR), and prolonged disease-free and overall survival. However, the procedure is not curative but results in significant prolongation of survival.<sup>5</sup> On the other hand, allogeneic bone marrow transplantation (Allo-BMT) with bone marrow rescue from HLA-identical siblings is probably the only curative modality of treatment but the treatment-related mortality is excessive, up to 30%.<sup>5</sup> Therefore, mini-allogeneic BMT by virtue of non-myeloablative chemotherapy, which will render less treatment-related mortality, is currently under intensive research for its efficacy and safety in the treatment of MM.

## New agents in MM: mechanisms, safety and efficacy

### 1. Thalidomide

Thalidomide has been banned in the 1960s as a sedative because of teratogenicity. Thalidomide was approved by FDA for the treatment of MM in 1998. Clinical trials showed that upfront use of thalidomide plus dexamethasone results in a high response rate (>60%). The major side-effects are neuropathy, constipation, bradycardia and venous thrombosis (less common in the orientals). Revlimid is a derivative of thalidomide. However, the major side-effect is myelotoxicity instead of

neuropathy. Early data showed a high response rate of revlimid plus dexamethasone when used as salvage therapy in relapsing myeloma patients.

### 2. Bortezomib (Velcade)

NF- $\kappa$ B is a transcription factor which upregulates genes protecting myeloma plasma cells from apoptosis. However, normally NF- $\kappa$ B is inhibited by I $\kappa$ B by forming a cytosolic complex with I $\kappa$ B, precluding its access to promoter region of its target genes. Bortezomib is a proteasome inhibitor which protects I $\kappa$ B from proteosomal degradation, and thus keeps NF- $\kappa$ B in the cytoplasm, thereby preventing activation of anti-apoptotic genes and leads to apoptosis of myeloma plasma cells. Bortezomib has been shown to be an effective salvage therapy in heavily pretreated, relapsing myeloma patients.<sup>6</sup>

## Impact of novel therapeutic agents on induction therapy of MM

Upfront use of some of these novel therapeutic agents, in particular in combination with conventional chemotherapy, has been shown to increase CR rate from about 5% to up to 30%, which is a major advance in the treatment of MM. Moreover, apart from Revlimid, these agents are not myelotoxic, and thus can be used together with myelotoxic chemotherapeutic agents such as melphalan, doxorubicin or cyclophosphamide. Indeed, MPT (melphalan, prednisolone and thalidomide) combination has resulted in a CR or near CR rate of about 25%,<sup>7</sup> and importantly a prolonged survival compared to those receiving MP alone. Moreover, upfront use of bortezomib with MP results in high CR rate (32%) and total response rate of 89%, which is a major breakthrough in myeloma treatment.<sup>8</sup> Similarly, combination of velcade with doxorubicin and dexamethasone resulted in a CR or near CR rate of 25%.

## General treatment recommendations

Taking into account the difficulty in achieving CR in myeloma, which is a requisite to cure, the advances in the new therapeutic agents, and the survival advantage inherent with bone marrow transplantation, a general treatment recommendation may be devised based on the age of the patient (which limits the application of ABMT) and data from randomised clinical trials.<sup>9</sup> (Figure 2)

1. MM patients <65 years: autologous BMT after initial cytoreduction. There is some studies showing that tandem autologous BMT results in superior survival to one autologous BMT.<sup>9</sup> On the others hand, patients achieving > 90% reduction of M-protein do not benefit from tandem autologous BMT.<sup>9</sup>

2. Elderly MM patients: induction therapy with MPT (melphalan, prednisolone and thalidomide), Velcade plus MP, or MP

## Current Controversies

1. *One autologous BMT versus tandem (double) ABMT*  
ABMT has been shown in multiple randomised clinical trials to result in higher CR rate, superior progression-free

and overall survivals when compared with conventional chemotherapy alone.<sup>8</sup> (Hira et al, 2006) With ABMT, an additional 15%-25% of myeloma patients may achieve CR or near CR.

Moreover, in patients who failed to achieve >90% reduction in M-protein levels after a ABMT, a recent clinical trial has shown superior survival in patients undergoing tandem autologous BMT compared with those undergoing a single autologous BMT. Ongoing clinical studies are conducted to compare the outcome of tandem auto-allo BMT with tandem autologous BMT.

**II. High-risk patients (with high  $\beta_2$ -microglobulin and deletion of chromosome 13)**

As yet, bortezomib is the only agent that appears to overcome the adverse prognostic impact of deletion 13, which impacts survival adversely even in the setting of super-intensive chemotherapy such as tandem autologous BMT. Tandem auto-allo BMT is potentially hazardous because of the inherent GVHD. Therefore, high-risk MM patients, such as those with high ISS stage or deletion 13 karyotype, should be enrolled into clinical trials. Moreover, maximal cytoreduction, preferably CR, should be achieved prior to autologous stem cell harvest, thereby minimising contamination of marrow graft with myeloma plasma cells. Achievement of CR has been largely impossible with conventional combination chemotherapy. Therefore, the increased CR rate associated with the use of these novel agents will hopefully render a high proportion of myeloma patients a CR, who may then undergo BMT with minimal amount of tumour cells.

**Summary**

MM has for a long time been an incurable disease but major advances in bone marrow transplantation and advent of novel therapeutic agents has enhanced the CR rate, the pre-requisite to cure. Optimisation of the application of BMT and novel agents will lead to prolonged survival and hopefully cure in the future. Moreover, bortezomib may overcome a hitherto unconquered adverse prognostic factor of deletion 13. Therefore, it is of utmost importance that chromosomal study has to be performed at diagnosis to risk-stratify the patient. Those with high-risk features may undergo clinical trials incorporating bortezomib induction, followed by auto-mini-allogeneic BMT at the time of minimal residual disease.

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Figure 1. Bone marrow microenvironment interacts with myeloma plasma cells, conferring proliferative and survival (anti-apoptotic) advantage to the tumour cells.

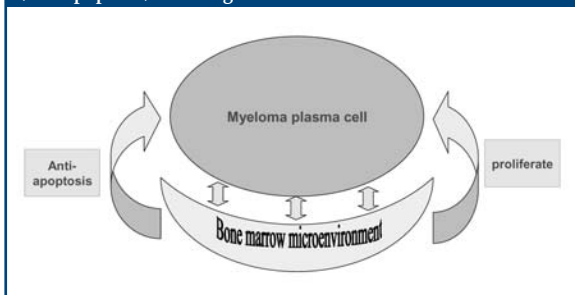
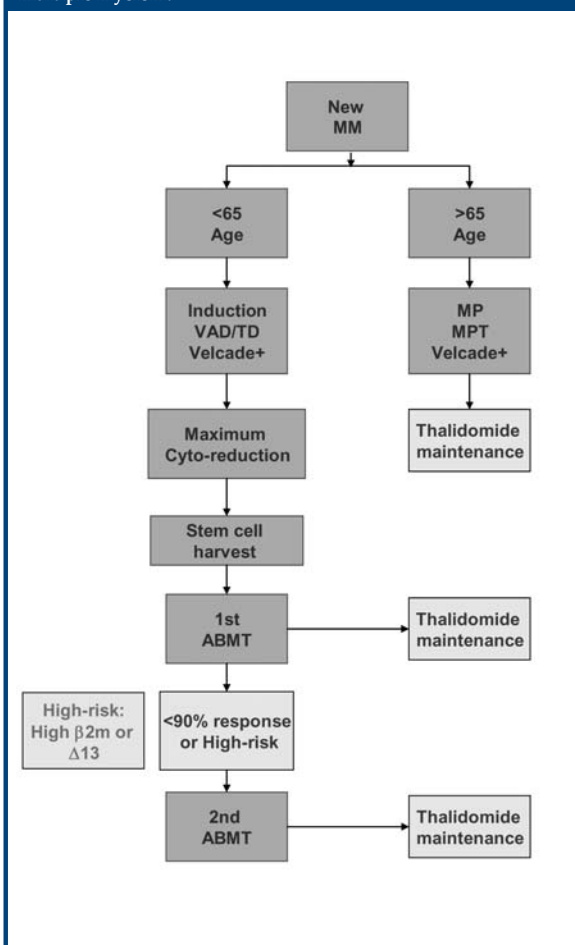
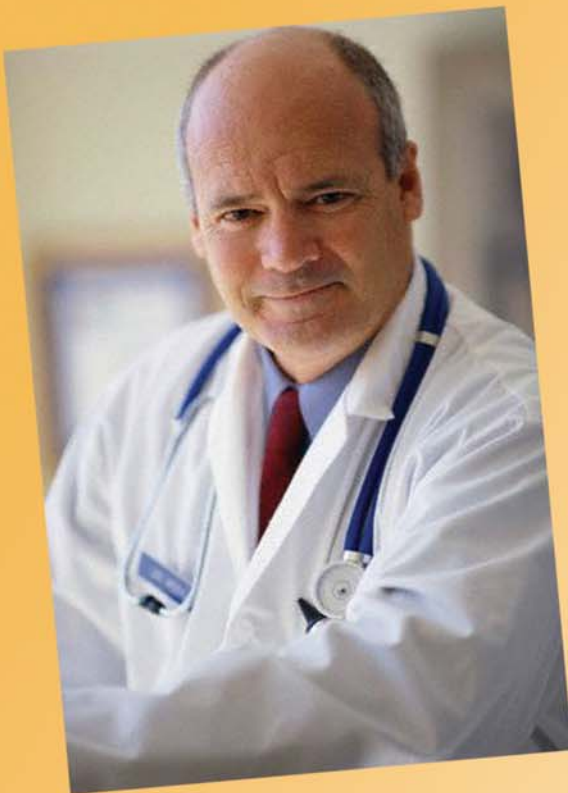


Figure 2. Proposed management algorithm for newly diagnosed multiple myeloma



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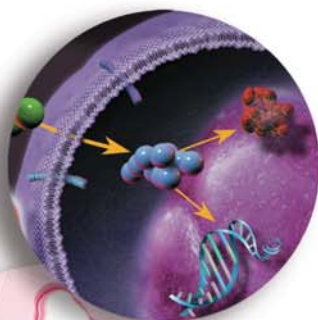
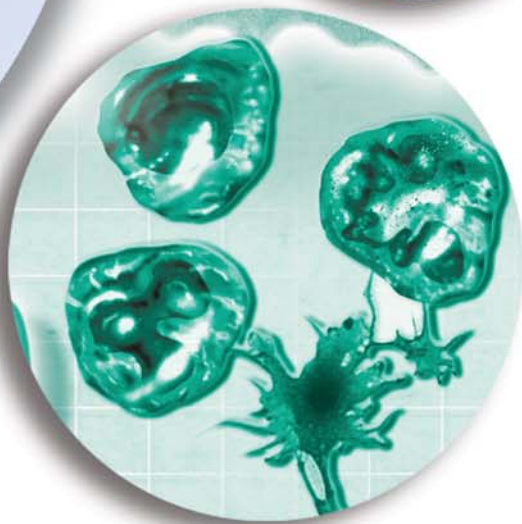
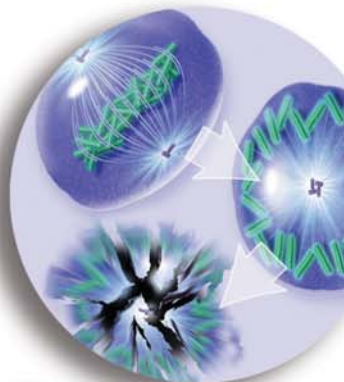
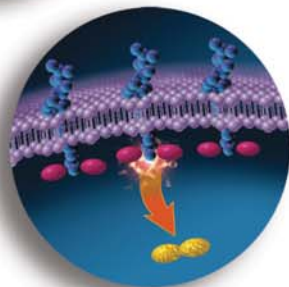
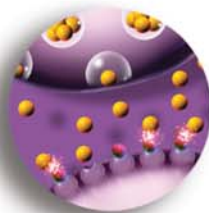
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# Advances in Management of Lymphoma

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## Introduction

The incidence of lymphoma has risen rapidly worldwide, especially in the well developed countries. In Hong Kong, it is one of the top ten commonest cancers with over 650 new cases seen every year. Over 90% of the patients have non-Hodgkin's lymphoma. Compared with the western populations, we have a much lower incidence of Hodgkin's lymphoma and low grade non-Hodgkin's lymphoma, such as follicular lymphoma and small lymphocytic lymphoma. Most cases seen in Hong Kong are aggressive high grade non-Hodgkin's lymphoma. There also appears to be a higher incidence of T-cell or natural killer cell lymphoma in Hong Kong.<sup>1-4</sup>

Although most lymphoma patients present with lymphadenopathy, an extra-nodal primary, such as stomach, nasal cavity and skin are not uncommon. (Figure 1) Lymphoma may practically arise from almost any organ or tissue of the body. A high index of suspicion is essential for early diagnosis.<sup>5, 6</sup> Common metastatic extra-nodal sites include the spleen, liver, bone marrow, pleura and the central nervous system. Systemic symptoms such as fever, night sweat and weight loss may also be present.

## Diagnosis

A well performed tissue biopsy is essential for precise diagnosis. It cannot be replaced by radiological imaging or a fine needle aspiration. Computerised tomography, Magnetic Resonance Imaging or Positron Emission Tomography may help to assess the extent of the involvement and guide the biopsy. A properly performed fine needle aspiration together with a flow cytometric study may strongly suggest a diagnosis of lymphoma, a tissue biopsy specimen if technically feasible however is always preferred for proper diagnosis and classification.

The WHO classification for lymphoma is now widely used. (Table 1-3) This new classification takes into consideration the clinical, morphological, immunological, cytogenetic and molecular genetic features. With more understanding of the pathological processes, the classification is evolving.<sup>7</sup> A new version of the classification is expected to be available in 2008.

## Assessment

The tissue biopsy specimens should preferably be reviewed by experienced pathologists familiar with

lymphoma. Accurate diagnosis and precise histological classification are essential for optimal management of the patients. The extent of the lymphoma involvement can be assessed by modern imaging (CT, MRI and PET).<sup>8</sup> Other important prognostic facts should also be determined. An international prognostic index, incorporating age, performance status, Ann Arbor staging, number of extra-lymphatic sites and serum lactate dehydrogenase level, has been used to predict prognosis of patients with diffuse large B-cell lymphoma.<sup>9</sup> Other prognostic indices have been formulated for other histological subtypes, such as follicular lymphoma.<sup>10</sup>

The patients should also be assessed for any other concomitant illnesses. All lymphoma patients must have their hepatitis B, hepatitis C and HIV status determined. Treatment of the lymphoma may reactivate pre-existing infections. In Hong Kong, 10% of the patients are hepatitis B carriers with a positive serum hepatitis B surface antigen. Chemotherapy given to them for the lymphoma may reactivate the hepatitis and is potentially fatal. This can be effectively prevented by prophylactic anti-viral therapy, such as lamivudine.<sup>11</sup>

## Treatment

Different types of lymphoma warrant different treatment strategies. Chemotherapy is now the mainstay of therapy for most cases of lymphoma. It may be supplemented by local radiotherapy. For Hodgkin's lymphoma, the standard ABVD chemotherapy consists of adriamycin, bleomycin, vinblastine and DTIC.

For follicular lymphoma, a small minority of the patients may have clinical localised disease. Involved field radiotherapy is recommended and gives a potential of cure in about half of the patients. For majority of the patients with more advanced follicular lymphoma, the tumour is considered incurable, despite the fact that it often runs a clinically indolent course. Therefore, an initial wait and watch policy is still recommended if the patient is asymptomatic or without any adverse prognostic factors, especially for elderly patients. When treatment is deemed necessary, a variety of chemotherapy regimens have been adopted, from single agent (chlorambucil or cyclophosphamide) to CVP (cyclophosphamide, vincristine and prednisolone) or CHOP (cyclophosphamide, adriamycin, vincristine and prednisolone). Fludarabine as a single agent or in combination with cyclophosphamide (FC) or mitoxantrone and dexamethasone (FND), is also widely



used. The humanised chimeric anti-CD20 monoclonal antibody has been shown to be an effective therapy for CD-20 positive B-cell lymphoma. It is now considered to be a standard to add the monoclonal antibody to chemotherapy. This practice has been shown to improve the duration of remission and survival. A newer form of therapy with radio-labelled anti-CD20 monoclonal antibody has also been shown to be effective in follicular lymphoma.<sup>12</sup>

For aggressive non-Hodgkin's lymphoma such as the diffuse large B-cell lymphoma, the CHOP chemotherapy, consisting of cyclophosphamide, adriamycin, vincristine and prednisolone, is the most widely used. The treatment offers a high potential for cure. Addition of anti-CD20 monoclonal antibody therapy to the regimen also appears to offer additional benefit. There is no evidence that the other more complicated regimens offer an advantage.<sup>13</sup> Treatment for lymphoblastic lymphoma simulates that for acute lymphoblastic leukaemia. Other subtypes of lymphomas, such as mantle cell lymphoma and peripheral T-cell lymphoma, usually respond poorly to the standard CHOP chemotherapy and a more effective strategy is desperately required.<sup>14</sup>

High dose chemotherapy with autologous peripheral stem cell rescue is mainly used for treating relapsed diseases. It is most effective when the lymphoma remains chemo-sensitive. An allogeneic bone marrow transplant may also be indicated in selected patients, for example when the bone marrow is involved and when an HLA identical donor is available.<sup>15</sup>

With the advances in therapy, the clinical outcome of lymphoma patients has improved significantly. However, the prognosis of some types of lymphoma, such as mantle cell lymphoma and T-cell lymphoma remains poor. Further research on lymphoma is urgently needed. Better understanding of lymphoma may provide effective measures for prevention and even more effective but less toxic therapy.

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**Table 1: WHO Classification for Hodgkin's Lymphoma**

- Classical Hodgkin Lymphoma:
  - Nodular sclerosing
  - Mixed cellularity
  - Lymphocyte rich
  - Lymphocyte depleted (worse prognosis)
- Nodular lymphocyte predominant Hodgkin Lymphoma

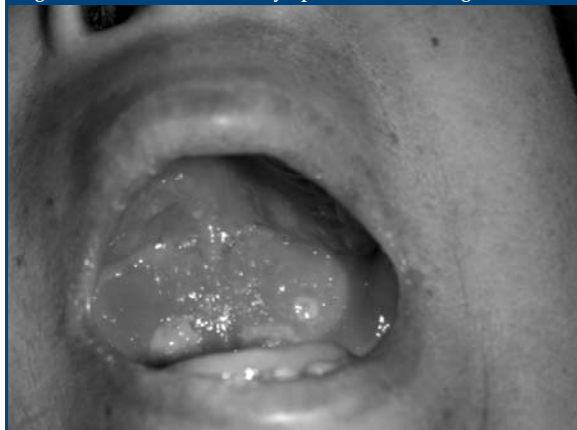
**Table 2: WHO Classification for B-cell Lymphoma**

- B-lymphoblastic lymphoma
- Chronic lymphocytic leukaemia or small Lymphocytic lymphoma
- B-Prolymphocytic Leukemia
- Lymphoplasmacytoid lymphoma
- Splenic marginal Zone lymphoma (Splenic lymphoma with villous lymphocytes)
- Hairy cell leukaemia
- Monoclonal gammopathy of unknown significance / plasmacytoma / myeloma
- Lymphoma of the Mucosa Associated Lymphoid Tissue (Maltoma)
- Mantle cell lymphoma
- Follicular lymphoma
- Nodal marginal zone lymphoma
- Diffuse large B-cell lymphoma
- Mediastinal diffuse large B-cell lymphoma
- Intravascular large B-cell lymphoma
- Primary effusion lymphoma
- Burkitt's lymphoma

**Table 3: WHO Classification for T-cell or NK-cell Lymphoma**

- T-lymphoblastic lymphoma
- T-prolymphocytic leukaemia
- Large granular lymphocyte leukaemia
- Aggressive NK cell leukaemia
- Adult T-cell leukaemia/lymphoma
- Cutaneous lymphoma:
  - Mycosis fungoides
  - Sezary syndrome
  - Cutaneous anaplastic large cell lymphoma
  - Lymphomatoid papulosis
- Extranodal NK/T cell lymphoma, nasal type
- Enteropathy-type T-cell lymphoma
- Hepatosplenic gamma delta T-cell lymphoma
- Subcutaneous panniculitis like T-cell lymphoma
- Peripheral T-cell lymphoma
- Angioimmunoblastic T-cell lymphoma
- Anaplastic large cell lymphoma (Systemic)
- Blastic NK cell lymphoma

**Figure 1: Nasal NK/T-cell lymphoma infiltrating the hard**







# Chronic Myeloid Leukaemia

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*This article has been selected by the Editorial Board of the Hong Kong Medical Diary for participants in the CME programme of the Medical Council of Hong Kong (MCHK) to complete the following self-assessment questions in order to be awarded one CME credit under the programme upon returning the completed answer sheet to the Federation Secretariat on or before 30 April 2007.*

## Introduction

Chronic myeloid leukaemia (CML) is one of the commonest leukaemias. In populations where chronic lymphocytic leukaemia is uncommon, such as Asians, CML is the most frequent leukaemia. The incidence of CML increases with age, although patients of all ages can be affected. It is probably the earliest leukaemia recorded in the literature, being referred to as leucocythaemia. CML is the prototype of haematological malignancy that involves a pluripotential haematopoietic stem cell. This means that leukaemogenesis occurs in a cell that is capable of differentiation into all the different lineages of blood cells. The natural history of CML is that of a triphasic disease, comprising the chronic, accelerated, and the final fatal blastic phases.

## Chronic phase(CP) CML

**Clinical features.** Patients are largely asymptomatic during the chronic phase, which lasts a median of 4 - 5 years. The diagnosis is usually made incidentally, either because of a high white cell count noticed in routine blood counts, or a palpable abdominal mass found during physical examination. Typically, the patient presents with hepatosplenomegaly. The spleen can vary from small to huge in size, extending well into the right lower quadrant. However, the nutritional status of the patient is still preserved, and the patient shows very few signs of an internal malignancy.

**Laboratory features.** The white cell count is increased, and can reach very high levels. The differential count shows the presence of white cells at various stages of maturation, ranging from blasts to mature leucocytes. However, a bimodal distribution is typical, with predominance of myelocytes and neutrophils. Blasts rarely exceed a few percent. There is also an increase in eosinophils and basophils. The haemoglobin is normal, but can be decreased. The platelet count is either normal or increased. The neutrophil alkaline phosphatase score is very low, although the test is infrequently performed. Bone marrow examination shows a hypercellular marrow, with severe granulocytic hyperplasia. There is no or minimal increase in fibrosis.

**Cytogenetic and molecular features.** CML is characterised by the chromosomal translocation

t(9;22)(q34;q21). The shortened derivative chromosome 22 is also known as the Philadelphia (Ph) chromosome, to commemorate the city where this chromosomal translocation, the first chromosomal translocation ever to be recognised in any human malignancy, was initially discovered. The chromosomal translocation results in the reciprocal fusion of the BCR gene on chromosome 22q21 to the ABL gene on chromosome 9q34 to form the chimeric BCR-ABL gene. The ABL gene encodes the ABL protein, which is a tyrosine kinase. ABL becomes constitutively activated in the BCR-ABL fusion protein, thus leading to dysregulated activation. This is the principal mechanism of leukaemogenesis.

**Diagnosis.** The pathognomonic test for CML is detection of t(9;22)(q34;q21) by cytogenetic tests, fluorescence in situ hybridisation (FISH), or molecular tests, including Southern blot analysis and polymerase chain reaction.

## Accelerated phase(AP) CML

**Clinical features.** Most patients will have a previous diagnosis of chronic phase CML. Occasional patients might not have a precedent chronic phase. In contrast to chronic phase, patients in accelerated phase are symptomatic. In addition to features of chronic phase CML, patients present with variable systemic symptoms, including fever, weight loss, bone pain and deteriorating anaemia or thrombocytopenia. The accelerated phase is a transitory period between the chronic and blastic phases, and lasts a median of 3 - 6 months, although in some patients it may be very brief and unnoticeable.

**Laboratory features.** Anaemia and thrombocytopenia of variable degrees develop. The white cell count becomes more difficult to control with medication. Blast and promyelocyte counts are increased in the peripheral blood and bone marrow. Other patients present with increasing eosinophil and basophil counts that cannot be controlled. Rarely, worsening and unrelenting thrombocytopenia may be a clinical manifestation.

**Cytogenetic features.** In addition to t(9;22)(q34;q21), additional karyotypic aberrations indicating clonal evolution are found. Typical additional aberrations include acquisition of an extra Ph chromosome, isochromosome 17q, and trisomy 8.



**Diagnosis.** The diagnosis relies on demonstration of an increase in blast count in the marrow or peripheral blood, and the detection of additional karyotypic aberrations on cytogenetic analysis.

## Blastic phase(BT) CML

**Clinical features.** The majority of patients have an antecedent chronic phase CML. At blastic phase, the patient has an acute leukaemia. Because CML involves a haematopoietic stem cell, blastic transformation can occur to myeloid and lymphoid lineages, so that acute myeloid, lymphoid or sometimes bilineage leukaemias may result. The clinical features are those of an acute leukaemia, with leucocytosis, anaemia and thrombocytopenia. The prognosis of blastic phase CML is poor, with patients surviving only a few months.

**Laboratory features.** There is an increase in blasts in the peripheral blood or bone marrow, exceeding 20% of the differential count.

**Cytogenetic features.** Karyotypic analysis may show chromosomal aberrations additional to t(9;22)(q34;q21). The changes may be those seen during the accelerated phase. Occasionally, chromosomal changes typical of de novo acute leukaemias may be observed, such as t(8;21) and t(15;17).

**Diagnosis.** Cytochemistry and immunophenotyping are necessary to determine the lineage of the acute leukaemia. Lineage definition is important for treatment purposes. Acute lymphoblastic transformation may respond to treatment for de novo acute lymphoblastic leukaemia, reaching a second CP. However, acute myeloblastic transformation in general are refractory to chemotherapy. However, rare cases of transformation into acute promyelocytic leukaemia with t(15;17) may respond favourably to treatment.

## Treatment of CML

The treatment of CML has undergone revolutionary changes in the last three decades. The target of treatment is to suppress the Ph-positive clone. CML used to be an incurable disease with conventional chemotherapy. Both low dose and high dose chemotherapy would result in hematological remission. However, the Ph-positive clone is almost always unaffected. Therefore, the natural history of the disease remains unchanged, and patients treated with chemotherapy invariably undergo fatal blastic transformation. The knowledge of the molecular pathogenesis of CML has now made possible therapy targeted specifically at the BCR-ABL fusion protein, which results in remarkable responses.

### Chemotherapy

Hydroxyurea treatment leads to reduction of leucocyte count. However, the natural history of the disease remains unchanged. Other than for initial leucocyte cytoreduction, chemotherapy plays no role in the modern management of CML.

### Interferon- $\alpha$ (IFN- $\alpha$ )

IFN- $\alpha$  has been shown to prolong survival of CML patients as compared with conventional chemotherapy. IFN- $\alpha$  combined with low-dose cytosine arabinoside improves the cytogenetic response rate, but does not impact on survival as compared with IFN- $\alpha$  treatment as a single agent. IFN- $\alpha$  based regimens give a 25 - 50% 10-year overall survival. Residual disease as positive BCR/ABL by PCR is detectable in the majority of IFN- $\alpha$  treated patients. IFN- $\alpha$  treatment is now largely superseded by tyrosine kinase inhibitors.

### Haematopoietic stem cell transplantation (HSCT)

Allogeneic HSCT used to be considered the best treatment option for CML patients with a suitable HSC donor, whether HLA identical siblings or match unrelated donors (MUD). CML-CP patients undergoing HSCT from a matched related donor have been reported to have overall survivals(OS) of 65% at 10 years and 50% at 18 years. CML patients(OS) transplanted at stages other than first CP have OS of about 20%. However, with the advent of tyrosine kinase inhibitors, HSCT can no longer be considered to be a first choice treatment. It should now only be considered a salvage treatment for patients failing tyrosine kinase inhibitor therapy. For HSCT in CML, several points are worthy of note. Firstly, the use of peripheral blood stem cell HSC is inferior to bone marrow HSC for patients in first CP. The use of peripheral blood HSC is, however, better in patients beyond first CP. For MUD, the use of peripheral blood HSC gives inferior outcome. Furthermore, there are recent concerns for healthy donors given haematopoietic growth factors for mobilisation of HSC. For these reasons, and particularly for CML patients in first CP, bone marrow appears to be the preferred source of HSC.

### First generation tyrosine kinase inhibitor

The first generation tyrosine kinase inhibitor imatinib mesylate has a high affinity for the ATP-binding site of the Abl part of the BCR/ABL fusion protein. It also binds other tyrosine kinases including PDGFR and c-kit. Imatinib is now the standard first line treatment of CML. At a standard dosage of 400 mg, imatinib induces complete haematologic responses in over 95% of patients, and complete cytogenetic responses in about 75% of patients. About half of the patients reaching cytogenetic remission will also achieve a major molecular remission, with > 3 log reduction in the baseline BCR/ABL fusion transcript on Q-PCR analysis. Progression free survival also exceeds 95% at two years. The annual progression to AP/BT in patients with CP on imatinib varies from 1-3%.

**Monitoring of imatinib therapy.** During imatinib therapy, complete haematologic response refers to normalisation of leucocyte and platelet counts, suppression of basophils to less than 5% of the differential count, and a non-palpable spleen. Cytogenetic response refers to the percentage of Ph+ cells, with minor and major responses set at Ph+ cells ranging from 36-65% and <36%. Complete cytogenetic response indicates absence of Ph+ cells. For the



quantification of BCR/ABL transcript in defining molecular response by quantitative polymerase chain reaction (Q-PCR), an international scale has been established for reference. Complete molecular response refers to absence of BCR/ABL as determined by this sensitive Q-PCR assay.

**Definition of responses.** As patients continue to improve with imatinib therapy, a timeline is needed to assess responses. At three months, patients are expected to reach complete haematologic response. Failure to reach complete haematologic response is a suboptimal response, and absence of any haematologic response constitutes failure. At six months, at least a minor cytogenetic response and a complete haematologic response should be achieved. Failure to reach minor cytogenetic response is suboptimal, while no cytogenetic response or inability to reach complete haematologic response is failure. At 12 months, complete cytogenetic response should be expected. Failure to do so is suboptimal, while a less than minor cytogenetic response is failure. At 18 months, a less than major molecular response is suboptimal, while a less than complete cytogenetic response is failure. During any time, if the patient loses haematologic or cytogenetic response, and are detected to develop mutations that are insensitive to imatinib, treatment failure is also diagnosed.

**Dosage of imatinib.** The standard initial dosage of imatinib is 400 mg daily. An increase of the initial dosage to 600 and 800 mg has been tested. There is an apparent improvement of cytogenetic and molecular responses initially at short follow-up, but there is insufficient information on whether there is any long-term difference. Patients not responding to 400 mg imatinib may respond to dose escalation to 600 and 800 mg. Also, patients treated at AP achieve better responses to imatinib at 600 mg. Patients not tolerating imatinib at 400 mg may respond to lower doses, although the long term impact of a lower dose of imatinib on disease progression is unknown.

**Discontinuation of imatinib therapy.** There is currently no information on how long imatinib should be continued. Discontinuation of imatinib therapy is obviously not an option in patients with complete cytogenetic remission and a major molecular remission, but with BCR/ABL still detectable. As for patients with prolonged negative BCR/ABL on PCR analysis, discontinuation of imatinib leads to disease recrudescence in at least half of the patients, with a follow-up of less than 2 years. Therefore, unless more information indicates to the contrary, imatinib therapy should not be discontinued in patients with molecular remission.

**Imatinib therapy during pregnancy.** Female patients on imatinib should practice effective contraception. For female patients who become pregnant while on imatinib, cessation of therapy is indicated. There is no evidence that babies born of mothers who have been exposed to imatinib in the early stages of pregnancy may have increased chances of congenital anomalies. However, the period of

discontinuation of imatinib during pregnancy may cause the mothers to lose the response to imatinib on resumption of treatment after delivery.

**Imatinib resistance.** Imatinib resistance develops through mutations of the BCR/ABL kinase domain that interferes with imatinib binding, amplification of BCR/ABL, clonal evolution and decreased imatinib bioavailability. BCR/ABL mutations are more frequent in patients with AP and BT, in patients in CP who have an increasing instead of decreasing BCR/ABL transcript quantity during imatinib therapy, and may even be detected before imatinib therapy. An increase of imatinib to 600 - 800 mg may be effective in patients with imatinib resistance. However, the long-term treatment of patients with imatinib resistance may have to rely on the use of second generation tyrosine kinase inhibitors or allogeneic haematopoietic stem cell transplantation.

### **Second generation tyrosine kinase inhibitors**

Second generation tyrosine kinases in general binds BCR/ABL with much higher avidity than imatinib mesylate. Significant data on the use of two second generation tyrosine kinase inhibitors nilotinib and dasatinib have been accumulated, showing that both agents are able to overcome suboptimal response or resistance to imatinib mesylate. However, the T315I mutation fails to respond to first and second generation tyrosine kinase inhibitors, and patients with this mutation are candidates of HSCT if suitable donors are available.

## **Conclusions**

CML is the first leukaemia where a detailed knowledge of molecular pathogenesis has enabled revolutionary treatment strategies to be developed. The use of tyrosine kinase inhibitors has superseded all forms of treatment as the preferred initial therapy for CML in all stages of diseases. However, the successful treatment of CML requires knowledge in cytogenetic and molecular monitoring, in order to optimise treatment outcome. For this reason, CML treatment should be conducted in centres where expertise in monitoring and detection of mutations is available.

## **Suggested readings**

1. Baccarani M, Saglio G, Goldman J, et al. Evolving concepts in the management of chronic myeloid leukemia: recommendations from an expert panel on behalf of the European LeukemiaNet. *Blood* 2006;108:1809-1820.
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MCHK CME Programme Self-assessment Questions

Please read the article entitled "Chronic Myeloid Leukaemia" by Prof. Yok-lam Kwong, and complete the following self-assessment questions. Participants in the MCHK CME Programme will be awarded 1 CME credit under the Programme for returning completed answer sheets via fax (2865 0345) or by mail to the Federation Secretariat on or before 30 April 2007. Answers to questions will be provided in the next issue of The Hong Kong Medical Diary.

Questions 1-10: Please answer T (true) or F (false)

- 1. CML is as common in children as in adults.
2. The most important diagnostic test in CML is bone marrow examination.
3. The typical natural history of CML is a triphasic disease, with chronic, accelerated and blastic phases.
4. CML transforms into both acute myeloid and acute lymphoblastic leukaemias.
5. In t(9;22)(q34;q11), the Philadelphia chromosome is the shortened chromosome 22.
6. Molecular testing for the BCR/ABL fusion gene helps to establish the diagnosis of CML.
7. The clinical goal of CML treatment is to decrease the percentage of blasts.
8. Tyrosine kinase inhibitors are only indicated in the salvage treatment of CML
9. Bone marrow transplantation is currently the first choice of treatment for CML patients.
10. The molecular goal of CML treatment is to decrease the quantity of BCR/ABL transcript.

ANSWER SHEET FOR APRIL 2007

Please return the completed answer sheet to the Federation Secretariat on or before 30 April 2007 for documentation. 1 CME point will be awarded for answering the MCHK CME programme (for non-specialists) self-assessment questions.

Chronic Myeloid Leukaemia

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Contact TelNo.: \_\_\_\_\_

Answers to March 2007 issue

Update on the Management of Infantile Haemangiomas

- 1. c 2. a 3. c 4. a 5. e 6. d 7. d 8. e 9. a 10. a



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- Gradual dose escalation and appropriate premedication minimises infusion-related side effects<sup>2</sup>

#### References:

1. Keating MJ, Finn L, Jain V, et al. Therapeutic role of alemtuzumab (Campath-1H) in patients who have failed fludarabine: results of a large international study. *Blood* 2002;99:3554-61.  
2. Rai KR, Fritzer CE, Merrier RJ, et al. Alemtuzumab in previously treated chronic lymphocytic leukaemia patients who also had received fludarabine. *J Clin Oncol* 2002;20:3891-7.

**Name of the medicinal product:** MabCampath® 30 mg/ml concentrate for solution for infusion. **Qualitative and quantitative composition:** Each vial contains 30 mg alemtuzumab. Alemtuzumab is a genetically engineered humanised IgG1 kappa monoclonal antibody specific for a 21-28 kD lymphocyte cell surface glycoprotein (CD52). The antibody is produced in mammalian cell (Chinese Hamster ovary) suspension culture in a nutrient medium. **Therapeutic indications:** MabCampath® is indicated for the treatment of patients with chronic lymphocytic leukaemia (CLL) who have been treated with alkylating agents and who have failed to achieve a complete or partial response or achieved only a short remission (less than 6 months) following fludarabine phosphate therapy. **Contraindications:** Hypersensitivity or anaphylactic reactions to alemtuzumab, to murine proteins or to any of the excipients; in patients with active systemic infections; in patients infected with HIV; in patients with active secondary malignancies; pregnancy and breast-feeding. **Undesirable effects:** More than 80% patients may be expected to experience adverse reactions; the most commonly reported reactions usually occur during the first week of therapy. The frequencies of the adverse reactions reported below (very common >10%, common >1-10%) are based on clinical trial data in CLL patients and post-marketing data. **Application site:** common - injection site reaction. **Body as a whole:** very common - rigors, fever, fatigue, anorexia; common - back pain, neutropenic fever, chest pain, pain, oedema mouth, asthenia, malaise, influenza-like symptoms, oedema, temperature change sensation. **Cardiovascular:** very common - hypotension; common - hypertension, tachycardia, vasospasm, flushing, palpitation. **Central and peripheral nervous system** including vision, hearing & special senses: very common - headache; common - taste loss, tremor, hypoesthesia, dizziness, hyperkinesia, conjunctivitis, paraesthesia, vertigo. **Gastrointestinal, liver & biliary:** very common - vomiting, nausea, diarrhoea; common - abdominal pain, gastrointestinal haemorrhage, stomatitis, mucositis, hepatic function abnormal, constipation, dyspepsia, stomatitis ulcerative, flatulence. **Haematological:** very common - granulocytopenia; common - pancytopenia, leukopenia, lymphopenia, purpura. **Metabolic & nutritional:** common - hyponatremia, dehydration, weight decrease, hypocalcaemia, thirst. **Musculo-skeletal:** common - skeletal pain, arthralgia, myalgia. **Psychiatric:** common - confusion, anxiety, insomnia, depression, depression. **Resistance mechanism:** very common - sepsis, Herpes simplex; common - cytomegalovirus infection, Pneumocystis carinii infection, moniliasis, Herpes zoster infection, infection fungal, abscess. **Respiratory:** very common - pneumonia, dyspnoea; common - pneumonitis, bronchospasm, sinusitis, coughing, hyponoxia, upper tract infection, bronchitis, pharyngitis, haemoptysis. **Skin & appendages:** very common - urticaria, rash, pruritus, sweating increased; common - rash erythematous, bullous eruption. **Urinary:** common - urinary tract infection. **Special warnings and special precautions for use:** Acute adverse reactions, which may occur during initial dose escalation due to the release of cytokines, include hypotension, rigors, fever, shortness of breath, chills and rashes. If these events are moderate to severe, then dosing should continue at the same level prior to each dose escalation, with appropriate premedication, until each dose is well tolerated. If therapy is withheld for more than 7 days, MabCampath® should be reinitiated with gradual dose escalation. Transient hypotension has occurred in patients receiving MabCampath®. Caution should be used in treating patients with ischaemic heart disease, angina and/or in patients receiving antihypertensive medication. It is recommended that patients be premedicated with oral or intravenous steroids 30-60 minutes prior to each MabCampath® infusion during dose escalation and as clinically indicated. The recommended premedication is hydrocortisone 100-200 mg, or equivalent, which may be reduced once dose escalation has been achieved. In addition, an oral antihistamine, e.g. clemastine 1 mg, and an analgesic, e.g. paracetamol 500 mg, may be given. In the event that acute infusion reactions persist, the infusion time may be extended up to 8 hours from the time of reconstruction of MabCampath® in solution for infusion. Profound lymphocyte depletion, an expected pharmacological effect of MabCampath®, inevitably occurs and may be prolonged. CD4 and CD8 T-cell counts begin to rise from weeks 8-12 during treatment and continue to recover for several months following the discontinuation of treatment. The median time to reach a level of 200 cells/µl is 2 months following last infusion with MabCampath® but may take 6 months or longer to approximate pretreatment levels. This may predispose patients to opportunistic infections. It is highly recommended that anti-infective prophylaxis (e.g. trimethoprim/sulfamethoxazole 1 tablet twice daily, 3 times weekly, or other prophylaxis against Pneumocystis carinii pneumonia (PCP) and an effective oral anti-herpes agent, such as famciclovir, 500 mg twice daily) should be initiated while on therapy and continued following the completion of treatment with MabCampath® until the CD4 count has recovered to 200 cells/µl or greater. If CD4 counts are not obtainable, then patients should remain on anti-infective prophylaxis for 4 months. Patients may have allergic or hypersensitivity reactions to MabCampath® and to murine or chimeric monoclonal antibodies. Males and females of childbearing potential should use effective contraceptive measures during treatment and for 6 months following MabCampath® therapy. No studies have been conducted which specifically address the effect of age on MabCampath® disposition and toxicity. In general, older patients (over 65 years of age) tolerate cytotoxic therapy less well than younger individuals. Since CLL occurs commonly in this older age group, these patients should be monitored carefully. No studies have been conducted to investigate the safety and efficacy of MabCampath® in children and in patients with renal and hepatic impairment. **Date of revision of the text:** July 2006. For current prescribing information refer to the package insert and/or contact the company at the address and phone number as below.

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# Haemopoietic Stem Cell Transplantation for Adults with Haematological Malignancies

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## Introduction

Haemopoietic stem cell transplantation (HSCT) is a procedure where haemopoietic stem cells (HSC) from a donor are given to a recipient (i.e. patient) with an aim to repopulate and replace the haemopoietic system of the recipient. With conventional myeloablative HSCT, prior to the infusion of donor HSC, conditioning regimen comprised of high-dose chemotherapy with/without total body irradiation is given for the purpose to heavily immunosuppress the recipient to prevent graft rejection, as well as to eradicate possible residual malignant cells in the recipient. Subsequently, the recipient is protected in reverse isolation environment with supportive therapy to overcome the severely pancytopenic phase until regeneration of the donor HSC and recovery of blood counts. HSCT is a recognised treatment in many types of haematological malignancies with curative potential. With allogeneic transplantation, the HSC are from another person, whereas autologous transplantation uses the recipient's own HSC. Syngeneic transplantation refers to situations where the donor is a monozygotic twin.

## Autologous vs Allogeneic

With autologous transplantation, there is no need to search for a donor. However, the HSC of the recipient may be contaminated by malignant cells, which may lead to disease relapse. Prior treatment with chemoradiotherapy before the collection of autologous HSC poses the risk of secondary leukaemia as late complication. Allogeneic HSC from a normal healthy donor is free from risks of tumour cell contamination or secondary leukaemia, but matching of the Human Leucocyte Antigens (HLA) at the pairs of A, B and DR loci is required. Hence, donors are usually searched for among siblings. Even with full HLA-matched sibling donors, there are risks of graft rejection leading to graft failure, or graft-versus-host disease (GVHD) where donor immunocompetent cells attack the recipient tissues. The likelihood of these two complications increases with increasing HLA disparity, such as using siblings with some degree of mismatch at the HLA-A, B or DR loci, or with matched unrelated donors. Furthermore, allogeneic HSCT is associated with graft-versus-leukaemia effect that helps to enhance tumour control and prevent relapse.<sup>1,2</sup> This effect is not to be expected with autologous or syngeneic HSCT. Hence, the choice between autologous and allogeneic HSC source is of significant clinical importance. As autologous HSCT is associated with relatively fewer complications, age limit of recipients can usually be taken up to 65 year-old,

whereas 55 to 60 would be the usual limit for allogeneic HSCT. Nevertheless, proper detail assessment of individual patient is always necessary before making the final decision.

## Bone Marrow vs Peripheral Blood vs Cord Blood

In the early clinical attempts of HSCT of the late 1950s, bone marrow was the only source of HSC. It is now also possible to obtain adequate HSC for transplantation from peripheral blood of patients or donors, as well as from placental/ umbilical cord blood (CB) of newborns. Peripheral blood HSC of patients are usually collected after administration of chemotherapy followed by granulocyte-colony stimulating factor (G-CSF) which mobilise marrow HSC into circulation.<sup>3</sup> The circulating HSC are then collected using an apheresis machine. Similarly, HSC from normal healthy donors, mobilised with G-CSF alone, can also be collected for use. After obtaining consent from the pregnant mother prior to delivery, CB can be collected and cryopreserved for future use. Hence, the term 'BMT' now usually refers to blood and/or marrow transplantation, instead of bone marrow transplantation alone.

There are pros and cons for the clinical use of different sources of HSC. As mentioned above, recipients of HSCT go through a period of severe pancytopenia. Neutrophil engraftment is usually defined as a sustained recovery to  $0.5 \times 10^9/L$  for 3 or more days, while platelet engraftment is attained with a count maintained at  $20 \times 10^9/L$ , independent of platelet concentrate transfusion. In a conventional allogeneic bone marrow HSCT using high-dose chemoradiotherapy conditioning, engraftment is expected to occur between 3 to 4 weeks after HSC infusion. Using allogeneic peripheral blood HSC, engraftment is often earlier by 5 to 10 days, shortening the period at high risk of infection and bleeding.<sup>3</sup> On the other hand, there is now adequate evidence in the literature to show that peripheral blood HSC is associated with a higher risk of chronic graft-versus-host disease (cGVHD).<sup>4</sup> Hence, it is not always in the best interest of the patient to use peripheral blood HSC. At our centre, bone marrow is the preferred source for early stage diseases, while peripheral blood is used in diseases at advanced stage or with high risk of relapse.

With autologous HSCT, prior exposure to excessive chemoradiotherapy has negative effect on HSC collection and engraftment kinetics.<sup>5</sup> Therefore, timing of autologous HSC collection should be taken into account



early on in the management plan. Once again, engraftment with peripheral blood is earlier than with bone marrow. Since cGVHD is not an issue in autologous HSCT, peripheral blood is the preferred option in general.

CB collections are usually of limited volume. When used for transplantation in adults, the HSC dose per kilogramme body weight of the recipient is much less than using bone marrow or mobilised peripheral blood.<sup>6</sup> The engraftment is expected to be slower by 2 weeks or more, prolonging the period at risk of severe complication. Hence, the use of CB transplantation in adults is usually reserved for patients where a suitable donor cannot be readily identified and further delay in transplantation may jeopardise the chance of cure.

## Indications

It must be emphasised that the role of HSCT for haematological malignancies changes according to availability and efficacy of alternative treatment options. A good example would be chronic myeloid leukaemia (CML). In the past, conventional treatment of CML with hydroxyurea inevitably results in blastic transformation and ultimate death. Hence, the recommendation was to transplant all young patients with CML while they are still in the chronic phase. For those who did not have an HLA-matched sibling donor, unrelated donor HSCT would still be recommended despite the associated higher risk of morbidity and mortality. However, with the advent of specific targeted therapy using imatinib to inhibit the mutated tyrosine kinase fusion protein in CML, most patients enjoy a prolonged period of progression-free survival with very good quality of life.<sup>7</sup> Hence, HSCT is no longer the recommended first line treatment for patients with CML in chronic phase. Haematological malignancies where HSCT would be indicated are discussed below.

### *Acute myeloblastic leukaemia*

Patients in first remission but with high risk of relapse and those in second or subsequent remission are indicated for allogeneic HSCT. Risk factors for relapse include: unfavourable cytogenetic abnormalities, failure to achieve remission after one course of standard induction chemotherapy, high white cell count ( $>100 \times 10^9/L$ ) at presentation, marrow trilineage dysplasia, preceding myelodysplastic syndrome and secondary acute myeloblastic leukaemia. On the other hand, transplant in first remission is not recommended for patients with favourable cytogenetic subtypes t(8;21), inv(16) and t(15;17) in general. In fact, high remission rate and prolonged survival is observed locally in relapsed t(15;17) treated with oral arsenic trioxide, rendering allogeneic HSCT rarely necessary.<sup>8</sup> Moreover, with the limitation of resources autologous HSCT in first remission is hardly performed locally, though this is a widely accepted indication in many overseas centres.

### *Acute lymphoblastic leukaemia*

Similarly, patients in first remission having poor risk factors and those in second or subsequent remission are indicated for allogeneic HSCT. Poor risk factors include: unfavourable cytogenetic abnormalities (e.g. t(9;22) or t(4;11)), delayed remission, high white cell count ( $>30 \times 10^9/L$ ) and significant organ or tissue infiltration at presentation.<sup>9</sup> Autologous HSCT is of unproven value in first remission patients and not recommended for

second or subsequent remission.

### *Chronic myeloid leukaemia*

As mentioned above, imatinib is the recommended upfront therapy for chronic phase patients. Nevertheless, allogeneic HSCT should be considered as a treatment option for those who are resistant or intolerant to imatinib. The alternative treatment recently available would be to commence these patients on second line targeted therapy, such as dasatinib.<sup>9</sup> Allogeneic HSCT is also indicated for accelerated or blastic phase controlled with imatinib. Recommendation for advanced stage CML may be further modified in the future depending on the progress with targeted therapy.

### *Myeloproliferative diseases (excluding CML)*

Polycythaemia vera, essential thrombocythaemia and chronic idiopathic myelofibrosis are clonal proliferative conditions that are usually managed conservatively. However, allogeneic HSCT has been shown to have curative potentials in these conditions.<sup>10,11</sup> It should be considered in young patients suffering from significant cytopenia or at risk of disease progression to blastic transformation.

### *Myelodysplastic syndromes*

In general, there is no specific therapy for myelodysplastic syndrome (MDS) and treatment remains largely supportive. Recently, the use of lenalidomide has been demonstrated to achieve haematological as well as cytogenetic remission in a significant proportion of patients with 5q- syndrome.<sup>12</sup> So far, the agent is not yet available locally. Hence, for young patients who suffer from significant cytopenia or with high grade MDS, allogeneic HSCT remains the only curative treatment option.

### *Chronic lymphocytic leukaemia*

Most patients with chronic lymphocytic leukaemia are elderly and are usually poor candidates for HSCT. The use of purine analogue, fludarabine, and monoclonal antibodies, such as rituximab and alemtuzumab, either as single agent or in combination with conventional chemotherapeutic agents can offer prolonged period of satisfactory disease control. Allogeneic HSCT is usually reserved only as salvage treatment with curative potentials for young patients refractory to other forms of therapy.

### *Hodgkin's lymphoma*

Autologous HSCT is the standard therapy for relapsed patients. It is also indicated for patients refractory to first line therapy but remains chemo-sensitive to salvage therapy. Allogeneic HSCT is of curative potential but carries significant transplant related morbidity and mortality.

### *Non-Hodgkin's lymphoma*

With low grade lymphoma, autologous HSCT is an accepted standard therapy for chemosensitive relapsed patients in overseas centres. Locally, such patients are usually treated with conventional chemotherapy, purine analogue and/or rituximab; and few go on to HSCT.

For aggressive B-cell lymphoma, autologous HSCT is the standard therapy for relapsed patients.<sup>13</sup> Patients in first remission but at high risk of relapse, such as lymphoblastic lymphoma, Burkitt's lymphoma or bulky mediastinal B-cell lymphoma, may benefit from autologous HSCT as consolidation therapy. Allogeneic



HSCT offers a possible curative treatment option to patients who relapsed after autologous HSCT, with initial disease involvement of the bone marrow or with poor risk T-cell diseases.

### Multiple myeloma

Autologous HSCT is becoming the standard treatment for patients with disease under-controlled using first line therapy. Double autologous HSCT may offer further survival benefit in selected patients.<sup>14</sup> However, autologous HSCT is not of curative potential and most patients do eventually relapse. On the other hand, allogeneic HSCT may offer a cure but is associated with considerable transplant-related mortality and is reserved for younger patients with high-risk disease.

### Outcome

Long-term survival rates of various conditions transplanted at Queen Mary Hospital are listed in Table 1. Results are comparable to international data.

### Complications

A myriad of complications can occur with HSCT. In the early post-HSCT period, particularly the first 4 to 6 weeks, regimen-related toxicity resulting from high-dose chemoradiotherapy affects both haematological (neutropenia, thrombocytopenia and anaemia) as well as non-haematological (such as mucositis, haemorrhagic cystitis, cardiomyopathy) tissues. The immunological barrier between the donor and recipient poses problems of graft rejection and graft-versus-host disease (acute and/or chronic), while prolonged immunosuppression may lead to various opportunistic infections including viral reactivation (e.g. herpes simplex, herpes zoster and cytomegalovirus), fungal infection or reactivation of previous foci, pneumocystis pneumonia and reactivation of previous tuberculous foci. Gonadal failure, thyroid dysfunction, diabetes mellitus, cataract and secondary malignancy may also occur as late sequelae of HSCT. Last but not least, relapse of the primary haematological malignancy continues to be an important hurdle to overcome.

### Reduced intensity conditioning transplantation

As conventional high-dose myeloablative allogeneic HSCT is associated with significant regimen associated toxicity, conditioning regimen using lower doses of chemoradiotherapy has been explored as an alternative. In general, reduced intensity conditioning transplantation (RICT) results in reversible myelosuppression even in the absence of donor HSC infusion and reduced risk of non-haematologic toxicity, yet still achieving engraftment of donor HSC. Though early regimen-related toxicity is reduced, GVHD following donor HSC engraftment and infective complication resulting from prolonged immunosuppression remains significant and requires special expertise management. RICT offers a treatment opportunity for patients who in the past may be excluded from HSCT due to age criteria or impaired organ function.<sup>15</sup> The role of RICT in the treatment of less aggressive conditions, such as low grade lymphoma,

myeloma, chronic lymphocytic leukaemia and myelodysplastic syndromes, is yet to be better defined and is being actively explored by many centres.

### Conclusion

It is clear that HSCT has improved the prospect of better disease control, increased survival rates and, in many cases, offers a cure for a variety of haematological malignancies. Nevertheless, one should always bear in mind the possible associated morbidity and mortality with both autologous and allogeneic HSCT. The risks and benefits in each individual patient have to be considered in the context of the underlying disease, prognostic factors, alternative treatment options and patients general condition before embarking on the procedure.

**Table 1: 5-year Overall Survival Rates of Adults Transplanted at Queen Mary Hospital**

Disease	Disease Status	Allogeneic		Autologous
		Sibling % (n)	Unrelated % (n)	% (n)
AML	CR1	65(90)	67(18)	-
	CR≥2	45(50)	30(18)	-
ALL	CR1	47(54)	72(16)	-
	CR≥2	28(24)	40(5)	-
CML	CP	80(138)	55(22)	-
	AP	35(33)	40(18)	-
MDS		60(35)	-	-
HL		-	-	75(20)
NHL		45(39)	-	55(117)
MM		55*(12)	-	32(38)
		35 <sup>a</sup> (33)		

n: number of patients transplanted in each category

\*: conventional myeloablative transplant

<sup>a</sup>: reduced intensity conditioning transplant

AML: Acute myeloblastic leukaemia

ALL: Acute lymphoblastic leukaemia

CML: Chronic myeloid leukaemia

MDS: Myelodysplastic syndrome

HL: Hodgkin's lymphoma

NHL: Non-Hodgkin's lymphoma

MM: Multiple myeloma

CR1: First complete remission

CR 2: Second or subsequent complete remission

CP: Chronic Phase

AP: Accelerated phase

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## Recent Advances in the Management of Chronic Lymphocytic Leukaemia

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## Epidemiology

Chronic lymphocytic leukaemia (CLL) is a rare neoplasm, but is the commonest adult leukaemia in the western population accounting for 24% to 38% of all leukaemias<sup>1,2</sup>. Among Chinese, according to two hospital-based series, it constitutes 12.5% and 4.6% of all leukaemias in Hong Kong<sup>3</sup> and Beijing<sup>4</sup> respectively. Annual incidence rates of CLL reported in the 1990s were 2.3 to 4.5 per million in the western countries<sup>5</sup>, 0.5 per million in China Mainland<sup>6</sup>, and 0.15 per million in Hong Kong<sup>7</sup>. Similarly low incidence rates of CLL were also reported among other Asian races like Japan, Korea and India. Current data attribute such racial variations in incidence pattern of CLL to familial or genetic rather than environmental factors.

## Demographic features

In all populations, the majority of CLL patients are above 50 years of age at the time of presentation, with a median age between 65 and 70 years, and a male to female ratio of approximately 2:1<sup>8</sup>. Pooled data from three local studies<sup>3,7,9</sup> showed 93% of 103 Chinese patients with CLL were above the age of 50 at the time of diagnosis and the male to female ratio was 1.5:1.

## Diagnosis

Patients with CLL may present with symptoms of anaemia, lymphadenopathy, or systemic symptoms of malaise and weight loss. In the present era, an increasing number of patients are being diagnosed as an incidental finding of lymphocytosis on routine blood test. A definitive diagnosis requires the combination of (i) a peripheral lymphocytosis, (ii) characteristic lymphocyte morphology, and (iii) characteristic immunophenotype. The WHO recommends a persistent lymphocyte count  $> 10 \times 10^9/L$  for the diagnosis of CLL<sup>10</sup>, but a diagnosis with lymphocyte count  $< 10 \times 10^9/L$  is possible provided the morphology and immunophenotype are typical of CLL. According to most international guidelines formulated in the recent decade - the US National Cancer Institute<sup>11</sup>, the UK CLL Working Group<sup>12</sup>, the Italian Society of Hematology<sup>13</sup>, an absolute lymphocytosis with a lower limit of  $> 5 \times 10^9/L$  is required for the diagnosis of CLL. The morphology of typical CLL cells is one of mature, small or medium sized lymphocyte with clumped chromatin, indistinct or absent nucleoli, and scanty cytoplasm. The variant CLL with increased prolymphocytes (CLL/PL) is defined by  $>10\%$  but  $< 55\%$

prolymphocytes. Immunophenotypes can be demonstrated by means of flow cytometry or by a panel of monoclonal antibodies, and immunophenotyping should be performed in all cases especially those requiring treatment. Typical CLL lymphocytes should co-express CD5, CD19, CD23, together with kappa or lambda light chain restriction, a low density of surface immunoglobulin (SmIg), and a weak CD20. Following the introduction of the WHO classification<sup>10</sup>, only B-CLL exists. The disease entity T-CLL no longer exists but appears as variant T-cell chronic prolymphocytic leukaemia (T-PLL) or T-cell large granular lymphocyte leukaemia (T-LGL). With the demonstration of monoclonality of lymphocytes in the peripheral blood, most centres now consider marrow examination not essential for the diagnosis of CLL. Nonetheless, marrow examination is valuable for providing diagnostic information in atypical cases as well as for providing prognostic information. A greater than 30% lymphocytes in the marrow is consistent with the diagnosis of CLL. Likewise lymph node biopsy is not necessary in the initial diagnostic workup of CLL, but may be indicated when the diagnosis is uncertain, or in patients who develop bulky lymphadenopathy where biopsy may help to exclude transformation to large cell lymphoma (Richter's transformation of CLL) which may occur in up to 5% of CLL patients.

## Prognostic Stratification

With the advancement of medical technology, diagnostic workup of many diseases is nowadays coupled with identification of prognostic factors. The clinical staging systems developed by Binet in 1981 and Rai in 1975 (Table 1) are still widely used and remain the cornerstone in risk stratification of CLL patients. They are easy to apply and well-validated, but do not accurately segregate patients with a rapid disease progression from those with an indolent course. Other prognostic factors that are independent of the clinical stage can now help to refine the outcome prediction. These include patient's gender (poorer outcome in male), serum LDH, lymphocyte doubling time, pattern of marrow infiltration, and serum  $\beta_2$  microglobulin ( $\beta_2M$ ). Newer biological markers<sup>12,13</sup> comprise interphase cytogenetics by fluorescence in situ hybridisation (FISH), CD38 positivity, mutational status of immunoglobulin heavy chain variable region (IgVH), and cytoplasmic expression of zeta-associated protein (ZAP-70) which correlates with lack of IgVH gene mutation. High-risk features for CLL include Rai stage III/IV or Binet stage C; elevated serum  $\beta_2M$ ; CD38 expression in  $>30\%$  of lymphocytes; ZAP-



70 expression in >30% of lymphocytes; lack of somatic mutations (germline) of IgVH genes; and aberrations in chromosomes 11(11q-) or 17 (17p-).

**Table 1 Staging systems for chronic lymphocytic leukaemia**

Binet	Involvement	Median survival (yr)	Rai's	Involvement	Median survival (yr)
Stage A	< 3 lymphoid regions*	> 10	Stage 0	Lymphocytosis only	> 10
			Stage I	Lymphadenopathy	7
Stage B	≥ 3 lymphoid regions	5	Stage II	Splenomegaly or hepatomegaly	7
Stage C	Hb < 10g/dL or platelet < 100x10 <sup>9</sup> /L (non-autoimmune)	2	Stage III	Hb < 11g/dL (non-autoimmune)	1.5
			Stage IV	Platelet < 100x10 <sup>9</sup> /L (non-autoimmune)	

\* 5 regions-cervical/ axillary/ inguinal/ spleen/ liver

## Treatment

In the past, treatment of CLL was of palliative intent. With the availability of highly effective and potentially curative treatment modalities, and the establishment of reliable patient risk stratification algorithms, individualised patient care is now possible. Treatment modalities for CLL in the 21<sup>st</sup> century include purine analogues, immunotherapy/chemo-immunotherapy, and nonmyeloablative stem cell transplantation.

According to most guidelines<sup>11,12,13</sup>, treatment for CLL patients should be considered if they have CLL related symptoms, or progressive lymphocytosis with an increase of >50% over a two-month period, or immune anaemia / thrombocytopenia responding poorly to corticosteroid therapy. This includes most of the Binet stage B and C patients, and some of the stage A patients with progressive disease. CLL patients with autoimmune haemolytic anaemia / thrombocytopenia should have treatment for their immune cytopenia and may not require antileukaemic treatment. High lymphocyte count alone without rapid lymphocyte doubling time may not warrant treatment as lymphocytosis rarely causes hyperviscosity. Treatment of CLL patients with chlorambucil in their early stage (Binet A) had been shown to have no survival advantage when compared to deferring treatment until progression<sup>14</sup>.

**Chemotherapy:** If treatment is indicated, chlorambucil has been the standard first-line therapy since 1960s until the appearance of purine analogues in 1990s. Fludarabine as a single agent has been shown by large randomised studies and a meta-analysis of randomised studies to be able to induce higher complete remission rates when compared with chlorambucil. Response rates are further improved by fludarabine-containing combination regimens especially by the fludarabine plus cyclophosphamide combination<sup>15</sup>. It is recommended that this therapy is the treatment of choice for CLL patients who have no contraindications to fludarabine. However in elderly patients, especially those with comorbidities, the toxicity and side effects of such therapy might counterbalance the potential efficacy. First-line chlorambucil may be more suitable for these patients. Fludarabine is now available in Hong Kong in both the intravenous and the oral form. Ongoing studies are testing the clinical benefit of early treatment with fludarabine-based chemotherapy in a specific population of CLL patients with stage A disease and poor risk biological features.

**Immunotherapy /chemo-immunotherapy:** Promising effect is seen when rituximab (R), an anti-CD20 monoclonal antibody, is used in combination with fludarabine-base therapy, especially the fludarabine and cyclophosphamide (FCR), which has been demonstrated to achieve complete remission rates as high as 70%<sup>16</sup>. Alemtuzumab (anti-CD52), another unconjugated, humanised, monoclonal antibody given intravenously or subcutaneously has been proven to be an effective salvage therapy for CLL patients refractory to alkylating agents and fludarabine. The overall response rate is about 33%<sup>17</sup> and most studies reported a median response duration of about 12 months.

**Stem cell transplantation:** For selected poor risk CLL patients, or patients who relapse after the above treatment, stem cell transplantation may be an option. Autologous stem cell transplantation may prolong remission duration but is not curative and carries a 5-10% transplant related mortality. Allogeneic stem cell transplantation is the only potentially curative treatment. Unfortunately it has a procedure-related mortality as high as up to 50%<sup>18</sup>. It has been observed that this high mortality rate may be reduced if patients identified as having high risk of progressive disease are transplanted at an earlier course of the disease when they are less heavily treated before the transplant. Its other setback is that most CLL patients are above 55 years of age and are not suitable candidates for allogeneic stem cell transplantation with conventional conditioning regimen. Recent advances in non-myeloablative stem cell transplant may be a more tolerable alternative.

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# Papers from the Federation's Annual Scientific Meeting 2006: Stem Cells -From Bench to Bedside

## "Stem Cells - From Bench to Bedside" - Neurological Application

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### Introduction

The use of stem cell therapy in the treatment of central nervous system disorders is a natural extension of the recently developed concept of 'restorative neurology'. At the same time, the role of neurosurgery in the treatment of neurological diseases is evolving from disease modification and cerebral protection to regenerative therapy. The latter is concerned with the restoration of lost neuronal populations by means of the induction of endogenous neurogenesis and/or the implantation of progenitor stem cells. Conceptually, stem cell therapy may have potential roles in the treatment of a variety of conditions. (Table 1) The so-called 'neurotransplantation' is a particularly exciting field which has attracted considerable attention and research effort. In this review, the author aims to provide an overview of the recent developments in the clinical application of stem cells therapy in the treatment of neurological disorders,

### Experimental studies

A wide range of cell sources have been studied as potential candidates for stem cell therapy. (Table 2) The wealth of information generated from *in vivo* and *in vitro* experimental studies is beyond the scope of this review.<sup>11</sup> Briefly, stem cells have been shown to survive and proliferate in host animals. Some are able to maintain metabolic activities, and migrate within the neuroaxis, sometimes across the cerebral hemispheres, towards artificially induced lesion sites (e.g. infarction). Differentiation into neurons may occur although the tendency for glial differentiation predominates in most cases. Neuronal 'daughter' cells may form axon-like processes but it remains uncertain if these processes are target-directed and contain functional synapses. Animals with, for example, induced cerebral infarction, have been shown to obtain functional improvement following stem cell transplantation. While this may result from genuine repopulation of neuronal cells, other mechanisms may be at play, including induced neovascularisation and the release of trophic factors from the transplanted cells. Nonetheless, these findings have generated hope and impetus for further clinical studies on stem cell therapy.

### Clinical studies

#### *Cerebrovascular accidents*

Cerebrovascular accidents, including both ischaemic and haemorrhagic 'strokes', are devastating diseases which result in permanent loss of brain function. Stem cell

transplantation for stroke requires the repopulation of a combination of cell lineages, including neurons, glial cells and mesenchymal elements. Using the appropriate cell source is of paramount importance.

Initial effort in this clinical application included a pilot study which transplanted porcine lateral eminence basal ganglion cells into human adults with basal ganglion (BG) stroke. Despite mild improvement in some patients, the study was suspended due to adverse side-effects.<sup>12</sup> Further clinical studies on patients with BG stroke have been conducted using human teratocarcinoma-derived neuroprogenitors demonstrated both safety and technical feasibility. Position Emission Tomography (PET) in the transplanted patients showed enhanced metabolism around the areas of infarction which correlated well with clinical improvement. Post-mortem study in one patient who died from an unrelated cause also harboured donor-derived neurons within the transplanted site.<sup>9</sup>

Kondziolka et al, conducted a Phase-II study, which included 18 patients with ischaemic or haemorrhagic stroke. Post-mitotic human graft neurons were transplanted stereotactically into multiple target sites around the BG.. Post-operative immunosuppression was used. None of the patients suffered from any significant morbidities. Although there was no significant change in motor function, measurable improvement in European Stroke Scale (ESS) was observed in the treatment group.

Mesenchymal stem cells (MSC) derived from the bone marrow stromal cells have been investigated as an abundant and autologous source of neural progenitor cells. MSC may be introduced into the central nervous system either intra-arterially or intravenously. Bang et al, conducted a randomised controlled trial using intravenously administered MSC on patients with middle cerebral artery (MCA) infarction.<sup>1</sup> There were no adverse effects and the transplanted patients showed improvement in both Barthel Index and Modified Rankin's Score. One key issue is the ability of MSC, which are mature differentiated 'adult' cells, to 'transdifferentiate' into cells of the neural lineage. This has been questioned by some authorities, who suggested that apparent transdifferentiation was in fact the results of fusion with other mature cells. Further studies are underway to investigate the precise roles of MSC in neurotransplantation.

#### *Spinal Cord Injury (SCI)*

Neurotransplantation for SCI has received increasing attention in the past several years. Again, MSC has emerged as a promising cell source. In a pilot study using human MSC graft, Sykova et al, have demonstrated improved function in SCI patients.<sup>13</sup> The results also suggested that patients in the subacute stage might do better than those in the chronic stage of SCI. The mode of delivery may also affect the outcome, with intra-arterial delivery being more efficacious than intravenous administration of MSC. Artificial 'vehicles' for graft cells have been developed for stem cell transplantation in animals, including a three-dimensional hydrogel, which has



been shown histologically to integrate well within the SCI injury site.

Contrary to the classical teaching, neurogenesis is now believed to occur in human adults in the subgranular layer of the hippocampal gyrus and the subventricular zone. Stem cells from the subventricular zone migrate to the olfactory bulb, where there is continuous proliferation of neural progenitor cells. The olfactory mucosa is therefore an attractive graft site for neurotransplantation since it contains both multipotent neural stem cells as well as olfactory ensheathing cells, which may potentially enhance remyelination of the injured spinal cord. It also has the advantage of being autologous (i.e., non-immunogenic) and harvesting can be achieved using minimally invasive surgical techniques through the nasal passage.

Lima et al, reported a pilot clinical study on the use of autologous olfactory mucosa graft for the treatment of SCI.<sup>6</sup> The olfactory mucosa was transplanted as solid tissue mass into the site of SCI in seven patients. All patients demonstrated improvement in their motor scores. Some patients also exhibited the return of limb and bladder sensation as well as voluntary anal sphincter contraction. However, without histopathological correlations, the mechanism behind these apparent clinical benefits is unknown.

Neurotransplantation for SCI using olfactory ensheathing cells obtained from aborted foetuses has been extensively reported by some researchers from the China Mainland.<sup>5</sup> More than 300 patients have been treated so far. The treatment approach and study methodology, however, were met with criticism and the value of this approach remains to be proven in future controlled studies.<sup>3</sup>

#### **Parkinson's disease (PD)**

Foetal mesencephalic dopaminergic neurons have been transplanted into the striatum of human patients with PD. The initial clinical benefits were significant, with many patients being able to reduce their L-dopa requirement. Two randomised controlled trials have demonstrated significant benefits in the transplanted group when compared with the control group.<sup>4,10</sup> The clinical benefits, however, diminished after several months. Subsequent reports also indicated that many patients suffered from 'off-medication' dyskinesia.

Despite the set-backs, these pioneering studies lend themselves to guide future cell-based therapy for PD. It appears now that neurotransplantation would benefit mostly young patients with clearly defined dopaminergic lesions (e.g. prior good response to L-dopa) and less severe forms of PD. The composition of the graft, its pre-transplant storage and culturing methods, may affect outcome. Co-treatment with immunosuppressants also appears to be beneficial.<sup>7</sup>

Human embryonic stem cells (ESC) transplantation currently holds great promise for the treatment of PD. This approach involves the pre-differentiation of ESC into dopaminergic neurons prior to implantation. To the best of the author's knowledge, there is as yet no reported clinical study using this approach. One major concern with ESC is the latter's potential to form tumours. In animal studies, transplanted human ESC has been found to develop teratoma in the hosts.<sup>2</sup>

#### **Other conditions**

Patients with traumatic brain injury, Huntington's disease and demyelinating conditions (e.g. multiple sclerosis) are also potential candidates for stem-cell therapy. Transplanted oligodendrocyte precursors have also been found to remyelinate. And autologous MSC directly transplanted into the spinal cord has been shown to slow down the clinical deterioration in patients with amyotrophic lateral sclerosis.<sup>8</sup>

## Issues in clinical stem cell therapy

Unlike the controlled condition created for defined experimental studies, the diseased nervous system represents a far more complex and multi-dimensional environment for the transplanted stem cells. Many critical issues remain to be solved before stem cell therapy can be soundly applied in patients. These include the timing of transplantation (acute / subacute / chronic), the site of implantation (intra-lesional / penumbra), the mode of delivery (intra-arterial / intravenous / intra-lesional), the function of the graft, the mechanisms behind functional changes, and the role of immunological response and immunosuppression. Oncogenicity, infection and ethical issues are other major concerns.

## Conclusion

Stem cell therapy is an exciting and rapidly developing field. Experimental studies have provided us with a solid foundation for the development of future treatment. The small number of reported clinical studies demonstrated both safety and feasibility although none has so far demonstrated significant and persistent clinical benefit. There is little doubt, however, that stem cell therapy will continue to develop and bring upon us a new era of treatment approaches to neurological disorders.

**Table 1. Neurological conditions potentially amenable to stem cell therapy**

- Cerebrovascular accidents
- Spinal cord injury
- Parkinson's disease
- Brain trauma
- Demyelinating disease
- Huntington's chorea
- Metabolic diseases

**Table 2. Examples of potential cell-sources for stem cell therapy**

#### **Endogenous**

Adult neural progenitors (e.g., olfactory bulb)  
Adult mesenchymal stem cell (e.g., bone marrow)

#### **Exogenous**

Immortalised cell-lines (e.g., human teratocarcinoma)  
Xenograft from animal (e.g., porcine neurons)  
Embryonic stem cell  
Human foetal neural progenitors  
Donor-derived umbilical cord stem cell

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## Rebuilding the Degenerated Intervertebral Discs by Bone Marrow Stem Cells

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### Low back pain and intervertebral disc degeneration

Low back pain (LBP) has an annual prevalence ranging from 15% to 45%<sup>1</sup> which is the most common cause of activity limitation in people younger than 45 years and the second most frequent reason for visits to physicians. It is also the fifth-ranking cause of admission to hospital and the third most common reason for surgical procedures<sup>2</sup>. Degeneration of intervertebral disc (IVD) is commonly associated with LBP and sciatica<sup>3</sup>. There is a lack of consensus concerning the aetiology of IVD degeneration but it is thought to be multifactorial as aging, mechanical factors, cigarette smoking, and genetic factors may contribute to its occurrence<sup>4</sup>. Despite the unclear cause, the earliest signs of the degeneration can be detected through magnetic resonance imaging (MRI) and radiographs, which include decreased water content in the disc, reduction of disc height, and bulging of the disc.

In general, IVD changes gradually after birth in terms of its structure, cellular content, and biochemical properties. Foetal or adolescent IVD composes of two cartilaginous layers called end-plates (EP) which sandwich a middle gelatinous structure called nucleus pulposus (NP). The NP is confined by a fibrous ring called annulus fibrosus (AF) to withstand mechanical load while at the same time provide mobility to the vertebral segments. The NP and AF contain abundant extracellular matrix, particularly collagens and proteoglycans<sup>5</sup>. In humans, the NP becomes dominated by chondrocyte-like cells and transforms into hyaline cartilage-like tissue as the IVD matures<sup>6-9</sup>.

Currently the pathophysiologic mechanisms of IVD degeneration are not clear, although a role of mechanical load and inflammatory pathways have been implicated in the degeneration, in the same way as osteoarthritis<sup>10-12</sup>. The process of degeneration begins with a loss of proteoglycans and water in the disc, which are important to maintain a hydrostatic pressure to resist disc collapse because of axial loading. The consequential loss of load-resisting capacity results in structural failure of the IVD, leading to microfracture and disc herniation. Current treatments for severe IVD degeneration and back pain do not address the underlying problem, but rather by-pass it by spinal fusion, thus rendering the segment immobile and putting more stress on adjacent mobile segments. Treatments that preserve motion are therefore desirable. Some trials suggest that an artificial disc replacement can successfully relieve pain and preserve motion in the short and medium term. However, such surgical procedures are associated with complications and a chance that the segment may undergo auto-fusion in the long term<sup>13</sup>.

### New ways to treat IVD degeneration

A number of research groups have been designing biological methods to heal or 'regenerate' the IVD in a natural way. At present, biological therapies under pre-clinical investigation aim to restore proteoglycan level or synthesis within the degenerated IVD. For instance, the use of intradiscal adenovirus-assisted gene therapy<sup>14-16</sup> or delivery of growth factors<sup>17-21</sup> has been shown to preserve the architecture of disc tissue and/or increase collagen and proteoglycan synthesis in animal models. On the other hand, cell therapy approaches, such as stem cell-based tissue engineering, have

been used to treat articular cartilage defects in animal models with satisfactory results<sup>22</sup>. In view of similar characteristics to osteoarthritis, the feasibility of using stem cells in arresting or even reversing the degeneration of intervertebral disc has recently been investigated.

### Rebuilding the disc with adult stem cells

Stem cells are defined as unspecialised cells capable of long-term self-renewal and differentiation into specialised cells. The maintenance, survival and activity of these stem cells is suggested to be dependent on the special micro-environmental niche<sup>23</sup>. Adult stem cells are the undifferentiated cells in adult tissues that retain differentiation potential to become cell types of their origin and their use is far less controversial than foetal or embryonic stem cells<sup>24</sup>. Adult stem cells normally play a role in local tissue turnover but appear to be 'plastic' as they can differentiate into tissue of another type (trans-differentiation) in vitro or in vivo<sup>25</sup>. Bone marrow has been the primary source for two adult stem cell populations: the haematopoietic stem cells (HSCs) and the stromal mesenchymal stem cells (MSCs). Recent animal studies have demonstrated the therapeutic effect of MSCs in tissue repair through either local implantation or via systemic delivery<sup>26, 27</sup>.

Therapeutic effects of autologous MSCs in IVD regeneration have recently been demonstrated pre-clinically in small animal models, suggesting they can overcome and counter the degeneration process to some extent. Using a rabbit model of induced degeneration, collagen-embedded MSCs injected into the degenerated IVD can survive over a 4-week period and the proteoglycan content can be enhanced in the discs after implantation<sup>28</sup>. In addition, they can preserve annular structure, re-establish a disc nucleus pulposus-like structure, as well as partial restoration of disc height and disc hydration<sup>29, 30</sup>. The mechanism of the regenerative effects has not yet been sufficiently evaluated but is believed to be either due to the differentiation of MSCs into disc cells, or the MSCs have acted as helper to induce endogenous repair.

### Possibility of allogeneic application and cell pre-modulation

Extending the concept of stem cell therapy further, investigators have exploited the use of allogeneic stem cells as this has the added advantage of off-the-shelf availability. Moreover, as the cause of disc degeneration is thought to be multifactorial, the use of allogeneic stem cells may eliminate potential autogenic precipitating factors of degeneration such as genetic predisposition<sup>31-35</sup> or the diminished potency of stem cells due to natural aging<sup>36</sup>. In fact, IVD is suggested to be immune-privileged due to its avascular nature. Moreover, immune rejection is even less likely for allogeneic MSCs since MSCs are capable of escaping from alloantigen recognition<sup>37, 38</sup>. In fact recent studies in rabbit and mouse models in our group have already indicated that allogeneic MSCs transplantation can arrest or reverse IVD degeneration and without any immune rejection, suggesting that allogeneic MSC therapy holds promises in IVD regeneration.

Enhancement for the stem cell therapy has also been investigated by pre-loading biological signals to MSCs prior to implantation in order to "direct" MSCs differentiation, or otherwise turn MSCs into signal carriers to stimulate host cell differentiation<sup>27, 39, 40</sup>. For instances, studies have attempted to stimulate MSCs to directly differentiate into disc-like cells using cytokines or genes encoding cytokines prior to implantation<sup>41, 42</sup>, or by co-culturing them with differentiated cells<sup>43, 44</sup>. It is believed that priming MSCs with cell-to-cell signals, cytokines, or genes coding the morphogens can provide additional



queues for MSCs activity and further enhance their efficacy in IVD regeneration.

## Road to the future

Current findings about the potential use of MSCs in IVD regeneration are encouraging. However, many issues still have to be addressed prior to clinical trials. Firstly, a clearer understanding of the aetiology of disc degeneration is necessary. Presence of endogenous disposing factors may render any therapy ineffective or only temporary. Secondly, little is known at present about how to discriminate pathological degeneration from natural age-related changes in the IVD, and therefore the choice of application at a particular age of subject can be difficult.

Current evidence of efficacy comes from degeneration models of small animals such as rabbit and rat, although they are less expensive and come along with a wealth of biological reagents for molecular studies, are supposed to be physiologically different to humans in terms of mechanical loading, cellular composition, and nutrient diffusion in the disc which may lead to different therapeutic outcomes<sup>45</sup>. Tests in larger animal models such as non-human bipedal primates should be performed to evaluate efficacy before proceeding to human clinical trials.

In summary, many challenges await to be addressed before recommending mesenchymal stem cell therapy as a treatment option of IVD degeneration. Nonetheless, as the science of stem cell progresses in leaps and bounds, we believe that such technology would benefit many potential back pain sufferers in the not too distant future.

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## Reflection on Some Ethical Concerns of Human Stem Cell Research

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### Introduction

Research using pluri-potent human embryonic stem cells (ESC) has raised hopes that tissues incapable of self-regeneration when damaged, e.g. brain, heart, pancreatic Islet cells etc., can now be replaced by coaxing ESC to become the damaged tissue, potentially curing heart disease, Parkinson's disease, multiple sclerosis, spinal cord injuries and diabetes. However, the use of ESC has also sparked an intense worldwide moral debate. This paper reviews and discusses the ethical issues of ESC research.

### Sources of stem cells (SC)

#### *(A) Stem cells derived from non-embryonic sources*

For the purpose of ethical analysis, it is convenient to classify human SC as (A) non-embryonic origin and (B) embryonic origin (Table 1), and only embryo-derived stem cells are of ethical concern as their derivation entails the destruction of human embryos. The sources of non-embryonic SC include (1) primitive foetal gonadal and somatic tissues, (2) adult somatic tissues including bone marrow, adipose tissue, central nervous system, muscle, (3) placenta and umbilical cord blood, and the ethical issues they raise are relatively simple. To harvest SC from aborted human foetuses, the pregnant woman's decision to terminate her pregnancy should be separated from her decision to donate foetal tissue for research by undergoing two consent processes. She should not be allowed to designate any SC transplant recipient(s). Adult somatic tissues and placental/umbilical cord blood have become popular among those who for ideological reasons prefer not to destroy human embryos. The disadvantages of adult SC include the limited quantity of SC that can be harvested from the small number of tissues containing SC. More importantly, it is believed that adult or placental/cord blood SC have only limited potential for further differentiation as they are restricted by their own lineage determined by the tri-laminar (ectoderm, mesoderm and endoderm) embryonic differentiation. Hence they are described as multi-potent rather than pluri-potent. Their capacities for self-renewal and cell-line cultures are also more limited than ESC. However, some recent studies have shown that adult SC from bone marrow and other tissues may cross lineage lines e.g. haematopoietic stem cells 'trans-differentiate' to become liver, heart and brain cells.<sup>1,2,3</sup> In 2002, Verfaillie et al. described a new adult SC from bone marrow that could produce cell types of all three embryonic lineages. Dubbing it a multi-potent adult progenitor cell (MAPC), Verfaillie speculated that it may serve as a universal repair mechanism for the adult body.<sup>4</sup> Some researchers have postulated that perhaps cellular trans-differentiation is a 'function' possessed by all SC and other primitive cell types capable of genome reprogramming to provide different phenotypes,<sup>5</sup> hence the most ethical approach to SC research is to explore both embryonic and non-embryonic sources of SC or SC-like progenitor cells in order to maximise their therapeutic potentials.<sup>6</sup>

#### *(B) Stem cells derived from embryonic sources*

The most potent SC are found in the inner cell mass of the embryo at the blastocystic stage between 4-6 days after fertilisation. When cultured in the proper medium, these cells can multiply indefinitely as immortal cells, and under proper coaxing conditions they can be directed to differentiate into any one of the 220 cell types of the human body. They are 'the "uncommitted" progenitors of the subsequent 3 germ layers of the embryo.'<sup>7</sup> The major disadvantage and most

contentious moral issue of human ESC is related to the obvious fact that their harvesting entails embryo destruction. Furthermore, ESC can be harvested from at least 3 different sources of human embryos and the moral assessment for each is significantly different: (1) 'surplus' embryos produced by in vitro fertilisation (IVF) for infertility treatment ('IVF-surplus embryo'); (2) embryos produced by IVF specifically for research purposes including harvesting SC ('IVF-research embryo'); (3) embryos produced by somatic cell nuclear transfer (NT) specifically for research purposes including harvesting SC ('NT-embryo').

### A hierarchy of moral contentiousness of human stem cells

Depending on the source of human SC, the moral consideration for their uses varies and there is a rough hierarchy of increasing moral contentiousness in the following order: (1) SC from umbilical cord blood; (2) adult or somatic SC; (3) SC from foetal gonadal and somatic tissues; (4) existing ESC lines; (5) ESC from 'IVF-surplus embryos'; (6) ESC from 'IVF-research embryos'; (7) ESC from 'NT-embryos' using human ova; (8) ESC from 'NT-embryos' using animal ova. Table 2 shows that SC with increasing moral contentiousness are permitted by a decreasing number of countries. For example, most countries including Hong Kong do not prohibit the use of human SC from cord blood, adult and foetal somatic tissues as long as proper informed consents are obtained from donors and safeguards against commercialization of tissues are in place. The use of existing ESC lines and ESC from 'IVF-surplus embryos' are also tolerated by many countries, but the number of countries allowing the creation of 'IVF-research embryos' drops significantly, and the number of countries that permit the production of 'NT-research embryos' drops even lower. In Hong Kong, the use of human SC is governed by the Human Reproductive Technology Ordinance (Cap 561) which implicitly or explicitly permits the use of adult somatic SC as well as ESC from 'surplus' IVF embryos, but creating embryos by IVF or NT for the sole purpose of harvesting SC or embryo research is prohibited.<sup>8</sup>

### Ethical principles guiding the use of SC

Some principles are applicable to both 'embryonic' and 'non-embryonic' SC and some are exclusively related to ESC only.

#### *(A) Principles useful for both 'embryonic' and 'non-embryonic' SC*

- (1) Principles of beneficence and non-maleficence: there is an obligation for the doctor to provide treatment with a net benefit rather than harm to the patient. This principle implies that the risk/benefit ratio for the therapeutic use of SC should meet the community's prevalent medical standard, and there should be a reasonable chance of medical benefit for the patient as a SC recipient. The dictum: 'first do no harm' has special relevance for SC therapy. The principle also regulates the interests of SC donors.
- (2) Proportionality principle: uses and procurement of tissues enriched in SC or, in the case of ESC, destruction of human embryos, should serve important and worthwhile goals and purposes e.g. to treat serious or life-threatening illnesses and not for trivial reasons or satisfaction of scientific curiosities.
- (3) Subsidiarity principle<sup>9</sup> stipulates that when the same results can be obtained through two different methods, the least offensive or problematic method should be employed, assuming a consensus of what is 'the least offensive or problematic'. In the context of SC research, this implies that: (a) SC or ESC should only be used if no reasonably suitable alternatives exist; (b) SC research should be first done on animals before humans; (c)





somatic SC should be used before ESC; (d) Surplus embryos should be used before research embryos are created.

- (4) Principle of Informed consent (IFC): is a key principle and process in SC research and therapy. For example, in U.K., IFC for donating and receiving embryos and other tissues rich in SC is statutorily required by the Human Tissue Act (2004) and the HFE Act (1990). The following are some of the most important items of the IFC process for embryo donation to harvest ESC:<sup>10</sup>
- Donors should be approached as early as possible, usually before ovary stimulation, to allow sufficient time to think all issues over carefully;
  - Comprehensive information must be given in a readily accessible form, and potential donors must be allowed to make a free and informed decision;
  - Donor couple must have given in principle consent for the use of embryos in research; and they may be required to re-consent immediately prior to the time of ESC derivation;
  - Donors can vary or withdraw the terms of their consent without giving any reason, at any stage until the point that the embryos are used for research;
  - Donors should be informed that SC/ESC lines will be successfully derived from donated tissues/embryos only in a few cases;
  - Stem cells lines created may continue indefinitely and may be used in many different research projects;
  - Donors cannot interfere with the subsequent research conducted with SC/ESC lines derived;
  - Donors understand that the derived SC/ESC lines may be used in research projects by other researchers;
  - Donors understand that any SC/ESC lines derived from their donated tissues/embryos, except when they are found to carry genetic defects, may potentially be used for treatment (including cell replacement therapies) purposes in the future;
  - Researchers accessing embryos or SC/ESC lines will not have access to any identifying information of the donor;
  - Donors either agree or disagree to be contacted in the future for information obtained from SC/ESC line studies that are of direct relevance to their own or family's health;
  - Embryo research will not lead to any direct medical benefit to the donors;
  - Donors will not share in any actual or potential financial benefits derived from the commercial uses of SC/ESC lines or patents of medical discoveries;
  - Donors know how the research is funded and any benefit which will accrue to researchers and/or their departments.

### **(B) Principles useful exclusively for ESC**

Ethical issues that are closely related to the derivation and uses of ESC derived from the 3 different sources of embryos are:

- The moral status of the embryo (applicable to all sources of embryos);
- Moral distinction between 'IVF-surplus embryos' and 'IVF-research embryos';
- Biological and moral differences between 'IVF-embryos' and 'NT-embryos';
- Slippery slopes from therapeutic to 'reproductive' cloning;
- Exploitation of economically disadvantaged women as ova suppliers.

#### **(1) The principle of respect of the embryo's moral right to life**

For many, the central ethical concern in human ESC research is the moral status of human embryos. The

prevalent divergent views have been influenced by a variety of concepts of human nature and personhood held by different cultures, religions and philosophies.<sup>11</sup> The extremely conservative view regards the destruction of human embryos as equivalent to the killing of human persons and should not be allowed in almost any circumstances. This conservative position can be defended on either religious or non-religious grounds, with the most popular religious ground being the sanctity of all forms of human life including the embryo, espoused by Judeo-Christian, Islamic, Hindu and Buddhist adherents.<sup>12</sup> Non-religious grounds typically include a special regard for the embodied basis of human nature and are critical of the ESC technology for reducing human embryos to transferable and transplantable "post-human" body parts.<sup>13</sup> Alternatively, moderately conservatives regard using embryos to derive ESC as intrinsically unethical because the technology 'instrumentalises' human life and exploits a vulnerable class of persons, namely, human embryos. Countries adopting this position include Ireland, Italy, Germany and the United States. In the U.S., moral objections to ESC take the form of restricting government funding only to certain existing ESC lines derived prior to August 9, 2001. In Germany, embryo research is essentially banned, but the importation of existing SC lines is permitted.

A second and extremely liberal view regards the early embryo possessing no more moral status or right-to-life than a clump of cells or isolated human tissue, and harvesting of ESC from human embryo is an important medical innovation that is morally justifiable. Countries that adopt this liberal position include Sweden, Belgium, U.K., China, Korea, Japan and Singapore, and they have implemented permissive policies allowing not only the use of 'IVF-surplus' embryos from infertility treatment programmes, but also the creation of IVF and NT (except Sweden) embryos for the sole purpose of research or harvesting ESC.

Between the two extremes is the 'middle-of-the-road' view that accords the human embryo an "intermediate" moral status: the human embryo is neither a full human person nor mere human tissue, but it possesses a unique status due to its potential to develop into a person. It deserves respect and protection, but not to the extent that goes with full personhood; under some circumstances, the use of human embryos for worthy medical research and harvesting ESC for therapy may be morally justifiable.<sup>14</sup> But even within the 'middle-of-the-road' camp, no consensus exists about the precise ways to respect or protect embryonic lives and under what circumstances can their lives be sacrificed, and this adds to the difficulty of making ethical public policy in a pluralistic society that respects diverse fundamental beliefs and does not want to be held hostage to any single view of embryonic life.<sup>15</sup>

#### **(2) Moral distinction between 'IVF-surplus' and 'IVF-research' embryos**

Three arguments have been commonly employed to defend using 'IVF-surplus' embryos to harvest ESC:

- 'reproductive intentionality' argument, (b) 'nothing is lost' argument, and (c) 'avoidance of waste' argument.

'Reproductive intentionality argument' asserts that 'IVF-surplus' embryos are intentionally created for reproduction, and as "surpluses" they are not destined for implantation and have no potential to develop to birth. Since the original intention has been defeated, using 'IVF-surplus' embryos to harvest ESC is deemed morally acceptable. The argument serves a good purpose to show that the difference in intentionality between reproduction and research is morally significant, but as



an argument to support the use of 'surplus' reproductive embryos, it is a weak argument on its own.<sup>16</sup> For if human embryos possess moral values and rights, 'IVF-surplus' embryos should raise questions about why they are in surplus, rather than what alternative 'uses' we can make of them. As an alternative argument to defend the use of 'IVF-surplus' embryos, Gene Outka has made use of a more classical ethical principle of 'nothing is lost' that justifies the killing of innocent life under two conditions: (1) the innocent will die in any case, and (2) other innocent lives will be saved. Since un-implanted 'IVF-surplus' embryos 'will die in any case, nothing more will be lost by their becoming subjects of research,<sup>17</sup> and for patients with Alzheimer and Parkinson diseases receiving ESC therapy, 'less will be lost, or, at least, *someone* may benefit.'<sup>18</sup> However, the argument has not addressed the fundamental question why embryos should be in surplus and their 'loss' can be morally justifiable if embryos have been created with reproductive intention and possesses moral values and rights or status. Outka has also neglected to include other important 'losses' related to the loss of the embryo's life in his utilitarian calculation. For, if the practice of destroying surplus human embryos becomes prevalent, the 'loss' of people's sensitivity to the value of human life must be counted as loss to the society. Lastly, the principle of 'nothing is lost' presupposes that some other innocent lives will be saved, and so far ESC therapy cannot provide this guarantee. Others have tried to buttress the 'nothing is lost' principle with an "avoidance of waste" argument, suggesting that greater use is made of the embryo's life (or death) by contributing its SC for research or therapeutic application. This is such a utilitarian way to think about human life and death that no decent society would contemplate. It seems that if 'IVF-embryos' created for reproductive intention have moral values or rights at all, the most ethical solution is to avoid having 'surplus-embryos' at all.

**(3) The biological and moral differences between deriving ESC from IVF- and NT- embryos**

An important argument in favour of creating 'NT-embryos' is to provide autologous ESC for transplant that avoids rejection problems and graft-versus-host diseases, and potentially to produce "designer stem cells" unique to a particular patient. The most prevalent objection is a 'slippery slope' effect that promoting 'NT-embryos' may unintentionally promote reproductive cloning.

However, skeptics wonder whether banning 'NT-research embryos' ('therapeutic cloning') will actually stop over-zealous scientists to clone human beings ('reproductive cloning'), given the incredible temptation inherent in the possibility of human cloning that even the law may not be able to deter.

Contrarily, we believe that there are several important differences between an 'IVF-embryo' and a NT-embryo that support the argument that it is more advantageous to use cloned embryos than IVF-embryos. Firstly, an IVF-embryo is a new human life produced by natural fertilisation that in virtue of its unique genome possesses a distinct genetic identity and ontological individuality. We concur that "IVF embryos should not be created a priori for any end other than reproduction, otherwise the embryo becomes a means and not an end itself."<sup>19</sup> On the other hand, NT-embryo is artificially produced by nuclear re-programming without creating a 'new' life with a unique genome. As one puts it: "SCNT resembles tissue culture...[it] is an engineered culturing of the nucleus of a somatic cell, accomplished by implanting this nucleus into an enucleated ovum..."<sup>20</sup> It can be seen as merely a 'copy' of the cloned cell, and if the NT-embryo is gestated in a woman's uterus, it will become a cloned human with blurry genetic and social

identity. Secondly, the intention to produce the two kinds of embryos is different. The intention to create IVF-embryos can be reproductive or therapeutic or both. But the production of NT-embryos is only for research or therapeutic uses since reproductive cloning is legally banned. If I suffer from a massive heart attack, and if it is technical possible for the doctor to use my own somatic cells and eggs donated by my wife and to produce ESC and heart cells that save my life, reproductive cloning has never entered into my intention. One is hard-put to argue that because in the process a human 'embryo' has been produced that potentially can become a human being I should be denied of the treatment.

There is another important reason why it is easier to justify producing ESC from NT-embryos and not IVF-embryos: the former has far less reproductive potential than the latter. This requires a brief explanation of the epigenetic phenomenon. The genomes in the male and female gametes are modified differentially during gametogenesis and are epigenetically distinct.<sup>21</sup> In the course of producing an IVF-embryo by natural fertilisation, the epigenetic differences of the parental genomes are retained, and this epigenetic memory persists in the developing embryo to adult life. In NT, the nuclear re-programming is faulty in the sense that the epigenetic differences in the nuclear genomes are lost. This 'epigenetic memory loss' creates nearly insurmountable "biological barriers" for the cloned embryo to develop properly, if at all, or to survive to adulthood without serious and multiple developmental abnormalities.<sup>22</sup> However, normally functional ESC can be harvested from a NT-embryo without its "epigenetic memory". In short, the therapeutic potential of NT-embryo is equivalent to IVF-embryo, but the reproductive potential of the two are vastly different. In the reproductive sense, the 'NT-embryo' is not a biologically normal embryo and that renders its use less morally problematic.<sup>23</sup> There is a recent alternative technology to NT called "altered nuclear transfer" (ANT) that purports to produce embryos that lack the capacity to develop into babies. This is a similar effort to ensure that it will be more ethically acceptable to produce ESC using ANT-embryos than IVF-embryos.<sup>24</sup>

**Conclusion**

The use of human stem cells will remain a contentious issue for the foreseeable future. This paper discusses some ethical issues for the different sources of SC. As new methods to harvest SC are proposed, they will have to be assessed separately. Each community will have to decide for itself which source(s) of SC will conform best to the prevalent values and norms adopted by the community. Since SC technology is relatively new, clinicians, scientists, ethicists and the general public should keep an open mind to future scientific discoveries and be sensitive to their moral implications.

**Table 1 Sources of human stem cells**

**(A) Stem cells not derived from embryos (minimally contentious)**

- Umbilical cord blood
- Somatic (adult) stem cells (bone marrow, blood, skin, brain, dipose tissue)
- Foetal germ cells and "adult" stem cells from foetuses

**(B) Stem cells derived from human embryos (highly contentious)**

- Existing ESC lines derived from IVF 'surplus' embryos
- ESC - IVF 'surplus' embryos
- ESC - IVF 'research' embryos
- ESC - NT embryos created w/ human ova
- ESC - NT embryos created w/ animal ova



**Table 2 Hierarchy of moral contentiousness of different sources of human SC and countries permitting the use of different SC**

Sources	Permitted countries
1. Umbilical cord blood	US, UK, Germany, Sweden, Belgium, France, Finland, HK, China Mainland, Japan, Singapore, South Korea, Australia, Canada
2. Somatic (adult) stem cells	US, UK, Germany, Sweden, Belgium, France, Finland, HK, China Mainland, Japan, Singapore, South Korea, Australia, Canada
3. Foetal germ cells & somatic stem cells	US, UK, Germany, Sweden, Belgium, France, Finland, HK, China Mainland, Japan, Singapore, South Korea, Australia, Canada
4. ESC - IVF surplus embryos	US, UK, Sweden, Belgium, France, Finland, HK, China Mainland, Japan, Singapore, South Korea, Canada
5. ESC - IVF created "research" embryos	US, UK, Sweden, Belgium, France, China Mainland, Japan, Singapore, South Korea
6. ESC - NT created w/ human ova	US, UK, Belgium, China Mainland, Japan, Singapore, South Korea,
7. ESC - NT created w/ animal oocytes	???

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## Unrelated Stem Cells Source

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Hong Kong Red Cross Blood Transfusion Service

Stem cells are primal undifferentiated cells that are characteristic to have self renewal (the ability to go through numerous cycles of cell division while maintaining the undifferentiated state) and unlimited potency (ability to differentiate into other cell types.) With these enormous and unlimited potentials, stem cells have been the focus in basic and clinical medicine for the past few decades. More recently a new branch of medicine, known as regenerative medicine has evolved because of its overwhelming potentials to change the fate of many human diseases by being used to repair specific tissues or to grow organs. Indeed exciting reports have already appeared in the medical literature since in the mid to late 90s. Some of them such as making use of embryonic stem cells in clinical conditions like Parkinson's disease and spinal cord damage even appeared in the headline of newspaper or TV. However, having fascinated by these future applications, there are still a lot of unresolved issues behind. It is in particular related to the underlying ethical issues in the collection, expansion and clinical use of the stem cells in human beings.

In human, there are two categories of stem cells - embryonic stem cells, derived from blastocysts and adult stem cells, derived from umbilical cord blood or bone marrow. The former, though has the greatest potential in future application (expansion and differentiation into different types of tissues) is the most controversial because of the ethical issue in the collection, expansion and use. On the other hand, the latter has its clearly defined and long history of clinical use i.e. the use of haematopoietic stem cells (HSC) derived from adult or cord blood for bone marrow transplantation (BMT). Haematologists and oncologists have been making use of HSC and BMT in treating a large number of benign and malignant blood diseases, some immunodeficiency and inherited metabolic conditions and recently on autoimmune diseases. This is reflected by the exponential growth in the number of BMT performed in the last two decades. However, with the recent development of stem cell biology, there are still ongoing arguments in particular on the use of stored cord blood for insurance purpose or application in regenerative medicine.

Although it is now known that we are able to isolate and obtain stem cells from other tissues such as human embryo, oocytes and adipose tissue, the presentation will limit only to source of unrelated HSC for BMT only. In BMT setting, HSC can be obtained from the patients, siblings and family members, unrelated healthy donors and cord blood (related or unrelated). While HSC from related donors are usually preferred in BMT because of the lesser chance of BMT related complications and usually relatively easier in availability. However, with a worldwide trend in smaller family size, the possibility to have a matched related donor is getting lower. Without this, these patients have to go for unrelated donors whether it is from an adult or cord blood. Although the less stringent HLA requirement and almost immediate availability from stored cord blood means much more easy to locate a suitable cord blood unit, it is limited by its smaller cell dose rendering it not suitable to an average size adult.

At present, it has been estimated that the global demand for HSC for BMT is about 150,000 - 160,000 annually. Only about one third of patients (55,000) have successfully identified a suitable donor out of which 7900 are from unrelated donors. It is therefore obvious that there is a need to further optimise unrelated marrow donor registries to help more patients in hope of BMT. These include (1) to recruit more unrelated donors in the registries to increase the chance of matching, e.g. the estimated chance in Hong Kong to have a HLA matched unrelated donor is about 1 in 5000; (2) to improve the baseline HLA typing of donors in the pools (from serologic to DNA typing) so that the chance of full matching can be better





predicted from initial matching results; (3) to increase the umbilical cord blood pool and hence their availability; and (4) to enhance the efficiency of donor clearance and stem cell collection. The last is of particular importance as from time to time, patients may develop relapse or other problems while they are waiting for the BMT. The shorter the time lapse, the better the chance to reach BMT is. Finally, there is a growing need to have more international co-operation so that donor searching and stem cells donation and transport can be enhanced.

In Hong Kong, the Blood Transfusion Service is the organisation providing such service. A centralised cord blood bank was established in 1998 whereas Hong Kong Bone marrow Donor Registry has taken up the previous work by Hong Kong Marrow Match Foundation since 1 September 2005 on donor recruitment, searching, and co-ordination of haematopoietic stem cell donation. Both services have been in full collaboration with local and overseas transplant centres in the provision of unrelated HSC to patients who are unable to have a related donor but require BMT to treat their underlying illnesses. Up to now, there are about 56,000 marrow donors in the registry and 2,000 units of stored cord blood units. It is committed to enhance the outcome of Chinese patients undergone BMT by its strong co-operation between China and Taiwan.

With regard to BMT, safety of donation, donor and recipient remains the most important concern. In the unrelated setting, the donation risk should always be minimal to the voluntary non-remunerated donors whereas the transplantation risk should be acceptable to the recipient. Therefore, it appears to have a need of consensus on requirement of stringent donor eligibility and quality control on the collection, testing and storage and their applications. Quality assurance and accreditation are some of the key issues to consider. Although there is no regulatory agent on the stem cells service locally, both professional and ethical standards have demand our service to adhere to the state of the art standards. Lastly, one

should not overlook the importance in ethical consideration of recruitment, donor confidentiality in searching, matching and donation and of course their clinical uses.

Though cord blood has all along been targeted for homologous use (unrelated BMT or directed sibling BMT), there are on-going arguments whether one should store their cord blood for potential future use. At present, reported use of autologous cord blood unit is very low. Recently the World Marrow Donor Association (WMDA) has finalised her policy statement on the utility of autologous or family cord blood unit storage. Basically, WMDA supports the use of cord blood bank for the presently well accepted indication and research (i.e. unrelated stem cell transplantation and directed donation to family members who suffer from BMT treatable disease). Interested readers could retrieve the full document from the WMDA website for their reference. (Ref: [http://www.worldmarrow.org/fileadmin/WorkingGroups\\_Su\\_bcommittees/DRWG/Cord\\_Blood\\_Registries/WMDA\\_Policy\\_S\\_tatement\\_Final\\_02062006.pdf](http://www.worldmarrow.org/fileadmin/WorkingGroups_Su_bcommittees/DRWG/Cord_Blood_Registries/WMDA_Policy_S_tatement_Final_02062006.pdf))

To conclude, haematopoietic stem cells from unrelated donors have emerged as an important source for patients in need of bone marrow transplantation. With the help of national donor registry and international co-operation, the success in identifying a matched donor has been improved. However, there is still further room of improvement as limited by chance of matching and increasing stringent requirement for HLA matching. Members of the public who are healthy are encouraged to join the registry as potential donors.

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Fax: 26048091



## Dermatological Quiz

### Dr. Ka-ho Lau

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



Dr. Ka-ho Lau



**Fig 1**  
Lesion at back of the baby



**Fig 2**  
Lesion at the lower limbs of the baby

A 6-month-old baby boy presented with itchy lesions at his trunk and limbs for a few weeks. His mother noticed that the skin lesions became more red and sometimes blister, especially after taking a bath. Except the skin rash, the baby was otherwise well with normal feeding and growth parameters.

#### Questions:

1. What is your diagnosis? What clinical sign can be elicited to support your diagnosis?
2. What relevant investigations should you perform to confirm your diagnosis?
3. How will you manage this baby?

(See P. 39 for answers)

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Sunday	Monday	Tuesday	Wednesday	Thursday	Friday	Saturday
<ul style="list-style-type: none"> <li>HKMA Structured CME Programme 07/08 (I) - Medicine</li> <li>Dragon Boat Practice Session</li> </ul> <p><b>1</b></p>	<p><b>2</b></p>	<ul style="list-style-type: none"> <li>健康服務助理員訓練課程 (Code no. TC-HCA-0107)</li> <li>HKMA News Letter Editorial Meeting</li> </ul> <p><b>3</b></p>	<p><b>4</b></p> <ul style="list-style-type: none"> <li>Spinal Dysraphism</li> </ul>	<ul style="list-style-type: none"> <li>HKMA Structured CME Programme with Hong Kong Sanatorium &amp; Hospital Year 2007 (IV) - Diagnosis &amp; Treatment of Gastroesophageal Reflux Disease</li> <li>HKMA Council Meeting</li> </ul> <p><b>5</b></p>	<ul style="list-style-type: none"> <li>健康服務助理員訓練課程 (Code no. TC-HCA-0107)</li> <li>健康服務助理員訓練課程 (Code no. TC-HCA-0107)</li> </ul> <p><b>6</b></p>	<ul style="list-style-type: none"> <li>HKMA Refresher Course for Health Care Providers 2006/2007 (VIII) - Cognitive Behavioural Therapy in Anxiety Disorder</li> </ul> <p><b>7</b></p>
<ul style="list-style-type: none"> <li>Dragon Boat Practice Session</li> <li>Joint Professional Basketball Competition 2007</li> </ul> <p><b>8</b></p>	<p><b>9</b></p>	<ul style="list-style-type: none"> <li>健康服務助理員訓練課程 (Code no. TC-HCA-0107)</li> <li>醫療護理業技能提升計劃 "醫療護理文件記錄及檔案處理" (Code No. SUS MH 008 0 (B))</li> </ul> <p><b>10</b></p>	<p><b>11</b></p> <ul style="list-style-type: none"> <li>醫療護理業技能提升計劃 "醫療護理文件記錄及檔案處理" (Code No. SUS MH 008 0 (B))</li> </ul>	<ul style="list-style-type: none"> <li>HKMA CME Luncheon Lecture on Achieving Glycemic Targets in Type 2 Diabetes</li> </ul> <p><b>12</b></p>	<ul style="list-style-type: none"> <li>健康服務助理員訓練課程 (Code no. TC-HCA-0107)</li> <li>Certificate Renal Nursing Course 2007</li> <li>Seminar "Get the job done in Complaint Management for frontline nurses &amp; nursing supervisors"</li> </ul> <p><b>13</b></p>	<p><b>14</b></p>
<ul style="list-style-type: none"> <li>Dragon Boat Practice Session</li> <li>Joint Professional Basketball Competition 2007</li> <li>HKMA Snooker Tournament</li> </ul> <p><b>15</b></p>	<p><b>16</b></p>	<ul style="list-style-type: none"> <li>健康服務助理員訓練課程 (Code no. TC-HCA-0107)</li> <li>醫療護理業技能提升計劃 "醫療護理文件記錄及檔案處理" (Code No. SUS MH 008 0 (B))</li> </ul> <p><b>17</b></p>	<p><b>18</b></p> <ul style="list-style-type: none"> <li>醫療護理業技能提升計劃 "醫療護理文件記錄及檔案處理" (Code No. SUS MH 008 0 (B))</li> </ul>	<ul style="list-style-type: none"> <li>Advanced Wound Care Management (Code No. TC-AWCM-0107-CNSG)</li> </ul> <p><b>19</b></p>	<ul style="list-style-type: none"> <li>健康服務助理員訓練課程 (Code no. TC-HCA-0107)</li> <li>Basic Wound Management (Code No. TC-BWC-0107-CNSG)</li> </ul> <p><b>20</b></p>	<ul style="list-style-type: none"> <li>Certificate Course on Medical Genetics</li> </ul> <p><b>21</b></p>
<ul style="list-style-type: none"> <li>Dragon Boat Practice Session</li> <li>HKMA Snooker Tournament</li> <li>HKMA Badminton Day</li> <li>HKMA Structured CME Programme Year 07/08 (I) - Surgery</li> </ul> <p><b>22</b></p>	<p><b>23</b></p>	<ul style="list-style-type: none"> <li>健康服務助理員訓練課程 (Code no. TC-HCA-0107)</li> <li>醫療護理業技能提升計劃 "醫療護理文件記錄及檔案處理" (Code No. SUS MH 008 0 (B))</li> </ul> <p><b>24</b></p>	<p><b>25</b></p>	<p><b>26</b></p>	<p><b>27</b></p>	<p><b>28</b></p>
<ul style="list-style-type: none"> <li>Dragon Boat Practice Session</li> <li>HKMA Snooker Tournament</li> <li>HKMA Badminton Day</li> <li>HKMA Structured CME Programme Year 07/08 (I) - Surgery</li> </ul> <p><b>29</b></p>	<p><b>30</b></p>					





Date / Time	Function	Enquiry / Remarks
<b>1</b> <b>SUN</b> 2:00 pm 3:00 pm (15, 22, 29)	<b>HKMA Structured CME Programme 07/08 (I) - Medicine</b> Organised by: The Hong Kong Medical Association & Queen Elizabeth Hospital Chairman: Dr. T.C. SHIH Speaker: Various # Lecture Theatre, G/F, Block M, Queen Elizabeth Hospital, Kowloon <b>Dragon Boat Practice Session</b> Organised by: The Hong Kong Medical Association Chairman: Dr. H YEUNG & Dr. I CHAN # Sai Kung, New Territories	Miss Nina HUNG Tel: 2861 1979 (Registration Fee is required) 3 CME Points Ms. Dora HO Tel: 2527 8285
<b>3</b> <b>TUE</b> 6:00 pm - 10:00 pm (6,10,13,17,20,24,27)	<b>健康服務助理員訓練課程 (Code no. TC-HCA-0107)</b> Organised by: College of Nursing, Hong Kong	Secretariat Tel: 2572 9255 Fax: 2838 6280
<b>10</b> <b>TUE</b> 8:00 pm	<b>HKMA Newsletter Editorial Meeting</b> Organised by: The Hong Kong Medical Association Chairman: Dr. H.H. TSE # HKMA Head Office, 5/F, Duke of Windsor Social Service Building, 15 Hennessy Road, Wanchai, Hong Kong	Ms. Tammy TAM Tel: 2527 8941
<b>11</b> <b>WED</b> 7:30 am	<b>Spinal Dysraphism</b> Organised by: Hong Kong Neurosurgical Society Chairman: Dr. S.C YUEN Speaker: Dr S.T WONG # Seminar Room, G/F, Block A, Queen Elizabeth Hospital, Kowloon, Hong Kong	Dr Y.C PO Tel: 2990 3788 Fax: 2990 3789
<b>12</b> <b>THU</b> 2:00 pm 8:00 pm	<b>HKMA Structured CME Programme with Hong Kong Sanatorium &amp; Hospital Year 2007 (IV) - Diagnosis &amp; Treatment of Gastroesophageal Reflux Disease</b> Organised by: The Hong Kong Medical Association & Hong Kong Sanatorium & Hospital Chairman: Dr. T.C. SHIH Speaker: Dr. CHAN Chi Wai Angus # HKMA Dr. Li Shu Pui Professional Education Centre, 2/F, Chinese Club Building, 21-22 Connaught Road Central, Hong Kong <b>HKMA Council Meeting</b> Organised by: The Hong Kong Medical Association # HKMA Head Office, 5/F, Duke of Windsor Social Service Building, 15 Hennessy Road, Wanchai, Hong Kong	Miss Nina HUNG Tel: 2861 1979 (Registration Fee is required) 1 CME Point Ms. Christine WONG Tel: 2527 8285
<b>14</b> <b>SAT</b> 2:30 pm	<b>HKMA Refresher Course for Health Care Providers 2006/2007 (VIII) - Cognitive Behavioural Therapy in Anxiety Disorder</b> Organised by: The Hong Kong Medical Association & Our Lady of Maryknoll Hospital Chairman: Dr. T.C. SHIH Speaker: Mr. Max WONG # Training Room II, 1/F, OPD Block, Our Lady of Maryknoll Hospital, 118 Shatin Pass Road, Wong Tai Sin, Kowloon, Hong Kong	Ms. Clara TSANG Tel: 2354 2440 2 CME Points
<b>15</b> <b>SUN</b> 3:00 pm (22)	<b>Joint Professional Basketball Competition 2007</b> Organised by: The Hong Kong Medical Association Chairman: Dr. M.H. IP & Dr. H YEUNG	Ms. Dora HO Tel: 2527 8285
<b>17</b> <b>TUE</b> 7:00 pm - 9:00 pm (18, 24, 25)	<b>醫療護理業技能提升計劃 "醫療護理文件記錄及檔案處理" (Code No. SUS MH 008 0 (B))</b> Organised by: College of Nursing, Hong Kong	Secretariat Tel: 2572 9255 Fax: 2838 6280
<b>19</b> <b>THU</b> 2:00 pm	<b>HKMA CME Luncheon Lecture on Achieving Glycemic Targets in Type 2 Diabetes</b> Organised by: The Hong Kong Medical Association Chairman: Dr. T.C. SHIH Speaker: Dr. TSANG Man Wo & Dr. Roger CHEN # Star Room, 42/F, Langham Place Hotel, 555 Shanghai Street, Mongkok, Kowloon	Miss Dorothy KOWK Tel: 2527 8452 1 CME Point
<b>20</b> <b>FRI</b> 2:30 pm - 4:30 pm (27) 6:00pm - 9:00pm	<b>Certificate Renal Nursing Course 2007</b> Organised by: The Federation of Medical Societies of Hong Kong Chairman: Dr HUNG Kwan Ngai Speaker: Various # Lecture Hall, 4/F, Duke of Windsor Social Service Building, 15 Hennessy Road, Wanchai, Hong Kong (Lecture) & Nephrocare Centre, Hong Kong St Paul's Hospital, 2 Eastern Hospital Road, Causeway Bay, Hong Kong (Field visit) <b>Seminar "Get the job done in Complaint Management for frontline nurses &amp; nursing supervisors"</b> Organised by: College of Nursing, Hong Kong Speaker: Mr. TSOI Wang Fat	Ms. Karen CHU Tel: 2527 8898 Fax: 2865 0345 Secretariat Tel: 2572 9255 Fax: 2838 6280 3 CNE Points
<b>22</b> <b>SUN</b> 2:00 pm (29)	<b>HKMA Snooker Tournament</b> Organised by: The Hong Kong Medical Association Chairman: Dr. H YEUNG & Dr. R CHEUNG # Prat Billiard Club	Ms. Dora HO Tel: 2527 8285
<b>26</b> <b>THU</b> 6:00pm - 8:00pm	<b>Advanced Wound Care Management (Code No. TC-AWCM-0107-CNSG)</b> Organised by: College of Nursing, Hong Kong Speaker: Mr. HO Chi Wai	Secretariat Tel: 2572 9255 Fax: 2838 6280 8 CNE Points
<b>27</b> <b>FRI</b> 6:00pm - 8:00pm	<b>Basic Wound Management (Code No. TC-BWC-0107-CNSG)</b> Organised by: College of Nursing, Hong Kong Speaker: Mr. HO Chi Wai & Team	Secretariat Tel: 2572 9255 Fax: 2838 6280 21 CNE Points
<b>28</b> <b>SAT</b> 9:30 am - 4:30 am	<b>Certificate Course on Medical Genetics</b> Organised by: The Federation of Medical Societies of Hong Kong & Hong Kong Society of Medical Genetics Chairman: Dr. HUNG Kwan Ngai & Dr. Ivan LO Speaker: Various # Lecture Hall, 4/F, Duke of Windsor Social Service Building, 15 Hennessy Road, Wanchai, Hong Kong	Ms. Karen CHU Tel: 2527 8898 Fax: 2865 0345
<b>29</b> <b>SUN</b> 2:00 pm 2:00 pm	<b>HKMA Badminton Day</b> Organised by: The Hong Kong Medical Association Chairman: Dr. H YEUNG & Dr. S.N. CHEONG # MacLehose Medical Rehabilitation Centre <b>HKMA Structured CME Programme Year 07/08 (I) - Surgery</b> Organised by: The Hong Kong Medical Association & Kwong Wah Hospital Chairman: Dr. T.C. SHIH Speaker: Various # Lecture Theatre, 10/F, Yu Chun Keung Memorial Medical Centre, Kwong Wah Hospital, Kowloon	Ms. Dora HO Tel: 2527 8285 Miss Nina HUNG Tel: 2861 1979 (Registration Fee is required) 3 CME Points



## Courses

1,4,8,11,15,18,22,25,29/5/2007, 1,5,8,12,15,19,22,26,29/6/2007, 3,6,10,13,17,20,24,27,31/7/2007, 3,7,10,14,17,21,24,28/8/2007	<b>健康服務助理員訓練課程 (Code no. TC-HCA-0107)</b> Organised by: College of Nursing, Hong Kong Enquiry: Secretariat Tel: 2572 9255 Fax: 2838 6280
2,4,9,11,16,18,23,25,30/5/2007 1,6,8,13,15,20,22,27,29/6/2007 4,6,11,13,18,20,25,27/7/2007 1,3,8,10,15,17,22,24,29,31/8/2007 5,7,12,14,19,21/9/2007 3,10,17/5/2007	<b>健康服務助理員訓練課程 (Code no. TC-HCA-0207)</b> Organised by: College of Nursing, Hong Kong Enquiry: Secretariat Tel: 2572 9255 Fax: 2838 6280
4,11,18,25/05/2007, 1,8,15,22,29/06/2007, 6/07/2007	<b>Advanced Wound Care Management (Code No. TC-AWCM-0107-CNSG)</b> Organised by: College of Nursing, Hong Kong Enquiry: Secretariat Tel: 2572 9255 Fax: 2838 6280
18,19/5/2007	<b>Basic Wound Management (Code No. TC-BWC-0107-CNSG)</b> Organised by: College of Nursing, Hong Kong Enquiry: Secretariat Tel: 2572 9255 Fax: 2838 6280
18,19/5/2007	<b>IOF Osteoporosis Diagnosis Course</b> Organised by: The Osteoporosis Society of Hong Kong, The University of Hong Kong (The Osteoporosis Centre & Research Centre of Heart, Brain, Hormone & Healthy Aging) Chairman: Prof. Annie KUNG # 6/F, Old Wing, The Hong Kong Convention & Exhibition Centre Enquiry: Ms. Cissy SOONG Tel: 2855 4353 Fax: 2855 1701
9,10,11/7/2007	<b>Definitive Surgical Trauma Care (DSTC) Course</b> Organised by: Department of Surgery, Li Ka Shing Faculty of Medicine, University of Hong Kong Medical Centre; Queen Mary Hospital & Hong Kong Chapter of the American College of Surgeons # Skills Development Centre, Department of Surgery, Li Ka Shing Faculty of Medicine, University of Hong Kong Medical Centre, Queen Mary Hospital, Pokfulam, Hong Kong Enquiry: Program Manager Tel: 2855 4885 Fax: 2819 3416 Email: hnsrg@hkucc.hku.hk Website: <a href="http://www.hku.hk/surgery">http://www.hku.hk/surgery</a>
24,25,26/8/2007	<b>Advanced Trauma Life Support (ATLS) Student Course</b> Organised by: Department of Surgery, Li Ka Shing Faculty of Medicine, University of Hong Kong Medical Centre; Queen Mary Hospital & Hong Kong Chapter of the American College of Surgeons # Skills Development Centre, Department of Surgery, Li Ka Shing Faculty of Medicine, University of Hong Kong Medical Centre, Queen Mary Hospital, Pokfulam, Hong Kong Enquiry: Program Manager Tel: 2855 4885 Fax: 2819 3416 Email: hnsrg@hkucc.hku.hk Website: <a href="http://www.hku.hk/surgery">http://www.hku.hk/surgery</a>

## Meetings

19-20/5/2007	<b>8<sup>th</sup> Regional Osteoporosis Conference</b> Organised by: The Osteoporosis Society of Hong Kong & The University of Hong Kong (The Osteoporosis Centre & Research Centre of Heart, Brain, Hormone & Healthy Aging) Chairman: Prof. Annie KUNG # 6/F, Old Wing, The Hong Kong Convention & Exhibition Center Enquiry: Ms. Cissy SOONG Tel: 2855 4353 Fax: 2855 1701
9-10/6/2007	<b>Sports Medicine And Rehabilitation Therapy Convention 2007</b> Organised by: CUHK-WHO Collaborating Centre for Sports Medicine and Health Promotion & Asian Federation of Sports Medicine # Postgraduate Education Centre, Prince of Wales Hospital, Shatin Enquiry: Miss Po-yee TONG & Miss Bell CHUNG Tel: 2632 2798, 2646 1477 Fax: 2646 3020 Email: poyee@ort.cuhk.edu.hk, bellise@ort.cuhk.edu.hk Website: <a href="http://www.cuhk.edu.hk/whoctr/smart07/">http://www.cuhk.edu.hk/whoctr/smart07/</a>
13-17/6/2007	<b>The 21<sup>st</sup> Congress of International Association of Paediatric Dentistry IAPD</b> Organised by: Hong Kong Society of Paediatric Dentistry # Hong Kong Convention & Exhibition Centre Enquiry: Mr. Daniel CHOK Tel: 2871 8896 Fax: 2871 8898 Email: info@iapd2007.com Website: <a href="http://www.iapd2007.com">http://www.iapd2007.com</a>
12/7/2007	<b>The 1<sup>st</sup> Nursing Forum</b> Organised by: Department of Surgery, Li Ka Shing Faculty of Medicine, The University of Hong Kong; American College of Surgeons, Hong Kong Chapter & Department of Nursing Studies, Li Ka Shing Faculty of Medicine, The University of Hong Kong # Underground Lecture Theatre, New Clinical Building, Queen Mary Hospital, Pokfulam, Hong Kong Enquiry: Forum Secretary Tel: 2855 4885 / 2855 4886 Fax: 2819 3416 Email: hksf@hkucc.hku.hk Website: <a href="http://www.hku.hk/surgery">http://www.hku.hk/surgery</a>
12-14/7/2007	<b>The 50<sup>th</sup> Hong Kong Surgical Forum</b> Organised by: Department of Surgery, Li Ka Shing Faculty of Medicine, The University of Hong Kong & American College of Surgeons, Hong Kong Chapter # Underground Lecture Theatre, New Clinical Building, Queen Mary Hospital, Pokfulam, Hong Kong Enquiry: Forum Secretary Tel: 2855 4885 / 2855 4886 Fax: 2819 3416 Email: hksf@hkucc.hku.hk Website: <a href="http://www.hku.hk/surgery">http://www.hku.hk/surgery</a>
17-18/11/2007	<b>Annual Scientific Meeting in Anaesthesiology 2007 - Expanding the Boundaries</b> Organised by: The Hong Kong College of Anaesthesiology & The Society of Anaesthetists of Hong Kong # Hong Kong Convention and Exhibition Centre Enquiry: CMPMedica Pacific Limited Tel: 2559 5888 Fax: 2559 6910 Email: meeting.hk@asia.cmpmedica.com Website: <a href="http://www.hkca.edu.hk/asm2007.htm">www.hkca.edu.hk/asm2007.htm</a>



## Society News

## News from Member Societies:

**Hong Kong Association of Rehabilitation Medicine**

New office-bearers for the year 2007-2008 are as follows: President: Dr. CHUI Tak Yi, Vice President: Dr. LEUNG Kwok Pui, Hon. Secretary: Dr. YU Kim Kam Teresa, Hon. Treasurer: Dr. FUNG Pui Man Mandy. Dr YU Kim Kam, Teresa has been appointed as the Association's Council Representative effective from 4th January 2007.

**Hong Kong Society of Cytology**

Mr. LONG Fuk Cheong has been appointed as the Society's Council Representative effective from 24th January 2007.



## Answer to Clinical Quiz

### Answer :

1. The diagnosis is urticaria pigmentosa (UP). It is the most common skin manifestation of mastocytosis in both children and adults. The lesions appear as small, yellow-tan to reddish-brown macules or slightly raised papules or plaques scattered over the body. Mild trauma, including scratching or rubbing of the lesions, usually causes urtication and erythema around the macules; this is known as the Darier's sign. This is the reason why the mother noticed urtication and blistering in some of the severe lesions (shown in the right infra-scapular area at the back) when rubbing dry the baby's body after bath. Patient with mastocytosis may develop gastrointestinal disease presenting with diarrhoea, abdominal pain and malabsorption. Internal organomegaly affecting the liver and spleen is rarely seen. Bone and marrow involvement presenting with bone pain, anaemia, leucopenia, thrombocytopenia and eosinophilia may occur in systemic disease. Fortunately, our baby did not show any symptoms suggestive of systemic involvement.
2. The diagnosis of UP is suspected on clinical grounds and confirmed by histology. Mast cells, which can be shown by special metachromatic stains such as toluidine blue and Giemsa, are found in increased numbers in dermal papillae, particularly near blood vessels. The greatest increase occurs beneath UP macules and papules where, on average, there is a fifteen- to twenty fold increase in mast cells. Hence, rubbing of these lesional macules degranulates the underlying mast cells and produces urtication and blister when the Darier's sign is elicited. Relevant systemic work up, depending on the signs and symptoms of systemic involvement, may include complete blood picture, liver and renal function tests, chest x-ray, bone scan/ skeletal survey, GI radio-imaging and endoscopic studies and bone marrow aspiration.
3. The aim of the treatment is to control mast cell mediator-induced signs and symptoms such as pruritus. H1 receptor antagonists such as hydroxyzine and doxepin are useful in reducing pruritus, flushing and tachycardia. The addition of H2 antagonists such as ranitidine or cimetidine may be beneficial. Disodium cromoglycate inhibits degranulation of mast cells and may have some efficacy in the treatment of mastocytosis. Topical corticosteroids, such as betamethasone dipropionate ointment applied under plastic-film occlusion may be used to treat extensive UP. Other appropriate treatment is used as indicated to control any systemic disease. As a group, patients with indolent mastocytosis and skin involvement alone have the best prognosis. Among children with isolated UP, as in our patient, at least 50 percent of cases resolve spontaneously by adulthood.

**Dr. Ka-ho Lau**

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

BMA AGM Dinner  
on Saturday May 12th  
at the Hong Kong Club

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Please join us for another exciting BMA AGM Dinner. This popular evening is guaranteed to be entertaining with great food, good wine and superb company. The theme is 'Casino Royale' so wear your best Bond outfits! Entertainment will be provided by a live band and casino charity gaming tables where you can try your luck!

Cocktails (Martinis of course!) will be served from 7 pm, dinner will be at 8 pm.

**AGM 7.30 - 8 pm- BMA[HK] members are invited to attend**

10 pm Dancing & Charity Gaming

12 pm: Carriages

Dress: Black Tie/ Bond Theme

Tickets (payable in advance): \$650 Tables of 10 @ \$6000

If you would like to attend, please send your name and contact details to the email address below, advising the number of tickets that you require.

Please make cheques payable to: British Medical Association (HK Branch)  
Please send your cheque to: Ms Allyson Smyth, 8/F AON China Building, 29 Queen's Rd Central, Hong Kong  
Enquiries: Ms Allyson Smyth T 3420 6666 F 2521 6381 E allyson.smyth@sp.hk



**Certificate Renal Nursing Course 2007  
(Course no. C117)**



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

**Objective:** The objective of the course is to furnish renal nurses with theoretical knowledge of clinical nephrology, haemodialysis, peritoneal dialysis, concepts of renal transplantation, information technology and medico-legal principles in nursing practice.

Date	Title of the Lecture /activities	Speaker
20 April, 2007	Opening Speech Clinical Nephrology and Renal Investigations Common Renal Diseases and Their Management	Dr C P Ho Dr T C Au
27 April, 2006	Clinical Management of Chronic Kidney Disease Dietary Management of Chronic Kidney Disease	Dr C P Ho Ms Mimi Sham
4 May, 2007	Principles and History of Haemodialysis Water Treatment System and Infection Control in Renal Units	Dr Tsang Wai Kei Dr C P Ho
11 May, 2007	Vascular Access, Bicarbonate Dialysis, Kt/V and Sodium Profiling in Dialysis. Care of Vascular Access	Dr C P Ho Ms Anna Mok
18 May, 2007	Acute Renal Failure and Acute Haemodialysis Problems. Care of the Renal Patients During Haemodialysis	Dr Jonathan U Ms T Chan
25 May, 2007	Long Term Dialysis Problems History and Medical Aspects of Renal Transplantation	Dr Tsui Hing Sum Dr Francis Wong
1 June, 2007	Transplant Immunology Made Simple The Role of The Transplant Co-ordination Team	Dr Gordon Siu Ms Angela Wong
8 June, 2007	Surgical Aspects of Renal Transplantation Commonly Used Drugs in a Renal Unit	Dr Y T Chan Ms Li Fu Keung
15 June, 2007	Satellite Dialysis Centres, PPI and the Use of IT in Renal Nursing Medico-legal Problems in Renal Units	Dr C P Ho Dr Kwok Chi Yeung
22 June, 2007	The Development of Peritoneal Dialysis Nursing Aspects of Peritoneal Dialysis	Dr Li Fu Keung Ms T Chan
29 June, 2007	Field Visit to Nephrocare /Group Discussion	Dr C P Ho/ Ms Stella Yim
6 July, 2007	Field Visit to Nephrocare /Group Discussion	Dr C P Ho/ Ms Stella Yim

Date : 20 April 2007 to 6 July 2007 (Friday)  
 Time : 2:30 pm – 4:30 pm  
 Venue (Lecture) : Lecture Hall, 4/F, Duke of Windsor Social Service Building, 15 Hennessy Road, Wanchai, Hong Kong  
 (Field Visit) : Nephrocare Centre, Hong Kong St Paul's Hospital, 2 Eastern Hospital Road, Causeway Bay, Hong Kong  
 Course Fee : HK\$1500  
 Language : Cantonese supplemented by English  
 Application Deadline : 2 April 2007  
 Entry Requirement : Registered nurse or enrolled nurse from public or private institutions  
 Certificate : Awarded to participants with a minimum attendance of 85%  
 Enquiry : The Secretariat of the Federation of Medical Societies of Hong Kong  
 Tel. : 2527 8898 Fax: 2865 0345 Email: [info@fmshk.org](mailto:info@fmshk.org)  
 CME/CPE Accreditation applied for  
 For downloading the application form, please refer to our website: <http://www.fmshk.org>

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# 50<sup>th</sup> Hong Kong Surgical Forum

Thursday to Saturday, 12 - 14 July 2007



## 1<sup>st</sup> Hong Kong Nursing Forum

Thursday, 12 July 2007

### Overseas Speakers:

Jacques Belghiti, *France*  
Kenneth D. Boffard, *South Africa*  
Ara W. Darzi, *United Kingdom*  
Richard J. Finley, *Canada*  
Yuman Fong, *USA*  
Ada S. Hinshaw, *USA*  
John G. Hunter, *USA*  
Jonas T. Johnson, *USA*  
Masaki Kitajima, *Japan*  
Anne Kolbe, *New Zealand*  
Fabrizio Michelassi, *USA*  
Carlos A. Pellegrini, *USA*  
Anne M. Rafferty, *United Kingdom*  
Nathaniel J. Soper, *USA*  
Donald D. Trunkey, *USA*

### Venue :

Underground Lecture Theatre  
Queen Mary Hospital  
Pokfulam, Hong Kong

### Organisers:

Departments of Surgery and Nursing Studies  
Li Ka Shing Faculty of Medicine  
The University of Hong Kong  
*and*  
Hong Kong Chapter  
American College of Surgeons

### Enquiry:

Forum Secretary  
Tel: (852) 2855 4885 / 2855 4886  
Fax: (852) 2819 3416  
E-mail: [hksf@hkucc.hku.hk](mailto:hksf@hkucc.hku.hk)



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<sup>†</sup> Clinical significance of in vitro activity is unknown

<sup>#</sup> Infections caused by susceptible micro-organisms

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**References:** 1. TYGACIL™ (tigecycline) product monograph.  
2. TYGACIL™ (tigecycline) prescribing information, Hong Kong.  
**Detail prescribing information available upon request.**