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The Cover Shot

寶劍鋒從磨礪出
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B.Sc., M. Phil, FGA, FGAHK, JJD
Forensic Scientist

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Editorial

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Editor

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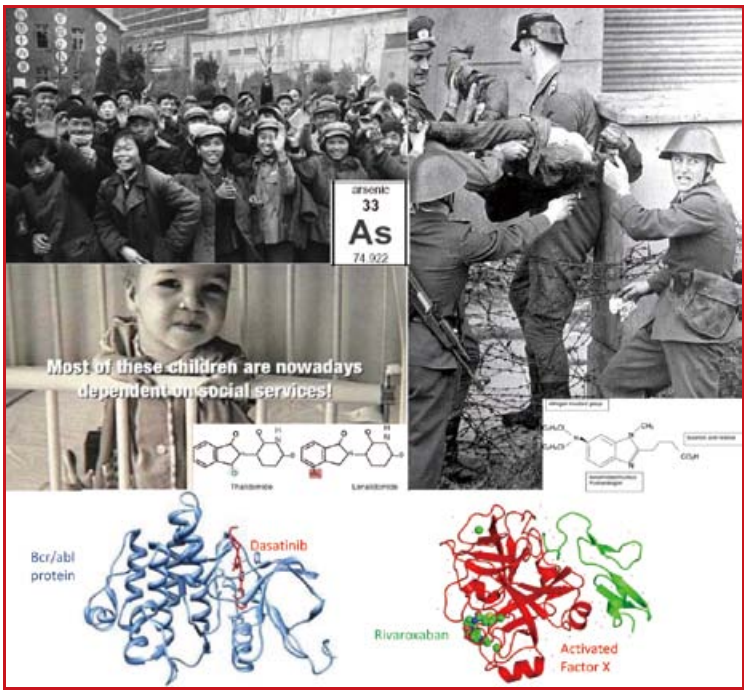
The New Year is a time for reflection. It is also a time to ponder the future. For decades, physicians and patients have endured many frustrations in haematology. We face the horrible side effects and failures of leukaemia chemotherapy and marrow transplantation, the cumbersome diet restrictions and INR monitoring of warfarin anticoagulation, and the pessimistic clinical course of myelomas and lymphomas. In this issue of the Diary, we look at six new drugs that have changed these predicaments. Some are amazing futuristic designer drugs tailored to switch off key molecules. More amazingly, others are simply re-discovered after being forgotten for years, decades or even centuries.



Past despair sometimes bears new hope. We start close to home with the fascinating story of **oral arsenic** therapy. Used for centuries in traditional Chinese medicine, arsenic is more a poison than a drug. During the poverty of the Cultural Revolution in Harbin in 1971, cheap arsenic trioxide was revived and tried unsuccessfully on many cancers. Amazingly however, it had near 100% activity against acute promyelocytic leukaemia (APL, formerly AML-M3). From China, it was re-introduced to the world in 1998. Today, it is replacing chemotherapy as APL cure. Likewise, during the Cold War hardship in 1963, scientists in East Germany made their own chemotherapy for all cancers: **bendamustine**. Forgotten after the 1989 unification, it was rediscovered a decade later. As a single agent, it out-performed multi-agent chemotherapy in lymphoma trials and became first line by 2008.

Finally, thalidomide was banned for 50 years after the 1950 horror epidemic of 10,000 limbless babies born to mothers taking it for nausea. Amazingly in 1999, it re-emerged with spectacular activity against myeloma and is now a first-line agent. Slight modification of the thalidomide structure gives the second generation agent **lenalidomide**, with 100 times increased potency in some biological properties.

In contrast, some drugs come from pure rational design with no precedent in history or nature. Since 1990s, investigators in Oregon screened thousands of designer compounds to fit and switch off the bcr/abl protein in chronic myeloid leukaemia (CML) and acute lymphoblastic leukaemia (ALL). In 2001 compound 571 (imatinib) became the oral magic bullet that can render CML undetectable in 3 months. Second generation products, nilotinib and **dasatinib**, are 10 and 100 times more potent respectively. Today, the 8-year survival of CML approaches 95%. Leukaemia becomes a chronic disease controlled by a pill. In non-malignant haematology, recombinant erythropoietin and G-CSF has existed for 20 years but thrombopoietin never worked. Finally in 2008, platelet growth factors arrived for ITP treatment. The trick in both **romiplostim** and eltrompopag is to engineer just a small part of thrombopoeitin to fit the receptor. Lastly, we look at designer antagonists that switch off the activated motif of coagulation factors (II or X) and halt the clotting cascade. **Rivaroxaban** (an oral Xa inhibitor) was approved in 2011 to replace warfarin (approved in 1954) for atrial fibrillation and venous thrombosis. It obviates the need for INR monitoring and dose adjustments.

Haematology is entering an exciting new era. For some APL and ALL patients, chemotherapy may be obsolete. Oral arsenic and dasatinib treatment alone can give 100% remission rates. I hope our readers can enjoy both the history and the science. Finally, I wish you all a healthy and prosperous New Year.

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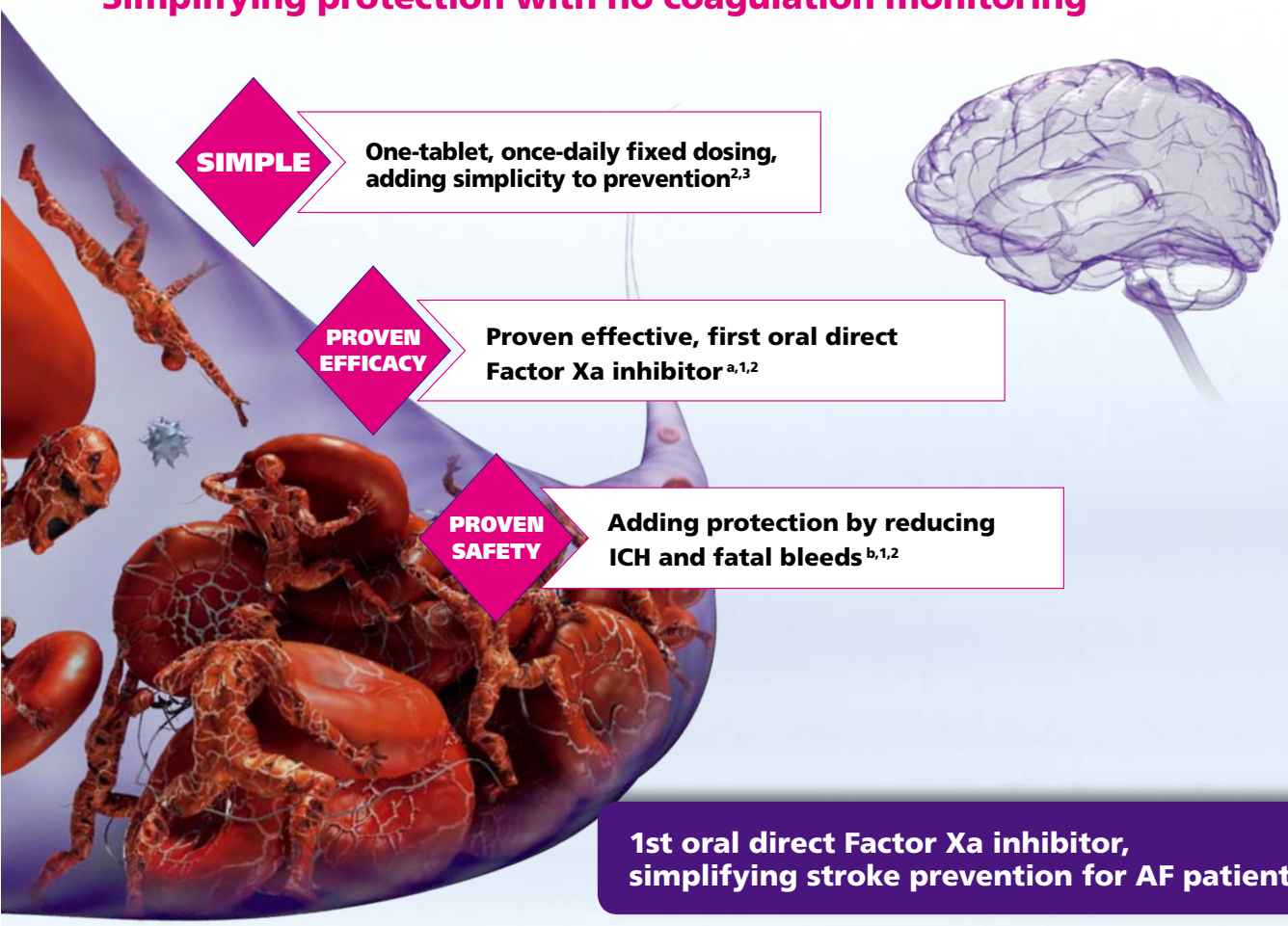

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[a]Per-protocol, on-treatment analysis. Event rate: Xarelto (1.7%/yr) vs warfarin (2.2%/yr), $P<0.001$ for non-inferiority.
[b]Fewer intracranial haemorrhage events: Xarelto (0.5%/yr) vs warfarin (0.7%/yr), $P=0.019$. Fewer fatal bleeding events: Xarelto (0.2%/yr) vs warfarin (0.5%/yr), $P=0.003$.

Patients on Xarelto had significant increases in the following major bleeding events: a ≥2 g/dL fall in haemoglobin (2.8% vs 2.3%, P=0.019) and transfusions (1.6% vs 1.3%, P=0.044). Major bleeding: bleeding associated with a ≥2 g/dL fall in haemoglobin or requirement for transfusion of ≥2 units of packed red blood cells or whole blood (clinically overt bleeding); the involvement of a critical site; or a fatal outcome.

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Oral Arsenic Trioxide in the Treatment of Acute Promyelocytic Leukaemia

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Introduction

Acute promyelocytic leukaemia (APL, formerly AML-M3 in FAB classification) is a unique type of acute myeloid leukaemia characterised by severe bleeding tendency. The leukaemic cells are heavily granulated with bundles of Auer rods. They release annexin II to trigger disseminated intravascular coagulation. Coupled with pancytopenia, early haemorrhagic deaths exceed 30%.

China introduces ATRA

In 1991, breakthrough came along from the Shanghai Ruijin Hospital (Prof Wang ZY). They demonstrated that orally all trans-retinoic acids (ATRA, a vitamin A derivative) can induce differentiation of APL cells to mature neutrophils. This dampens the bleeding tendency and produces remissions[1]. A combination of ATRA and chemotherapy, followed by two years of ATRA maintenance transformed APL from a deadly to curable leukaemia. However, up to 20% patients still relapse. Salvage with chemotherapy or allogeneic bone marrow transplantation (BMT) are both unsatisfactory[2].

The history of oral arsenic trioxide

Since the days of Li Sze Chun, arsenic trioxide was used in traditional Chinese medicine (TCM) for centuries. Its indications ranged from fever, cough and ulcers, but long-term toxicity is noted. In the late 19th century, a 1% arsenic trioxide oral solution was used in Europe as a medical remedy for asthma, malaria to psoriasis. It also found use as a stimulant for Senators, a health tonic for aristocrats and a performance enhancer for race-horses. Arsenicals became the first effective Western medicines. In Berlin, Nobel Laureate Paul Erlich introduced arsenic intramuscular injections to combat syphilis during World War One.[3] In Boston, Claude Forkner used oral arsenic to control leukocytosis and splenomegaly in chronic myeloid leukaemia. Oral arsenic trioxide was a standard hospital, including Queen Mary Hospital (QMH) item. The arrival of penicillin antibiotics and mustard chemotherapy rendered arsenic obsolete after the World War Two[4]. Nevertheless, it remained on the Merck index of medicine until 1989.

Arsenic makes its comeback

In 1971, during the Cultural Revolution, a medical team led by Prof. Zhang ZD was sent from Harbin to visit a rural TCM practitioner with a cancer panacea. They brought back a combination of arsenic, mercury and toad extracts. It was made into an intramuscular injection in March and named 713 Solution. Although it showed some activity in liver, colon and gynaecological cancers, it was too toxic. Zhang, a haematologist, continued the trials in leukaemia. A handful of patients survived and were all AML-M3 cases. He found that arsenic trioxide was the only active ingredient and can be given intravenously. Harbin began the production of 1% arsenic intravenous solution (Ailing Number1) which continues today[4]. Their remarkable success attracted national attention[5] The Shanghai Ruijin group (Prof. Chen Z) collaborated with the Harbin group (Prof. Ma J) to publish the pharmacokinetics and efficacy of arsenic in 1999. China stunned the APL world a second time[1,6]. The research was re-run in New York and the results re-published[7]. Unfortunately, the US group proceeded to conjure up a US patent claiming to have re-invented arsenic trioxide themselves. It was rapidly granted in USA and quickly sold for US$15-70 million to pharmaceutical companies (Cell Therapeutics, Cephalon, Teva, Lundbeck)[8]. Consequently, in most parts of the world except in China, India and Iran, hospitals were medico-legally forced to use their product that costs up to US$50,000.

Efficacy of intravenous arsenic

Despite its shady commercial history, intravenous arsenic trioxide (Trisenox in the West) showed spectacular activity. At a dose of 0.15mg/kg daily in relapsed APL, it gives remissions rates (RR) of over 95%. Remissions can be sustained with repeated courses of arsenic, showing that unlike ATRA, arsenic can eradicate minimal residual disease[9]. The role of BMT was relegated to true refractory cases.

Investigators in the East moved arsenic upfront. Since 2001, the Shanghai group used arsenic (Ailing No.1), ATRA and chemotherapy induction (6 cycles) and reported 94% RR and 89% 5-year disease free survival (5-yr DFS)[10]. In Iran[11] and India[12], once China reported arsenic therapy in 1998, physicians immediately replaced chemotherapy with inexpensive locally produced arsenic in all APL cases. Their 10-year experience showed 86% RR with 5yr DFS of 67-80% in all cases and 100% in low risk cases. Arsenic can synergise with chemotherapy and even rival or replace it completely.

Investigators in the West followed. In 2010 the US intergroup reported that adding arsenic consolidation (2 cycles) improved 3yr-DFS from 63% to 80%[13]. Australian data published in 2012 using upfront arsenic, ATRA and chemotherapy combination (3 cycles) followed by oral ATRA / chemotherapy for 2 years, essentially reproduced the Shanghai experience (95% RR, 88% 2-year DFS)[14]. In 2006, following the Indians and Iranians, the Houston group reported arsenic without chemotherapy in 25 elderly patients with 96% RR and

no relapse in 3 years[15]. Finally, in 2012, a German- Italian study reported randomizsing arsenic trioxide (5 cycles) against chemotherapy in low-risk APL cases. Arsenic showed superior efficacy (100% vs 95% RR, 97% vs 87% 2yr DFS) with less side effects[16] .

Intravenous therapy poses problems. Repeated infusions mean daily hospital visits, infusion reactions, phlebitis and cytopenia. Sudden arrhythmic deaths due to QTc prolongation occur due to the abrupt rise in arsenic level. Unlikely oral ATRA, prolonged intravenous arsenic maintenance is not practical.

The return of oral arsenic

Since 1% oral arsenic solution was used in QMH up to 1950, a project was started to revive it in 1998. The chemical methodology for solution preparation was obtained from Vancouver[4]. Oral arsenic yielded the same area under the curve (AUC) in terms of blood levels as intravenous arsenic trioxide[17]. It produced remissions in 11 of 12 relapsed APL patients[18]. Since 1999, intravenous arsenic was no longer required. A full oral combination of arsenic (5-10 mg daily) and ATRA (30-70 mg daily), used for 2 weeks every 2 months over 2 years, was adopted[19]. All patients were treated at home. The University of HK obtained a US patent in 2006 to protect the formulation against another repeat intellectual exploitation[4].

Efficacy of oral arsenic trioxide

Hong Kong is the only place in the world where oral arsenic trioxide is used systemically. The unique results challenge intravenous data in terms of clinical efficacy and side effect profile. Quality of life (QOL) and pharmacoeconomic studies, comparing in-patient commercial intravenous product versus out-patient oral free product (for all Hospital Authority (HA) patients), appeared redundant.

At 11year follow up, patients treated in relapse showed RR of 98% and 4-yr DFS of 71%.[20] Autologous BMT was used in 4 cases and with no allogeneic BMT performed at all. For patients treated at remission, the 5-year DFS was 88%[21], comparable to the best intravenous results for unselected cases. The series included 10 patients treated with no or limited chemotherapy, due to age or co-morbidity[21]. Among them, relapses were not seen. This could be due to selection bias or improved effect of upfront arsenic exposure. A total of 135 patients (age 6 to 83) were treated from 1998 to 2011[22]. Central nervous system relapse was the commonest failure and intrathecal prophylaxis and prevention of leukocytosis may improve future results [23].

The side effects were modest. No patient was taken off therapy due to side effects. QTc prolongation did not occur with oral therapy due to lower arsenic levels[17,24]. Mild discomforts (e.g. headache, dyspepsia) were relieved by dividing or reducing daily doses. In paediatric patients especially, the oral solution was easily dosed and obviated venous access[22]. There were however concerns with late solid tumours, since arsenic is a known carcinogen. Notably, for cases remitting since 2006, second cancer (n=3) has replaced APL relapse (n=0) as the cause of death[25]. However, second cancers were also noted in pre-arsenic APL survivors. Solid tumours were also seen only shortly after arsenic exposure[26]. It is arguable that APL per se may be linked to cancer risk. Furthermore, oral arsenic is no more carcinogenic than intravenous arsenic, and probably less so than chemotherapy.

The future of oral arsenic

The experience in oral arsenic trioxide so far comes from one city (HK) and largely from one hospital only. Oral arsenic is prepared in its own hospital pharmacy. The product, produced in one HA pharmacy, was not made available to other HA public hospital pharmacies, despite being overwhelming used at home by out-patients. It is obviously desirable for HK patients, physicians, hospitals and the authorities to see a wider access of this life-saving medication. A propriety product would also be preferable to in-house concoctions. This would allow usage outside HA and unburden HA pharmacy's current liability. It would also allow global access. This oral formulation will be a viable alternative to the expensive and cumbersome intravenous product. Indeed, HKU has pledged to provide humanitarian supply for developing countries[27] where patients are barred by patent driven prices and succumb unnecessarily. In 2010 such a pharmaceutical grade oral arsenic formulation (Arsenol) was registered by manufacturers with the HK Department of Health[4]. A Good Manufacturing Practice (GMP) production facility, designed to meet Australian and Canadian accreditation standards, will be completed in 2013. The GMP product could replace current QMH in-house production. The production is scaled to supply not only HK but also China Mainland and abroad. Pending approval from the Department of Health, this GMP grade oral arsenic trioxide product will become the first patented prescribed medication developed in HK, produced in HK, and supplied to the world. The next chapter in this amazing story of arsenic trioxide may stun the world once again.

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MCHK CME Programme Self-assessment Questions

Please read the article entitled "Oral Arsenic Trioxide in the Treatment of Acute Promyelocytic Leukaemia" by Dr. Wing-yan AU and complete the following self-assessment questions. Participants in the MCHK CME Programme will be awarded CME credit under the Programme for returning completed answer sheets via fax (2865 0345) or by mail to the Federation Secretariat on or before 28 February 2013. 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. Acute promyelocytic leukemia is a form of myeloid leukemia
2. The major cause of early death in patients with APL is thrombosis
3. All trans-retinoic acid is chemically related to vitamin B12
4. Differentiation therapy can induce leukemia blast to mature into normal blood cells to bring about leukemia remission
5. ATRA and arsenic trioxide treatments for APL are both invented in China
6. Bone marrow transplantation is the best treatment option for all young leukemia patients with available donors
7. Arsenic trioxide has been used in both Traditional Chinese Medicine and Western Medicine for a long time in history
8. Arsenic trioxide is both a poison and a medicine and may potentially cause cancer itself
9. Oral medicine usually compares favorably to intravenous medicine in terms of cost and convenience
10. Good Manufacturing Practice (GMP) is not a mandatory prerequisite for a drug product to be commercially available

ANSWER SHEET FOR FEBRUARY 2013

Please return the completed answer sheet to the Federation Secretariat on or before 28 February 2013 for documentation. 1 CME point will be awarded for answering the MCHK CME programme (for non-specialists) self-assessment questions.

Oral Arsenic Trioxide in the Treatment of Acute Promyelocytic Leukaemia

Dr. Wing-yan AU
MBBS (Hons) (HK) MD (HK) FRCP (Edin / London) FHKCP FHKAM
Private Haematologist

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

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

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Vital Basis/HK/12008/0201/AA

Bendamustine – an Old New Drug

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The past few decades have witnessed a dramatic advancement in the treatment of haematological malignancies. With the development of new therapeutic agents, such as the many types of monoclonal antibodies, better response rates and improved patient survivals have been achieved. However, the management in certain conditions, especially in relapsed or refractory cases, remains a great challenge.

Bendamustine, an alkylating agent which is also believed to possess significant antimetabolite activity, has attracted a lot of recent attention. Interestingly, this drug is not a product of the latest pharmaceutical technology; instead it was first manufactured by Ozegowski and colleagues in the early 1960s in the former East German Democratic Republic. In an attempt to develop a novel anticancer drug, many different compounds were synthesised at that time. One of them, with the chemical name 4-(5-[bis(2-chloroethyl)amino]-1-methyl-2-benzimidazolyl) butyric acid hydrochloride which was later named bendamustine hydrochloride, was found to have a more stable structure and therefore more sustained DNA damage when compared to other members in the nitrogen mustard group of alkylators. It was used in the former East German Democratic Republic for the treatment of chronic lymphocytic leukaemia (CLL), non-Hodgkin lymphoma (NHL), Hodgkin lymphoma (HL), multiple myeloma (MM) and breast cancer. Unfortunately, very few well-validated studies concerning its efficacy were available from its early days.

With the fall of the Berlin Wall, more about this drug became known to the Western world; but it was not until 2003 that bendamustine was first allowed into the market of North America under the brand name of Treanda. Basically the structure of bendamustine consists of 3 parts: a chloroethylamine alkylating group, a benzimidazole ring, and a butyric acid side chain. Common to some other alkylating agents, the chloroethylamine group is responsible for the crosslinking of DNA and hence the cytotoxic effect of the drug. However, it has been shown that bendamustine is superior in causing DNA breaks, both in number and sustainability, than other alkylators like cyclophosphamide and carmustine. It is possibly due to a different pattern of DNA damage, together with an ability to induce intrinsic apoptosis of tumour cells and inhibit repair mechanisms. In addition, the benzimidazole ring, which is also present in many purine analogs such as cladribine, is believed to contribute certain antimetabolite activity and thereby increasing the potency of the drug. More importantly, bendamustine does not show cross-resistance with other cytotoxic agents, which is a common phenomenon among some other drugs especially the alkylators. In a hallmark study, Leoni et al have demonstrated activity of bendamustine in tumour cells resistant to cyclophosphamide. This has translated into clinical significance by providing an alternative treatment option in patients with relapsed or refractory diseases who have been previously treated with other agents.

The efficacy of bendamustine in was demonstrated in the European Intergroup CLL study, which involved 305 previously untreated patients with a median age of 65 years. These patients were randomised to bendamustine 100mg/m^2 intravenously for 2 consecutive days, or oral chlorambucil 0.8mg/kg on days 1 and 15, of each 28-day cycle. Overall response rates (ORR) in 156 bendamustine- and 149 chlorambucil-treated patients were 68% (30% complete remission [CR]) and 39% (2% CR), respectively ($P < 0.0001$). Median progression-free survival (PFS) was 21.7 months for bendamustine versus 9.3 months for chlorambucil ($P<0.0001$). These results had led to the FDA approval of bendamustine as the first-line treatment of CLL on 20 March 2008, at the recommended dose of 100mg/m^2 intravenously on days 1 and 2 of a 28-day cycle, for up to 6 cycles. Subsequent studies have also shown favourable outcomes in patients with relapsed and previously treated CLL when combined with rituximab, a monoclonal antibody against CD20; but the recommended doseage would be reduced to 70mg/m^2 in this setting.

Another important application of bendamustine is in the treatment of NHL. In a pivotal single-arm study involving 100 patients with rituximab-refractory indolent NHL (including follicular lymphoma [62%], CLL/SLL [26%] and marginal zone lymphoma [21%]), bendamustine was administered at 120mg/m^2 on days 1 and 2 of a 21-day cycle for 6-8 cycles. The ORR was 84% including 32% CR; the median response duration was 9.3 months and the median progression-free survival was 9.7%. These results had led to the FDA approval of bendamustine for the treatment of rituximab-refractory indolent B-cell NHL on 31 October 2008. When used in combination with other agents such as fludarabine and rituximab, the outcome of patients in this setting has also been shown to be promising in subsequent studies. A phase III trial by the German Study Group of Indolent Lymphomas to compare bendamustine-rituximab versus the traditional chemotherapy regime rituximab-CHOP as first-line treatment for indolent NHL is currently in progress, and the initial results are encouraging.

The safety of bendamustine has been well proven in the above studies and some other pharmacokinetic investigations. The most commonly reported non-haematologic side-effects include nausea, vomiting, fever, infusion reactions, skin rash, headache and dyspnoea; while common haematologic adverse events include lymphopenia, anaemia, thrombocytopenia and neutropenia. The drug is not recommended in patients with moderate to severe hepatic or renal impairment, and is contra-indicated in pregnancy. In our experience, bendamustine is generally well-tolerated even in the relatively older patient population.

In summary, bendamustine is a novel agent which is gaining importance in the treatment of lymphoid malignancies. Further development of bendamustine-based regimes is likely to improve the outcome in these patients.

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Advances in the Treatment of Multiple Myeloma

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Introduction

Multiple myeloma (MM) is a malignant plasma cell disorder that accounts for approximately 10% of all haematologic cancers[1]. The disease is characterised by the neoplastic proliferation of a single clone of plasma cells producing an M-protein. The clone of plasma cells proliferates in the bone marrow and frequently invades the adjacent bone, producing skeletal destruction that results in bone pain and pathological fractures. Anaemia, hypercalcaemia and renal insufficiency are other common features. CRAB criteria are indications for therapy and they include hypercalcaemia, renal failure, anaemia and bone disease[2].

There were significant advances in the treatment of plasma cell myeloma in the last decade and the outcome has markedly improved. The incorporation of novel agents (thalidomide, lenalidomide and bortezomib) has improved the response rates and duration of response, enabling a higher complete remission rate to be achieved. The current standard of treatment is induction therapy followed by autologous stem cell transplant (ASCT) and consolidation and/or maintenance therapy.

Treatment should be started only in symptomatic MM. In asymptomatic or smoldering MM, long-term treatment with lenalidomide–dexamethasone delays the occurrence of symptomatic MM[3], but the impact on the efficacy of overt MM treatment and on overall survival is unknown and this approach should not be used outside a clinical trial.

Induction therapy for young or transplant-eligible patients

The choice of induction therapy has moved from conventional chemotherapy to newer regimens incorporating the immunomodulatory agents like thalidomide or lenalidomide and the proteasome inhibitor bortezomib. These drugs combine well with traditional therapies and with one another to form various doublet, triplet, and quadruplet regimens.

Triplet regimens are appropriate regimens for transplant eligible patients. Randomised studies have shown that triple combinations with thalidomide–bortezomib–dexamethasone (VTD regimen) are superior to double combinations with either thalidomide–dexamethasone (TD) or bortezomib– dexamethasone (VD) in terms of the complete remission (CR) rate both before and after ASCT[4-6]. With this type of induction treatment, it is possible to achieve up to 70% CR plus very good partial remission (VGPR) after ASCT. A high CR/near CR and VGPR rates were also achieved in Hong Kong Chinese patients receiving frontline or early bortezomib-based induction therapy[7].

Other triple combinations have been tested such as bortezomib–cyclophosphamide–dexamethasone (VCD), bortezomib–lenalidomide–dexamethasone (RVD) and yield encouraging results. Quadruple combinations do not appear to be superior to triple combinations and may even be more toxic [8]. In patients presenting with acute renal failure, both thalidomide- and bortezomib-based regimens can be safely given, whereas lenalidomide requires dose reductions and frequent monitoring of blood counts. In patients at high risk of thromboembolic complications, a bortezomib-based regimen may be preferable. In contrast, the presence of neuropathy at baseline might suggest excluding bortezomib-based or thalidomide-based treatments in favour of a regimen, such as lenalidomide-dexamethasone[8].

Three to six cycles of induction therapy were usually given prior to ASCT to maximise the depth of response and it is also a reasonable balance between maximum benefit and minimum toxicity[8].

Consolidation and maintenance therapy after autologous stem cell transplant

Consolidation therapy can enhance the rate and quality of response obtained with the previous treatment. Several phase 2 and 3 studies have explored the role of thalidomide, lenalidomide and bortezomib as single agents or combined with one another to improve outcomes after ASCT, either single or double.

Lenalidomide combined with standard-dose bortezomib plus dexamethasone (VRD) was explored as consolidation therapy. The rates of CR/stringent CR and very good VGPR were 42% and 26%, respectively, after ASCT; following RVD consolidation therapy, the corresponding values were 48% and 36%[9].

In comparison with TD, two cycles of VTD consolidation therapy significantly increased the rate of CR (47% vs. 61%) and CR/near CR (61% vs. 73%). With a median follow-up of 30.4 months from the landmark of starting consolidation therapy, PFS at 3 years was significantly longer for VTD treated (60%) versus TD-treated patients

(48%) [10].

Maintaining results of successful induction therapy is an important goal in multiple myeloma. Complete remission is important and it has to be durable. More recently, the treatment paradigm for transplantation-eligible MM patients has continued to evolve with the introduction of the novel agents as maintenance therapies.

Two large phase 3 trials with lenalidomide maintenance treatment after autologous stem cell transplantation and one study after conventional melphalan, prednisone, and lenalidomide induction therapy showed a significant risk reduction for PFS and an increase in OS in one of the transplant trials[11-13].

In one phase 3 study, 614 myeloma patients were recruited in the study and they were given either lenalidomide (10 mg per day for the first 3 months, increased to 15 mg if tolerated) or placebo until relapse. The primary end point was progression-free survival. Lenalidomide maintenance therapy improved median progression-free survival (41 months, vs. 23 months with placebo; hazard ratio, 0.50; P<0.001)[11].

Another phase 3 study recruited 460 newly diagnosed transplant eligible myeloma patients with non-progressive disease after ASCT receiving lenalidomide or placebo, which was administered until disease progression. The starting dose of lenalidomide was 10 mg per day (range, 5 to 15). At a median follow-up of 34 months, 86 of 231 patients who received lenalidomide (37%) and 132 of 229 patients who received placebo (58%) had disease progression or had died. The median time to progression was 46 months in the lenalidomide group and 27 months in the placebo group (P<0.001). The 3-year overall survival was 88% and 80% in the lenalidomide and placebo groups respectively (p=0.03) [12].

An increase in the incidence of second primary malignancies (SPMs), including myelodysplastic syndromes (MDS) and/or acute myeloid leukaemia (AML), solid tumours was reported in the lenalidomide maintenance arm. If post-ASCT therapy with lenalidomide is planned, it is recommended that the benefits of extended disease control versus potential risks of second malignancies with continued lenalidomide therapy be discussed with patients[14]. The issue of second malignancies is significant but still overwhelmed by the benefits associated with lenalidomide maintenance.

Treatment of Multiple Myeloma in older or transplant-ineligible patients

Novel agents have been added to the treatment of elderly patients in three different ways: addition of one novel agent to the melphalan-prednisolone (MP) combination, addition of one novel agent to dexamethasone and maintenance therapy after induction treatment.

Induction therapy

Six randomised trials compared the combination of MP plus thalidomide (MPT) with the standard MP[15-20]. PR rate was 42-76% versus 28-48% with MPT and MP, respectively, and PFS was 14-28 versus 10-19 months. Although in three out of the six trials, the PFS advantage observed with MPT also translated into a significant OS advantage (37-52 vs. 28-32 months) in three trials.

A meta-analysis of pooled data of 1682 patients from the six MPT trials showed that the addition of thalidomide to MP as a frontline regimen in elderly MM patients is associated with a significant improvement in PFS (5.4 months of benefit; hazard ratio of 0.67 (0.55-0.80)) and a near-significant improvement in OS (6.6 months of benefit; hazard ratio of 0.82 (0.66-1.02)) [21].

In the randomised phase 3 VISTA trial, bortezomib plus MP (VMP) was compared with MP in a series of 682 newly diagnosed MM patients. The addition of bortezomib to MP (VMP) significantly improved ORR (71% vs. 35%, P <0.001) including CR rates of 30% and 4%, respectively (P <0.001). Data from the initial OS analysis, with a median follow-up of 16.3 months, showed that VMP was superior to MP[22]. An updated analysis, with a median follow-up of approximately 3 years, demonstrated a continued significant OS benefit with VMP[23].

Maintenance therapy after induction treatment

The most convincing is the phase III randomised trial (MM-015) which compared nine cycles of melphalan-prednisolone (MP), nine cycles of MP plus lenalidomide (MPR) and nine cycles of MPR followed by low dose lenalidomide maintenance (MPR-R) [13]. Response rates were also superior with MPR-R and MPR (77% and 68%, respectively, vs. 50% with MP; P<0.001 and P = 0.002, respectively, for the comparison with MP). The median progression-free survival was significantly longer with MPR-R (31 months) than with MPR (14 months; hazard ratio, 0.49; P<0.001) or MP (13 months; hazard ratio, 0.40; P<0.001).

Conclusion

The incorporation of novel agents has markedly improved the outcome of multiple myeloma. Ideally, treatment for transplant-eligible patients would include a triplet bortezomib-based induction, followed by autologous stem cell transplantation, and then consolidation therapy and finally lenalidomide maintenance therapy.

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Radiology Quiz

Radiology Quiz

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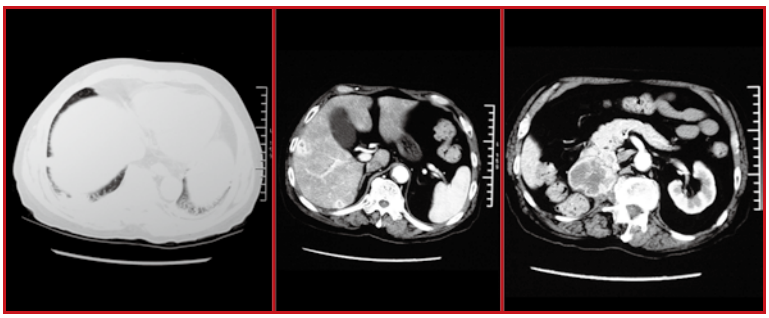


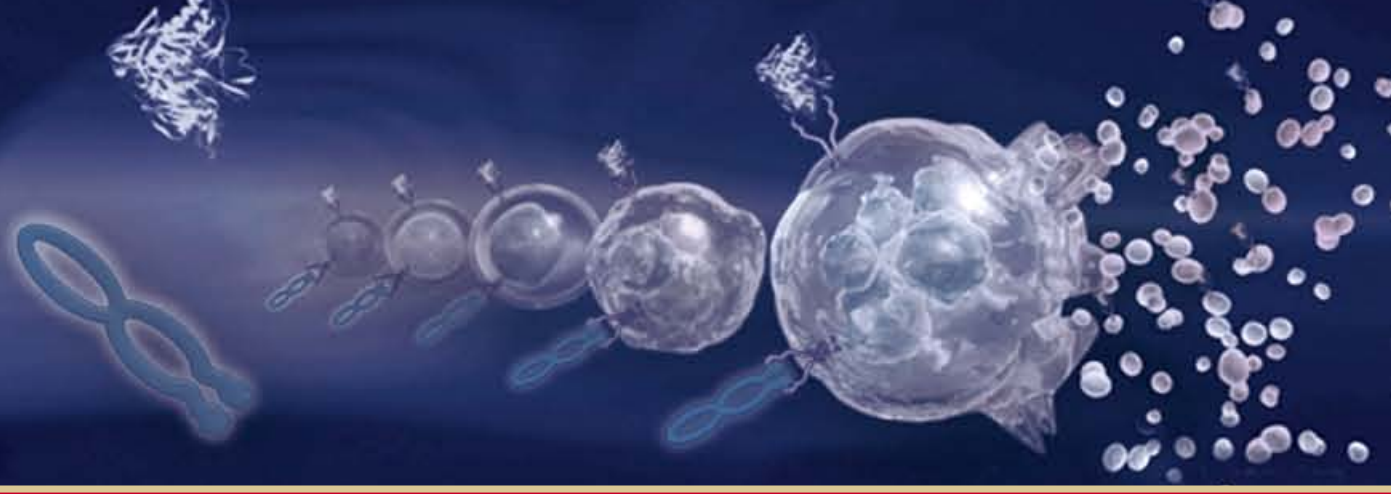
Clinical information:

An 81 year-old gentleman admitted for passing tarry stool for 1 week.

Questions:

1.What are the findings?
2.What is the diagnosis?

(See P.34 for answers)



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Update on Novel Oral Anticoagulants in the Treatment of Venous Thromboembolism

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Introduction

Venous thromboembolism (VTE), namely deep vein thrombosis and pulmonary embolism, is a common encounter in clinical practice. Prompt treatment of acute VTE is crucial in preventing potential fatality. According to recent statistics, pulmonary embolism accounted for about 0.09% of all registered deaths in Hong Kong by disease group in 2010[1]. The impact of the disease is clearly underestimated by the death toll alone, as many patients suffering from malignancy or co-morbidities resulting in immobilisation often succumb to VTE. The risk of recurrence of VTE is about 1% per year in patients with a transient risk factor. However, for unprovoked VTE, after discontinuation of anticoagulant therapy, the recurrence rate is as high as 10% annually[2]. Work up for thrombophilia and underlying malignancy is important in elucidating the full diagnosis of unprovoked VTE. Effective prophylaxis for VTE recurrence without excess bleeding risk remains a challenge to the clinicians.

Traditional anticoagulation therapy, namely, low molecular weight heparin followed by warfarin, has remained the mainstay of initial and maintenance treatment for the majority of patients suffering from VTE. Compared with unfractionated heparin, once daily body-weight adjusted low molecular weight heparin treatment allows convenient outpatient management and obviates the need for laboratory monitoring. Fondaparinux, the synthetic pentasaccharide indirect factor Xa inhibitor, may be employed in cases of heparin-induced thrombocytopenia[3]. However, all these treatments have to be given parenterally, which may necessitate clinic visits when patients are not willing or unable to administer on their own. Maintenance warfarin treatment, although effective, have some disadvantages that the novel oral anticoagulants now may surpass: no dietary restriction, less drug-drug interactions, simple dosing leading to convenience and better patient adherence, predictable pharmacokinetics and no need for regular monitoring.

In the article, a brief review of direct thrombin inhibitors (DTI) and direct Xa inhibitors in the prevention and treatment of VTE, laboratory monitoring and their drawbacks will be discussed.

Direct thrombin inhibitors (DTI) and direct Xa inhibitors

Thrombin plays a pivotal role in the coagulation pathway. It converts soluble fibrinogen to fibrin. DTIs exert multiple effects by binding to thrombin. They prevent fibrin formation and thrombin-mediated activation of factor V, VIII, XI and XIII. Moreover, they prevent thrombin-mediated activation of platelets, inflammation, fibrinolysis and protein C/protein S/thrombomodulin pathway. Lepirudin, argatroban and bivalirudin are examples of parenteral DTIs, which are employed in the treatment of heparin-induced thrombocytopenia and during percutaneous coronary interventions . The pioneer oral DTI, ximelagatran, was withdrawn from the market because of fatal hepatotoxicity. Dabigatran etexilate is the oral DTI that has been approved in clinical use recently.

The conversion of prothrombin to thrombin relies on the interaction of activated factor X and activated factor V. One molecule of factor Xa is able to generate 1000 molecules of thrombin[4]. Factor Xa inhibition in theory is very effective in thrombin inhibition and inhibition of the clot formation down in the coagulation pathway. Unfractionated heparin, low molecular weight heparin and fondaparinux are examples of indirect Xa inhibitors that work through antithrombin have to be given parenterally. Several oral direct Xa inhibitors have been tested in phase III clinical trials, namely, rivaroxaban, apixaban and edoxaban.

Advantages of DTI and direct Xa inhibitors

DTI and direct Xa inhibitors possess advantages over warfarin because of their pharmacologic characteristics (Table 1)[5,6,7]. The new oral anticoagulants have faster onset and offset of action when compared with warfarin. Fixed dosing is possible and therapeutic monitoring is not necessary. No dietary restriction is needed and few drug interactions are encountered. Dabigatran does not interact with the cytochrome P450 system. Plasma concentrations of dabigatran are increased when given with strong inhibitors of P-glycoprotein transporters such as amiodarone, verapamil and ketonconazole. Rivaroxaban and apixaban may interact with inhibitors of CYP 3A4 and P-glycoprotein transporters such as ketoconazole and protease inhibitors. Dabigatran is 80% renal excreted and it is contraindicated in patients with severely impaired renal function (CrCl<30 ml/minute). For rivaroxaban, dose adjustment is necessary in patients with CrCl < 50 ml/min and its use should be avoided when CrCl is < 15 ml/min.

Table 1. Pharmacological characteristics of DTI and direct Xa inhibitors

	Dabigatran	Rivaroxaban	Apixaban	Edoxaban
Target	Thrombin	Xa		
Time to peak effect	1 hr	2.5-4 hr	3h	1-2 hr
Half-life	12-14 hrs	7-11 hrs	12 hrs	8-10 hrs
Plasma protein binding	34-35%	92-95%	87%	40-59%
Metabolism	Inhibitors of P-glycoprotein transporter	Inhibitors of CYP3A4 and P-glycoprotein transporter		
Renal elimination	80%	35%	25%	40%
Coagulation monitoring		Not required		

Efficacy and safety of new oral anticoagulants in VTE

The new oral anticoagulants have a role in the prevention of VTE in orthopaedic surgery and in the treatment of VTE. They were tested in phase III trials for both primary prevention and prophylaxis against venous thromboembolism after total hip replacement (THR) or total knee replacement (TKR).

Prophylaxis

The major phase III randomised, double blind, non-inferiority trials of dabigatran vs enoxaparin on VTE prophylaxis were shown in Table 2[8,9,10,11].

The primary efficacy outcome was the composite of total VTE (symptomatic and asymptomatic) and death from all causes during treatment. Dabigatran 150 or 220 mg qd has demonstrated non-inferiority to subcutaneous enoxaparin once daily in most studies. There was no significant difference in terms of major bleeding. RE-NOVATE II was similar to RE-NOVATE in design and dabigatran was tested in a more diverse population including patients from North America. However, in the RE-MOBILIZE study, it failed to show non-inferiority to enoxaparin 30 mg bd. The discrepancy of the study findings may lie in the different designs and dosage regimens. The dosage of enoxaparin was higher than the others (30 mg bd vs 40 mg qd). Enoxaparin 30 mg bd is the typical North American dosage used for VTE prophylaxis in TKR. The starting dose of enoxaparin given at a mean of 20 hours after surgery and the mean duration of treatment of 13 days were different as well.

Table 2. Phase III randomised, double blind, non-inferiority trials of Dabigatran vs Enoxaparin on VTE prophylaxis

Study	RE-NOVATE[8]	RE-NOVATE II[9]	RE-MODEL[10]	RE-MOBILIZE[11]
Elective Operation	THR	THR	TKR	TKR
Dosage regimen	D: 150 mg qd and 220 mg qd vs E: 40 mg qd	D: 220 mg qd vs E: 40 mg qd	D: 150 mg qd and 220 mg qd vs E: 40 mg qd	D: 150 mg qd and 220 mg qd vs E: 30 mg bd
Treatment duration	28-35 days	28-35 days	6-10 days	12-15 days
VTE and all cause mortality	D 150 mg qd: 8.6% D 220 mg qd: 6% E: 6.7%	D 220 mg qd: 7.7% E: 8.8%	D 150mg qd: 40.5% D 220mg qd: 36.4% E: 37.7%	D 150 mg qd: 33.7% D 220 mg qd: 31.1% E: 25.3% Non-inferiority not demonstrated
Major/ minor bleeding	D 150 mg qd: 1.3%/ 8.4% D 220 mg qd: 2%/ 6.1% E: 1.6%/6.4%	D 220 mg qd: 1.4%/ 6.0% E: 0.9%/5.4%	D 150 mg qd: 1.3%/8.4% D 220 mg qd: 1.5%/8.8% E: 1.3%/ 9.9%	D 150 mg qd: 0.6%/22% D 220 mg qd: 0.6%/ 23% E: 1.4%/ 21%

TKR: Total knee replacement; THR: Total hip replacement
D: Dabigatran; E: Enoxaparin s.c.

The major phase III randomised, double blind trials[12,13,14,15] of rivaroxaban vs enoxaparin on VTE prophylaxis are summarised in Table 3. The primary efficacy outcome was any VTE and all-cause mortality while the primary safety outcome was major bleeding. Two studies were on patients undergoing THR while the other two on TKR. In 3 studies, the comparison was made with enoxaparin given according to the European regimen (40 mg qd starting preoperatively) and in the RECORD 4 study (TKR) enoxaparin was given according to the North American regimen (30 mg bd, first dose postoperative). Rivaroxaban was started postoperatively (first dose 6–8 hours after surgery) in all the studies. In the RECORD 3 and RECORD 4 studies, prophylaxis was continued up to 2 weeks after surgery. In the RECORD 2 study, 35 days of rivaroxaban were compared with 2 weeks of enoxaparin after THR. Across the studies, rivaroxaban started postoperatively was more effective than enoxaparin started pre or post-operatively in patients undergoing THR or TKR. No significant difference in major bleeding was observed.

Table 3. Phase III randomised, double blind trials of Rivaroxaban vs Enoxaparin on VTE prophylaxis

Study	RECORD 1[12]	RECORD 2[13]	RECORD 3[14]	RECORD 4[15]
Elective Operation	THR	THR	TKR	TKR
Dosage regimen	R: 10 mg qd vs E: 40 mg qd	R: 10 mg qd vs E: 40 mg qd + placebo	R: 10 mg qd vs E: 40 mg qd	R; 10 mg qd vs E: 30 mg bd
Treatment duration	34 days	R: 31-39 days E: 10-14 days followed by 21-25 days of placebo	10-14 days	10-14 days
Prevention of VTE and all cause mortality	1.1% vs 3.7% (p< 0.001)	2.2% vs 9.3% (p < 0.0001)	9.6% vs 18.9% (p< 0.001)	6.9% vs 10.1% (p =0.0118)
Major bleeding	0.3% vs 0.1% (p=0.18)	< 0.1% vs < 0.1% No significant difference	0.6% vs 0.5% (p=0.77)	0.7% vs 0.3% (p=0.1096)

TKR: Total knee replacement; THR: Total hip replacement
R: Rivaroxaban; E: Enoxaparin s.c.

Another Xa inhibitor apixaban was tested in 3 phase III trials for the efficacy and safety for prevention of VTE in patients who underwent THR or TKR surgery. In the ADVANCE 1 trial[16] in patients undergoing TKR, apixaban did not met the criteria for non-inferiority compared with enoxaparin (30 mg bd), an observation similar to dabigatran in the RE-MOBILIZE study. In the ADVANCE 2 (TKR) and in the ADVANCE 3 (THR) trials[17, 18], apixaban was more effective than enoxaparin (40 mg qd) in reducing the primary efficacy outcome with no increase in major bleeding. Moreover, apixaban 2.5 mg bd for 30 days was compared with enoxaparin sc 40 mg qd for 6-14 days in medically ill patients for the prevention of VTE[19]. Apixaban was not superior to a shorter course with enoxaparin and it was associated with significantly more major bleeding events.

Treatment

The recent Phase III trials of new oral anticoagulants for VTE treatment were shown in Table 4.

Dabigatran was tested versus warfarin in the treatment for acute VTE in the RE-COVER study. Six months of treatment of dabigatran 150 mg bd was compared with dose-adjusted warfarin after initial treatment with parenteral anticoagulation in the treatment of acute VTE[20]. It was non-inferior to warfarin in efficacy with a similar safety profile. Adverse events leading to

discontinuation of dabigatran and warfarin occurred in 9.0% and 6.8 % of patients respectively (p=0.05). Further studies are therefore needed to explore the long-term tolerance and discontinuation rate of dabigatran in patients with recurrent VTE who may require longer duration of treatment.

In EINSTEIN-DVT study, rivaroxaban was employed as monotherapy from the time of diagnosis of acute DVT[21]. Rivaroxaban 15 mg bd for 3 weeks, followed by 20 mg qd showed non-inferiority to subcutaneous enoxaparin followed by warfarin with no difference in major bleeding. Rivaroxaban was superior to placebo in preventing DVT recurrence after the initial 6 months of treatment[21]. Rivaroxaban was shown to be non-inferior to standard therapy for the initial and long-term treatment of pulmonary embolism[22].

AMPLIFY-EXT study has been published recently[23]. Extended anticoagulation with apixaban at either a 2.5 mg or 5 mg bd reduced the risk of recurrent VTE without increasing the rate of major bleeding. The number of patients who would need to be treated to prevent one episode of recurrent VTE (fatal or nonfatal) during the 1 year study period was only 14, whereas the number needed for treatment to cause one episode of major or clinically relevant non-major bleeding was 200. However, only 15% of the patients in the study were older than 75 years of age and few had a body weight below 60 kg or moderate or severe renal impairment. Therefore, more data are required to better determine the risk-benefit profile of apixaban with respect to bleeding in such patients.

Table 4. Phase III trials of new oral anticoagulants on VTE treatment

Study	RECOVER[20]	EINSTEIN DVT[21]	EINSTEIN PE[22]	EINSTEIN Extension[21]	AMPLIFY-EXT[23]
Drug Rx	Dabigatran vs warfarin	Rivaroxaban vs VKA	Rivaroxaban vs VKA	Rivaroxaban vs placebo	Apixaban vs placebo
Sample size	2564	3449	4832	1197	2486
Design	Double-blind Non-inferior	Open label Non-inferior	Open label Non-inferior	Double blind	Double blind
Dosage regimen	150 mg bd	15 mg bd for 3 weeks, followed by 20 mg daily	15 mg bd for 3 weeks, followed by 20 mg daily	20 mg daily	2.5 mg or 5 mg bd
Treatment duration	6 months	3, 6 or 12 months	3, 6 or 12 months	6-12 months	12 months
Recurrent VTE and related death	2.4% vs 2.1% P < 0.001	2.1% vs 3.0% P< 0.0001	2.1% vs 1.8% P< 0.003	1.3% vs 7.1% P< 0.0001	A 2.5mg bd: 1.7% A 5 mg bd: 1.7% P: 8.8%
Major bleeding	1.6% vs 1.9% (HR 0.82; 95% CI, 0.45-1.48)	8.1% vs 8.1% (p=0.77)	1.1% vs 2.2% (p=0.003)	0.7% vs 0% (p=0.11)	A 2.5 mg bd: 0.2% A 5 mg bd: 0.1% P: 0.5%

VKA: Vitamin K antagonist; A: Apixaban; HR: hazard ratio; P: Placebo

As there was no direct head-to-head comparison of the efficacy and safety among these new oral anticoagulants, whether there is any superiority of one over another is still unknown.

At present, dabigatran was approved in Europe and Canada for the prevention (but not treatment) of VTE in patients undergoing hip and knee replacement.

Similarly, apixaban was approved in Europe for the prevention of VTE in patients undergoing hip or knee replacement. Rivaroxaban was approved by the US Food and Drug Administration and European Medicines Agency for the prevention of VTE after knee or hip replacement surgery, treatment of acute VTE and prevention of VTE following the initial treatment.

Laboratory monitoring

Under certain clinical conditions such as serious bleeding, overdose and emergency surgery, it is useful to assess the anticoagulant status of a patient receiving DTI and Xa inhibitors. Prothrombin time (PT) tests the extrinsic and final common pathways whereas activated partial thromboplastin time (APTT) tests the intrinsic and common pathways. Thrombin time (TT) evaluates fibrinogen and the inhibition of thrombin action. It provides a direct measure of the activity of DTI. Ecarin clotting time (ECT) is a specific assay for thrombin generation. Dabigatran prolongs all these test results. The relationship of time of administration of the drug and time of blood sampling is important. PT/ International Normalised Ratio (INR) is relatively insensitive to the activity of dabigatran. From the drug packaging insert, an APTT > 80 seconds at trough is associated with a higher risk of bleeding. Both PT and APTT especially the former show a flattened dose response curve with dabigatran. ECT shows linear dose-response curves with dabigatran[24]. However, inconvenience of reconstitution from stock powder and lot-to-lot variability make it largely a research tool. TT is useful as a sensitive method to determine if any dabigatran is present but is too sensitive for emergency monitoring. The Haemoclot Thrombin Inhibitor (HTI) assay, the diluted thrombin test, is based on inhibition of a constant and defined concentration of thrombin. Dilute test plasma (1:8 to 1:20) is mixed with normal pooled plasma and clotting is then initiated by adding a constant amount of highly purified human alpha-thrombin. The HTI allows for quantitative measurement of dabigatran activity with a reportable range of 50-500 ng/ml[25]. A trough HTI value of 200 ng/ml (usually corresponding to a test result of > 65 s) is associated with an increased risk of bleeding. A suitable therapeutic range of dabigatran as determined by HTI assay remains to be defined.

The effect of rivaroxaban on PT is transient in contrast with warfarin. Rivaroxaban shows an even weaker effect on APTT. Anti-Xa chromogenic assay based on inactivation of Xa by heparin, preferably without addition of exogenous antithrombin, by direct Xa inhibitor is available for clinical use. Residual Xa is detected by chromogenic substrate. With appropriate rivaroxaban calibrators and controls, anti-Xa chromogenic assay is useful for monitoring rivaroxaban level. Note that the anti-Xa assay for rivaroxaban monitoring requires the use of different calibrators from the monitoring of heparin or low molecular weight heparin.

Management in severe bleeding and overdose

DTI and Xa inhibitors have no specific antidote. Supportive measures including stopping the anticoagulant, fluid resuscitation, blood transfusion, maintenance of diuresis, identification of bleeding source and surgical haemostasis should be given. For dabigatran, activated charcoal should be employed

within 2 hours of drug intake; haemofiltration and haemodialysis could be considered because of its relatively low (35%) plasma protein binding. Regarding haemostatic agents, human data are scarce. Fresh frozen plasma is not likely to be helpful. Efficacy of activated factor VIIa is unclear. Administration of prothrombin complex concentrates (PCC) may reverse the effect of rivaroxaban but not dabigatran[26]. However, only one dose of PCC was tested and surrogate endpoints were used. Factor VIII inhibitor bypass activity (FEIBA) may potentially reverse the effects of dabigatran and rivaroxaban[27]. Post-marketing surveillance, registry of bleeding management and further clinical studies are needed to clarify for any effective reversal agent. A fully humanised monoclonal antibody fragment as a specific antidote for dabigatran is in phase I clinical trial.

Conclusion

Novel oral anticoagulants, notably DTI and Xa inhibitors, have proved to be a breakthrough in anticoagulation medicine. They possess advantages over traditional anticoagulants in the prevention and treatment of VTE. Laboratory monitoring is available to assess their anticoagulant activity. However, lack of specific antidote and long-term safety issues remain to be settled by future studies, post-marketing surveillance and registry. Further studies of the use of these agents in particular subgroup of patients, e.g. malignancy, safety data in the elderly and impaired renal function and analysis on cost effectiveness are eagerly awaited.

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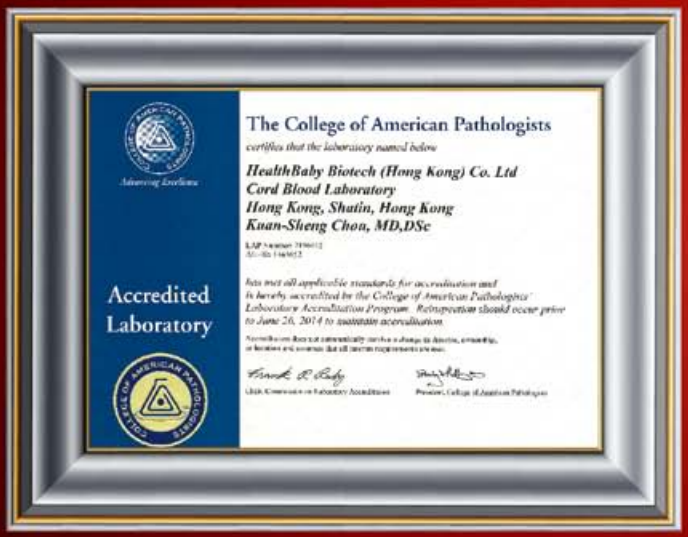

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Dasatinib: Current status

Dr. Herman LIU

MBBS (HK), FRCP (Edin; Glas), FHKAM, FHKCP

Consultant
Department of Medicine, Pamela Youde Nethersole Eastern Hospital

Dr. Herman LIU

Imatinib was the first tyrosine kinase inhibitor (TKI) for treatment of chronic myeloid leukaemia (CML) since 1998 and dramatically improved the outcome of patients. In the IRIS study (International randomised study of interferon vs STI571) of first-line treatment with imatinib or interferon and cytarabine in patients with newly diagnosed chronic phase (CP)-CML, patients in the imatinib arm had an 8-year overall survival rate of 85% and the freedom from progression to advanced disease was 92%.[1]

However, despite the responses observed with imatinib, a proportion of patients develop resistance to imatinib or cannot tolerate its side effects. This led to the development of newer TKIs of BCR-ABL: Dasatinib; Nilotinib and Bosutinib. Dasatinib (BMS-354825, Sprycel®) is an oral, multi-targeted inhibitor of receptor tyrosine kinases (RTKs), including BCR-ABL fusion protein, stem cell factor receptor (c-KIT), platelet-derived growth factor receptor (PDGFR), and Src family kinases (SFKs). It is about 325 times more potent than imatinib in cells expressing unmutated BCR-ABL in vitro and has a completely different chemical structure to imatinib and, unlike imatinib and nilotinib, binds BCR-ABL in the active conformation.

Currently, Dasatinib is indicated for (1) Newly diagnosed adults with Philadelphia chromosome-positive (Ph+) chronic myeloid leukaemia (CML) in chronic phase. (2) Adults with chronic, accelerated, or myeloid or lymphoid blast phase Ph+ CML with resistance or intolerance to prior therapy including imatinib. (3) Adults with Philadelphia chromosome-positive acute lymphoblastic leukaemia (Ph+ ALL) with resistance or intolerance to prior therapy.

Recently, Dasatinib obtained label extension for newly diagnosed CML patients based on data from DASISION (Dasatinib versus imatinib study in treatment-naive CML patients) trial, an international, multicentre, randomised phase 3 trial of dasatinib 100 mg QD vs imatinib 400 mg QD (n = 519)[2]. In this study, Dasatinib showed higher rates of complete cytogenetic response (CCyR: 85% vs 82%; P = 0.001); major molecular response (MMR: 64% vs 46%; P < 0.0001) and BCR-ABL reduction to <0.0032% (4.5-log reduction) in 17% vs 8% at 24 months. Transformation to AP/BP CML on study occurred in 2.3% with dasatinib versus 5.0% with imatinib. (Figure 1)

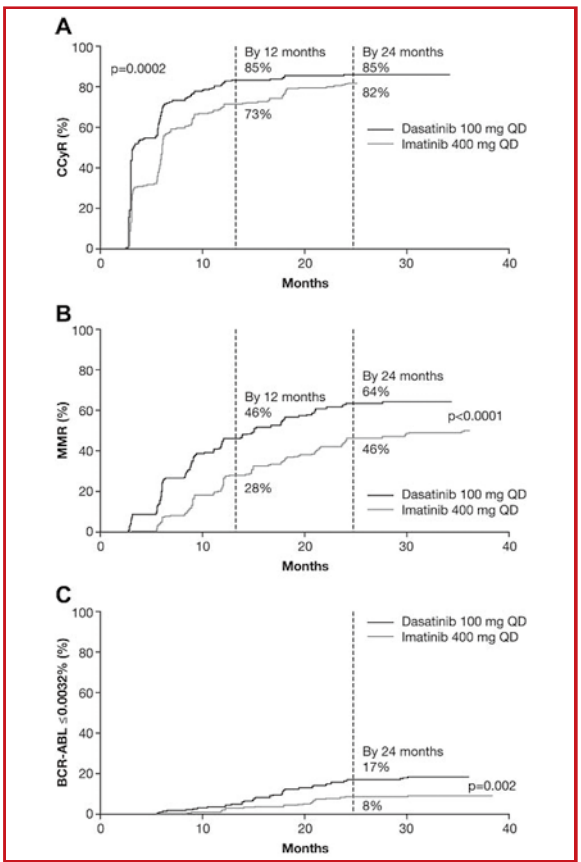

Figure 1: Cumulative incidences of response in dasatinib and imatinib arms. *(A) Complete cytogenetic response. (B) Major molecular response. (C) BCR-ABL transcript level reduction to < 0.0032%. CCyR indicates complete cytogenetic response; and MMR, major molecular response. (From Blood 2012:119(5):1123-1129)*

In the DASISION study, the adverse events of gastrointestinal disturbance and peripheral oedema were less common while pleural effusion was more common when compared to imatinib. Pleural effusion can be managed either by dose interruption, reduction, discontinuation, diuretics, corticosteroids or therapeutic thoracentesis. Gastrointestinal bleeding or other bleeding events occurred at a similar frequency in both treatment arms

The recommended starting dose for chronic phase CML is 100 mg administered orally once daily while that of accelerated phase CML, myeloid or lymphoid blast phase CML, or Ph+ ALL is 140 mg administered orally

once daily. The use of concomitant strong CYP3A4 inducers or inhibitors should be avoided if possible as these agents may decrease or increase the plasma concentrations of dasatinib respectively.

During the initial treatment, complete blood counts should be performed weekly for the first two months and then monthly thereafter, or as clinically indicated. Myelosuppression is more frequent in patients with advanced phase CML or Ph+ ALL than in chronic phase CML and Grade 3 or 4 myelosuppression was reported less frequently in patients treated with 100 mg once daily than in patients treated with other dosing regimens. It should be managed by either dose interruption, reduction or discontinuation of dasatinib according to the following guideline.

Chronic phase CML (starting dose 100mg once daily)	Absolute Neutrophil Count (ANC) < 0.5 x 10^9/L or platelet < 50 x 10^9/L	1. Stop drug until ANC ≥ 1.0 x 10^9/L and platelet ≥ 50 x 10^9/L 2. Resume drug at the original starting dose if recovery occurs in less than 7 days 3. If platelet <25x 10^9/L or recurrence of ANC <0.5 x 10^9/L for more than 7 days, repeat Step 1 and resume drug at a reduced dose of 80mg once daily for second episode. For third episode, further reduce dose to 50mg once daily (for newly diagnosed patients) or dicontinue (for patients resistant or intolerant to prior therapy including imatinib)
Accelerated phase, Blast Phase CML and Ph+ ALL (starting dose 140mg once daily)	ANC <0.5 x 10^9/L or platelet < 10 x 10^9/L	1. Check if cytopenia is related to leukaemia (marrow aspirate or biopsy) 2. If cytopenia is unrelated to leukaemia, stop drug until ANC ≥1.0 × 10^9/L and platelets ≥20 × 10^9/L and resume at the original starting dose 3. If recurrence of cytopenia, repeat Step 1 and resume drug at a reduced dose of 100 mg once daily (second episode) or 80 mg once daily (third episode). 4. If cytopenia is related to leukaemia, consider dose escalation to 180 mg once daily

For patients with chronic, accelerated, or myeloid or lymphoid blast phase Ph+ CML with resistance or intolerance to prior therapy including imatinib, second generation TKIs should replace imatinib. The choice between Nilotinib or Dasatinib may be made after the mutation analyses of the kinase domain which can help to identify BCR-ABL mutations not sensitive to particular TKI: V299, T315I and F317 are associated with clinical resistance to dasatinib; Y253, E255, T315 and F359 are associated with clinical resistance to niloinib. For patients with no mutations detected, it is recommended that the decision to be based on the safety profile for the particular TKI. For example, Dasatinib should be more appropriate for patients with compliance problem (once instead of twice daily and no relationship to meal time); hyperbilirubinaemia and diabetes mellitus while Nilotinib should be more appropriate for patients with history of pleural effusion and gastrointestinal bleeding.

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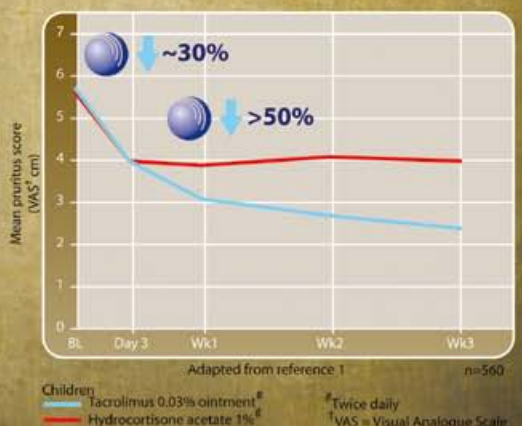

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Reference:
1. Astellas Pharma data on file.
2. Reitamo S, et al. Br J Dermatol. 2004; 150: 554–562.

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Novel Parenteral Thrombomimetic Therapy and Alternate Pathway of TPO Activation

Dr. Raymond SM WONG

MBChB, MD, FRCP(Lond), FHKCP, FHKAM(Medicine)

Consultant, Department of Medicine & Therapeutics, Prince of Wales Hospital

Since thrombopoietin (TPO) was first cloned in 1994, TPO receptor (TPO-R) agonists have been developed which have shown significant clinical activity in various conditions characterised by thrombocytopenia. First-generation TPO-R agonists were recombinant forms of human TPO. The clinical development of these molecules was discontinued after one of them, the pegylated recombinant human megakaryocyte growth and development factor, was associated with the development of neutralising autoantibodies cross-reacting with endogenous TPO.[1]

Second-generation TPO-R agonists are now available, which present no sequence homology to endogenous TPO. Two of these new agents, romiplostim and eltrombopag, have been granted marketing authorisation for use in patients with primary immune thrombocytopenia unresponsive to conventional treatments.

Romiplostim

Romiplostim represents a new class of therapeutics called "peptibodies." It is a synthetic fusion protein produced in Escherichia coli by recombinant DNA technology and is designed to evade the immune response to recombinant thrombopoietin and to stimulate the production of new platelets. The molecule consists of two human IgG1 Fc domains linked covalently (the "-body") to a peptide that contains two TPO receptor-binding domains (the "pepti-") for a total of four binding sites (Figure 1). In this format, the peptide "warhead" interacts with TPO receptor and activates the downstream signalling pathway leading to increased platelet production. The IgG1 Fc domain binds to FcRn receptors and undergoes endothelial recirculation just like normal IgG. The Fc conjugation also increases the molecular mass above the threshold for renal clearance. Both mechanisms extend the half-life of the compound.[2]

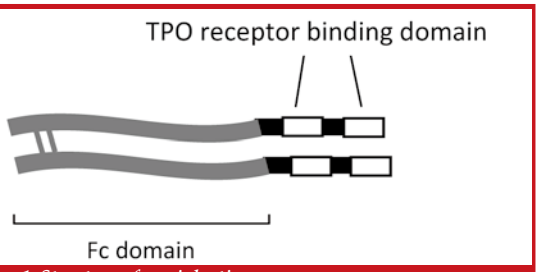

Figure 1. Structure of romiplostim

Pivotal Clinical Trials in Immune Thrombocytopenia (ITP)

The pathophysiology underlying primary immune thrombocytopenia (ITP) has shown that not only accelerated peripheral platelet destruction but also suppression of the production of new platelets can be responsible for the persistence of thrombocytopenia. Several prospective and well-designed trials have shown that weekly subcutaneous administration of romiplostim induces more durable platelet responses and less treatment failures compared with placebo or standard of care. (Table 1)

Table 1. Pivotal clinical studies of romiplostim in ITP patients

Study	Number of patients, type	Treatment	Overall response rate (%)	Patients receiving rescue therapeutics (%)
Kuter et al[3]	63, splenectomised	Romiplostim Placebo	78.6% 0%	26.2% 57.1%
Kuter et al[3]	62, non-splenectomised	Romiplostim Placebo	87.8% 14.3%	17.1% 61.9%
Kuter et al[4]	234, non-splenectomised	Romiplostim SOC	71-92% 26-51%	Splenectomy 9% Splenectomy 36%

SOC = standard of care

Two Phase III, multicentre, randomised, placebo-controlled trials were conducted in 63 ITP patients who were splenectomised and 62 patients who were not splenectomised.[3] Eligible patients were aged >18 years, had a mean initial platelet count <30,000/μl and had received at least one line of therapy. Concurrent therapy was allowed as long as it was maintained at a constant dose and schedule. They were randomised in a 2:1 ratio to receive romiplostim subcutaneously (sc) or placebo weekly for 24 weeks. The initial dose of romiplostim was 1 μg/kg/week. Doses were adjusted up to a maximum of 15 μg/kg/week to maintain platelet counts between 50 and 200,000/μl. A platelet count of ≥50,000/μl was achieved by 25% of patients after 1 week and by 50% within 2–3 weeks. A durable platelet response, defined as a platelet count ≥50,000/μl during 6 of the last 8 weeks of treatment, was seen in 49% of patients receiving romiplostim (38% for patients with a previous splenectomy and 61% for patients without splenectomy) versus 2% of patients receiving placebo. Overall platelet responses (durable plus transient) were achieved in 83% (69/83) with romiplostim (88% for patients non-splenectomised and 79% for patients splenectomised) versus 7% (3/42) with placebo ($P < 0.001$). Rescue medication, defined as an increase of dose of a concurrent ITP therapy or the start of a new drug to increase platelet count, was administered in 22 and 60% of patients assigned to romiplostim or placebo.[3]

Another Phase III, intercontinental, multicentre, randomised, open-label study was conducted in 234 adult patients with ITP, who had not undergone splenectomy.[4] They were randomised in a 2:1 ratio to receive romiplostim sc weekly or standard of care (SOC) for 52 weeks. The initial dose of romiplostim was 3 μg/kg/week and the maximum dose allowed was 10 μg/kg/week. The percentage of patients with a platelet response (a platelet count >50,000/μl at any scheduled visit) ranged from 71 to 92% in the romiplostim arm and from 26 to 51% in the SOC group. Splenectomy was performed significantly less frequently in patients receiving romiplostim (9%) than in those receiving SOC (36%). The mean (± standard error) weekly dose required to maintain the platelet count between 50 and 200,000/μl was 3.9 ± 2.1 μg, which remained stable after the first 12 weeks.[4] Clinically meaningful improvements from baseline in HR-QOL scores were seen with romiplostim.

Long Term Efficacy Data in ITP

A long-term extension study was created for ITP patients who had completed a previous romiplostim study to monitor the long-term safety and efficacy of continued romiplostim treatment. Results are available from a final analysis after 5 years of follow-up that included 292 patients who had received romiplostim for a median 78 weeks (range 1–277 weeks).[5] A platelet count of ≥50 X 109/L was achieved by 94.5% of patients during the study, with >50% of patients having a platelet count of ≥50 X 10^9/L on ≥90% of all visits.[5] After the first week of romiplostim treatment, median platelet counts remained within the target range of 50–200 X 10^9/L. Of the 37 patients receiving concurrent ITP therapy at baseline, 30 (81%) were able to discontinue concurrent therapy or reduce the dosage of concurrent therapy by >25%.

Safety and Tolerability

Subcutaneous romiplostim was generally well tolerated in patients with ITP. In the final report of the extension study, 98% of patients reported at least one adverse event (AE) that was rated as mild or moderate in severity. Headache (38%), nasopharyngitis (34%) and fatigue (32%) were reported most frequently.[5] AEs did not increase with longer duration of treatment.

Although romiplostim has been generally well tolerated in clinical trials, there are concerns about the risk for reticulin fibrosis and thrombosis. A high-index of suspicion for bone marrow reticulin fibrosis is warranted in case of loss of efficacy or the appearance of an abnormal blood smear. Because most thrombotic events in the extension trial occurred in patients with risk factors for thrombosis, it may be appropriate to use romiplostim with caution in such patients. Sustained beneficial effects have been associated only with continued administration of the drug. Decreases in platelets to pretreatment counts or, in some cases, a transient decrease to less than pretreatment counts ("rebound thrombocytopenia"), have been found within 2 weeks after treatment discontinuation.

Summary

Comprised of peptide and carrier components in an overall structure superficially resembling an antibody, romiplostim is the prototype of a new class of protein therapeutics called peptibodies. In contrast with agents designed to suppress immune function or hinder the processes of platelet destruction, romiplostim works by stimulating the production of new platelets. It was proven to increase platelet counts, reduce the need for other ITP therapies and emergency treatments. Romiplostim has been shown to have overall a very favourable safety profile and to be well tolerated relative to other ITP treatments. Its use in the treatment of other conditions, such as myelodysplastic syndrome and chemotherapy-associated thrombocytopenia, are being investigated.

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The Federation Annual Dinner 2012

On 31 December 2012, the Federation of Medical Societies of Hong Kong held our Annual Dinner at the Run Run Shaw Hall of the Hong Kong Academy of Medicine Jockey Club Building as per the good tradition, to celebrate the New Year's Eve together with our members, friends and families. The Dinner event was another success exemplified by the Federation spirit, and was attended by near 300 guests from our member societies and partners from medical & healthcare communities.

With the theme "Federation Got Talents", we were very glad to have distinguished performers, Ms. Mimi LO and Ms. Suzan GUTERRES, to celebrate this important moment with us. We are also privileged to have talented performers amongst our professional colleagues, including distinguished guests Dr. LEE Ka-yan; Ms Sally POON (President of the Hong Kong Practising Dietitians Union) and Ting Lok; Mr Samuel CHAN (President of the Hong Kong Occupational Therapy Association) and his band; Ms Annabel CHOY 2nd year medical student at the University of Hong Kong; and young violinists Airiana CHAN and Mike WONG from the Takako NISHIZAKI Violin Studio. The dinner was indeed a star-studded event with much entertainment and fun.

Considered to be the biggest raffle in recent years, the exciting array of prizes was worth up to $100,000. The lucky winners won a super luxury travel package to Maldives, a pair of round trip tickets to Taipei, 1 night hotel accommodation for two at the Banyan Tree Macau and many other fabulous prizes.

All guests had a wonderful time with the exciting magic show, elegant harp performance, challenging game booths of "Minute to Win It", wine tasting, photo exhibition of the project for Bereaved Children and Federation activities, portrait shooting, table games, bingo game, song dedication and the climax of the night – countdown to the New Year 2013. The event was well-received by all attendees with everyone already looking forward to next year's events.

We would like to show our sincere gratitude to all our sponsors and may we wish you all a happy, healthy and prosperous year of 2013!

The Federation Annual Dinner 2012

The Federation Annual Dinner 2012

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					1	* Refresher Course for Health Care Providers 2012/2013 2
3	* Huge Penile Mass 4	* FMSHK Officers' Meeting * HKMA Council Meeting 5	6	7	8	9
10	11	12	13	14	15	16
* HKMAPS Birds Photo Taking Tour: Magic of Migration (追蹤候鳥之旅) 17	18	19	* Hong Kong Neurosurgical Society Monthly Academic Meeting –Vertebral Artery Dissection 20	* FMSHK Executive Committee & Council Meeting 21	22	23
24	25	* HKMA Kowloon City Community Network- Maximizing Bronchodilation in COPD Management * HKMA CME - Osteoarthritis of the knee joint - Recent advancement in evaluation and treatment 26	27	* HKMA New Territories West Community Network- Managing Type 2 Diabetes: Target the Pathophysiology 28		

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(d) Satisfy the examiners in a qualifying examination, if required.

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Date / Time	Function	Enquiry / Remarks
2 SAT 2:30 pm	**Refresher Course for Health Care Providers 2012/2013** Organiser: The Hong Kong Medical Association, Speaker: Dr. Cheung Kit Ying, Andy, Venue: OLMH	Ms. Clara Tsang Tel: 2354 2440 2 CME points
4 MON 7:30 pm	**Huge Penile Mass** Organiser: Hong Kong Urological Association, Chairman: Dr. Chan Chun Ki, Speaker: Dr. Chan Chun Ki, Venue: Multi-disciplinary Simulation and Skills centre, 4/F, Block F, QEH	Dr. Hing-hoi HUNG Tel: 2958 6006 1 CME point (College of Surgeons of Hong Kong)
5 TUE 8:00 pm	**FMSHK Officers' Meeting** Organiser: The Federation of Medical Societies of Hong Kong, Venue: Gallop, 2/F., Hong Kong Jockey Club Club House, Shan Kwong Road, Happy Valley, Hong Kong	Ms. Nancy CHAN Tel: 2527 8898
8:00 pm	**HKMA Council Meeting** Organiser: The Hong Kong Medical Association, Chairman: Dr. TSE Hung Hing, Venue: HKMA Head Office (5/F., Duke of Windsor Social Service Building, 15 Hennessy Road, Hong Kong)	Ms. Christine WONG Tel: 2527 8285
17 SUN 9:00 am	**HKMAPS Birds Photo Taking Tour: Magic of Migration (追蹤候鳥之旅)** Organiser: The Hong Kong Medical Association, Venue: Mai Po	Mr. Benjamin CHAN Tel: 2527 8285
20 WED 7:30 am	**Hong Kong Neurosurgical Society Monthly Academic Meeting –Vertebral Artery Dissection** Organiser: Hong Kong Neurosurgical Society, Chairman: Dr. PANG Kai Yuen, Speaker: Dr. HO Lok Yan, Faith, Venue: Seminar Room, Ground Floor, Block A, Queen Elizabeth Hospital	Dr. Gilberto LEUNG Tel: 2255 3368 1.5 CME points
21 THU 7:00 pm	**FMSHK Executive Committee & Council Meeting** Organiser: The Federation of Medical Societies of Hong Kong, Venue: Council Chamber, 4/F, Duke of Windsor Social Service Building, 15 Hennessy Road, Wanchai, Hong Kong	Ms. Nancy CHAN Tel: 2527 8898
26 TUE 1:00 pm	**HKMA Kowloon City Community Network- Maximizing Bronchodilation in COPD Management** Organiser: HKMA Kowloon City Community Network, Speaker: Dr. CHU Chung Ming, Venue: Spotlight Recreation Club (博藝會) 4/F., Screen World, Site 8, Whampoa Garden, Hunghom, Kowloon	Ms. Candice TONG Tel: 2527 8285
2:00 pm	**HKMA CME - Osteoarthritis of the knee joint - Recent advancement in evaluation and treatment** Organiser: The Hong Kong Medical Association, Speaker: Prof. Hideo MATSUMOTO, Venue: Diamond Ballroom 1, Basement 1, Eaton Smart Hotel, 380 Nathan Road, Kowloon	HKMA CME Dept. Tel: 2527 8452 1 CME point
28 THU 1:00 pm	**HKMA New Territories West Community Network- Managing Type 2 Diabetes: Target the Pathophysiology** Organiser: The Hong Kong Medical Association, Speaker: Dr. Ho Yiu Yan, Andrew, Venue: Maxim's Palace Chinese Restaurant, Tuen Mun Town Hall, 3 Tuen Hi Road, Tuen Mun	Miss Hana YEUNG Tel: 2527 8285 1 CME point

Upcoming Meeting

30-31/3/2013	**9th CT Coronary Angiography Teaching Course 2013 – Intermediate & Advanced Level** Organiser: Hong Kong College of Radiologists, Speakers: Dr. Szilard Voros, Dr. Stephen Cheung, Dr. Jack Shu, Dr. Sonny Chiu & Dr. John Hoe, Venue: Pamela Youde Nethersole Eastern Hospital, Chai Wan, Enquiry: Ms. Lai Wai Yee, Ada Tel: 2871 8788
10-13/7/2013	**9th Asian Dermatological Congress 2013** Organisers: Asian Dermatological Association, Hong Kong College of Dermatologists & the Hong Kong Society of Dermatology and Venereology, Chairman: Prof. Henry HL CHAN, Venue: Hong Kong Convention & Exhibition Centre, Enquiry: ADC 2013 Secretariat Tel: 3151 8900

Answer to Radiology Quiz

Findings:

- Previous right nephrectomy is evident.
- An irregular arterially enhancing mass is noted in right renal fossa, which is abutting the right psoas muscle and the 2nd/3rd part of duodenum, could represent recurrence of renal cell carcinoma eroding into the duodenum. No active contrast extravasation is evident.
- Multiple small arterial enhancing lesions in both hepatic lobes, could represent liver metastases.
- Biliary ducts are not dilated. Portal vein is patent.
- No ascites. No pneumoperitoneum.
- Gallstones.
- A 1.2 cm soft tissue density nodule in right lung base, could represent lung metastasis.
- Bilateral small pleural effusion. Bilateral basal atelectasis.

Diagnosis:

History of right renal cell carcinoma with right nephrectomy-
Recurrence of renal cell carcinoma in right renal fossa, with probably erosion into the duodenum in view of active gastrointestinal bleeding.
Liver and pulmonary metastases.

Dr. WY WONG
MBChB, FRCR
Department of Radiology, Queen Mary Hospital

Eraxis® – for candidemia & other forms of candidia infections Proven efficacy, favorable tolerability[1]

Proven efficacy[1,*]

- 76% successful global response against *Candida spp* (versus 60% for fluconazole, $P = 0.01$)[†]
- 81% successful global response against *C albicans spp* (versus 62% for fluconazole, $P = 0.02$)[†]

Favorable safety and tolerability profile

- No known clinically relevant drug interactions (eg. cyclosporin, voriconazole, tacrolimus, amphotericin B, rifampicin)[2]
- No dose adjustments required for renal or hepatic insufficiency[2,3]

Convenient once-daily dosing[2]

* Results of a randomized, multicenter, double-blind study of 256 patients with candidemia and/or other forms of invasive candidiasis. Patients received either Eraxis (200-mg loading dose, 100-mg maintenance dose) or IV fluconazole (800-mg loading dose, 400-mg maintenance dose); either agent could be followed by oral fluconazole after 10 days of IV therapy. Global success required clinical cure or improvement and documented or presumed microbiologic eradication.[1]

† Centre effect considered in statistical analysis

ERAXIS™ POWDER FOR INJECTION ABBREVIATED PACKAGE INSERT: 1. TRADE NAME: ERAXIS™ (anidulafungin) POWDER FOR INJECTION. **2. PRESENTATION:** 100mg of sterile, lyophilized, preservative-free anidulafungin powder in a single-use vial. Refrigerate at 2°C to 8°C. Do not freeze. **3. INDICATIONS:** Treatment of fungal infections: candidemia and other forms of *Candida* infections (intra-abdominal abscess, and peritonitis). **4. DOSAGE & ADMINISTRATION:** Single 200mg loading dose on Day 1, followed by 100mg daily dose thereafter. Antifungal therapy should be based on the patient's clinical response but generally should continue for ≥14 days after last positive culture. **Must be reconstituted with sterile water for injection and subsequently diluted with only 5% Dextrose Inj., USP or 0.9% NaCl Injection, USP (normal saline). 5. CONTRAINDICATIONS:** Known hypersensitivity to anidulafungin, any components of ERAXIS, or other echinocandins. **6. WARNINGS & PRECAUTIONS: Development of abnormal liver function during therapy:** monitor for evidence of worsening hepatic function and evaluate for risk/benefit of continuing therapy. **7. INTERACTIONS:** No dosage adjustment of either drug is recommended when anidulafungin is co-administered with voriconazole or tacrolimus or amphotericin B or rifampin or cyclosporine. No dosage adjustments are required for patients with any degree of renal/ hepatic insufficiency or those in other special populations *(see full prescribing information for more details).* **8. PREGNANCY AND LACTATION:** Category C; Eraxis should be used during pregnancy and administrated to nursing mother only if potential benefit justifies the risk. Anidulafungin was found in milk of lactating rats. Not known whether it is excreted in human milk. **9. SIDE EFFECTS:** Possible histamine-mediated symptoms, including rash, urticaria, flushing, pruritis, dyspnea, and hypotension. Date of preparation: JAN2011; Identifier number: ERAW0111.

References: 1. Reboli AC, Rotstein C, Pappas PG, et al, for the Anidulafungin Study Group. Anidulafungin versus fluconazole for invasive candidiasis. N Engl J Med. 2007; 356:2472-2482. **2.** Eraxis Hong Kong Package Insert version July 2009. **3.** Vazquez JA. Anidulafungin: a new echinocandin with a novel profile. Clin Ther. 2005;27:657-673.

Please review full product information before prescribing.
Full prescribing information is available upon request.

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Eraxis® (anidulafungin IV)

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