www.fmshk.org

THE HONG KONG MEDICAL DIARY

香 港 醫 訊

VOL.19 NO.10 October 2014

Haematology

OFFICIAL PUBLICATION FOR THE FEDERATION OF MEDICAL SOCIETIES OF HONG KONG ISSN 1812 - 1691

Humalog® KwikPen™
insulin lispro (rDNA origin) injection

Humalog® mix25™ KwikPen™
25% insulin lispro (rDNA origin) injection
75% insulin lispro protamine suspension

Humalog® mix50™ KwikPen™
50% insulin lispro (rDNA origin) injection
50% insulin lispro protamine suspension

It gets patients the insulin they need without getting in the way of life.

- Easy to learn, easy to use[1]
- Low, smooth injection force[2]
- Lightweight[2]

For complete instructions on Humalog® KwikPen™, Humalog® Mix25™ KwikPen™, Humalog® Mix50™ KwikPen™ please refer to the full user manual provided with the Pen.

References:
1. Ignaut DA, Schwartz SL, Sarwat S and Murphy HL. *Diabetes Educ* 2009;35:789-798.
2. Ignaut DA, Opincar M and Lenox S. *J Diabetes Sci Technol* 2008;2:533-537.

Further information is available upon request.

Eli Lilly Asia, Inc.
Unit 3203-3208, 32/F Ace Tower Windsor House, 311 Gloucester Road, Causeway Bay, Hong Kong
Tel: (852) 2572 0160 Fax: (852) 2572 7893
www.lilly.com.hk

HKLIAD0411JS1
Vital Base/HK/11026/0222/AA

Contents

Scan the QR-code

To read more about The Federation of Medical Societies of Hong Kong

New Edition of Medical and Dental Directory
Submit your data NOW!
http://www.fmshk.org/directory2012.php

Disclaimer

The Cover Shot

This picture with forks of lightning was captured in Kerala, India, just after sunset when a thunderstorm struck a town in the vicinity.

Dr Howard HN WONG
MBBS, MRCP
Resident Trainee,
Department of Medicine,
Pamela Youde Nethersole Eastern Hospital

Published by
The Federation of Medical Societies of Hong Kong

Design and Production
A-PRO MULTIMEDIA LTD www.apro.com.hk

Editorial

Dr Herman SY LIU

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

Consultant, Department of Medicine,
Pamela Youde Nethersole Eastern Hospital

Editor

Dr Herman SY LIU

There are five articles on Haematology and one on life-style in this issue of the Medical Diary.

Management of bleeding diathesis is always a challenge to clinicians. The emergence of new long-acting coagulation factors marked a major breakthrough in the field of haemophilia, improving patients' quality of life and treatment compliance. Dr Howard Wong and Dr Bonnie Kho's article brings you updates of the development and the current clinical evidence. Thrombocytopenia in pregnancy is not an uncommon condition and a systematic approach and management is very important for the safety of the mother and the foetus. Dr SY Lin's article covers the essentials and up to date discussion of this clinical scenario. According to the statistics of the Hong Kong Red Cross and Blood Transfusion Centre, the utilisation of platelet concentrates is increasing annually, Dr CY Ha highlights the 'dos' and 'don'ts' in this clinical decision.

For decades, management of Acute Myeloid Leukaemia remains a challenge to haematologists. Professor YH Leung walks you through the recent advances in the diagnostic tools and better understanding of the underlying heterogeneity. With that in mind, a personalised approach seems to be around the corner eventually.

Lastly, the article by Dr Raymond Wong covers another successful story of a 'bench to beside' approach in the management of Myelofibrosis and it is followed with questions for the purpose of CME.

I sincerely hope you find this issue on Haematology interesting to read and would like to thank all the authors for their kind contributions. Lastly, a special thanks to Dr Howard Wong for the fascinating cover photo and Dr Edmond Ma for his sharing as a wine enthusiast.

Treat DVT and PE
Protect Your Patients

Xarelto®: The Single-Drug Solution Matters

- **Fast onset of anticoagulation for rapid patient protection[1-2]**
- **Simplified treatment with efficacy comparable to standard treatment[3-5]**
- **Significantly lower risk of major bleeding[4-5]***
- **Non-major clinical relevant bleeding and adverse events comparable to standard treatment[3-5]**

* Only in EINSTEIN PE and pooled EINSTEIN

APPROVED FOR DVTx AND PEx

First in ORAL, Direct Factor Xa Inhibition

Xarelto®
rivaroxaban

Simple Protection for More Patients

Abbreviated Prescribing Information
(Please refer to the full prescribing information before prescribing)

Xarelto 15 mg / 20 mg film-coated tablets
Composition: Active ingredient: 15 mg / 20 mg rivaroxaban. Excipients: Microcrystalline cellulose, croscarmellose sodium, lactose monohydrate, hypromellose, sodium laurilsulfate, magnesium stearate, macrogol 3350, titanium dioxide (E171), iron oxide red (E172). **Indication:** Prevention of stroke and systemic embolism in adult patients with non-valvular atrial fibrillation with one or more risk factors, such as congestive heart failure, hypertension, age ≥ 75 years, diabetes mellitus, prior stroke or transient ischaemic attack. Treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE), and prevention of recurrent DVT and PE in adults. **Posology:** *Prevention of stroke and systemic embolism* Recommended dose is 20 mg once daily, which is also the recommended maximum dose. *Treatment of DVT, treatment of PE and prevention of recurrent DVT and PE* The recommended dose for the initial treatment of acute DVT or PE is 15 mg twice daily for the first three weeks followed by 20 mg once daily for the continued treatment and prevention of recurrent DVT and PE. **Renal impairment** No dose adjustment is necessary in patients with mild renal impairment (creatinine clearance 50 - 80 ml/min). In patients with moderate (creatinine clearance 30 - 49 ml/min) or severe (creatinine clearance 15 - 29 ml/min) renal impairment the following dosage recommendations apply: • For the prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation, the recommended dose is 15 mg once daily. • For the treatment of DVT, treatment of PE and prevention of recurrent DVT and PE: Patients should be treated with 15 mg twice daily for the first 3 weeks. Thereafter, the recommended dose is 20 mg once daily. • Limited clinical data for patients with severe renal impairment (creatinine clearance 15 - 29 ml/min) indicate that rivaroxaban plasma concentrations are significantly increased; therefore, Xarelto is to be used with caution in these patients. • Use is not recommended in patients with creatinine clearance < 15 ml/min. **Contraindications:** Hypersensitivity to the active substance or any of the excipients; clinically significant active bleeding; hepatic disease associated with coagulopathy and clinically relevant bleeding risk including cirrhotic patients with Child Pugh B and C; pregnancy and breast feeding. **Warnings and Precautions:** Not recommended: in patients receiving concomitant systemic treatment with strong concurrent CYP3A4- and P-gp-inhibitors, i.e. azole-antimycotics or HIV protease inhibitors; in patients with severe renal impairment (creatinine clearance < 15 ml/min); in the treatment of acute pulmonary embolism; due to lack of data: in patients below 18 years of age, in patients with prosthetic heart valves, in patients concomitantly treated with dronedarone. Use with caution: in patients with severe renal impairment (creatinine clearance 15 – 29 ml/min) or with renal impairment concomitantly receiving other medicinal products which increase rivaroxaban plasma concentrations; in patients treated concomitantly with medicinal products affecting haemostasis or with strong CYP3A4 inducers; in patients with increased bleeding risk. In patients at risk of ulcerative gastrointestinal disease prophylactic treatment may be considered. Clinical surveillance in line with anticoagulation practice is recommended throughout the treatment period. There is no need for monitoring of coagulation parameters during treatment with rivaroxaban in clinical routine, if clinically indicated rivaroxaban levels can be measured by calibrated quantitative anti-Factor Xa tests. Specific dose recommendations apply for patients with moderate to severe renal impairment. Xarelto contains lactose. **Undesirable effects:** Common: anaemia, dizziness, headache, syncope, eye haemorrhage, tachycardia, hypotension, haematoma, epistaxis, gastrointestinal tract haemorrhage, gastrointestinal and abdominal pains, dyspepsia, nausea, constipation, diarrhoea, vomiting, pruritus, rash, ecchymosis, pain in extremity, urogenital tract haemorrhage, fever, peripheral oedema, decreased general strength and energy, increase in transaminases, post-procedural haemorrhage, contusion, wound secretion. Uncommon: thrombocythemia, allergic reaction, dermatitis allergic, cerebral and intracranial haemorrhage, haemoptysis, dry mouth, hepatic function abnormal, urticaria, cutaneous and subcutaneous haemorrhage, haemarthrosis, renal impairment, feeling unwell, localised oedema. Increases in: bilirubin, blood alkaline phosphatase, LDH, lipase, amylase, GGT. Rare: jaundice, muscle haemorrhage, bilirubin conjugated increased. Frequency not known: pseudoaneurysm following percutaneous intervention, compartment syndrome or (acute) renal failure secondary to a bleeding.

Bayer HealthCare
拜耳醫療保健有限公司
Bayer HealthCare Limited
Nos. 803-808, 8/F Shui On Centre
6-8 Harbour Road Wanchai, Hong Kong
Tel: (852) 2814 7337 Fax: (852) 3526 4755

References: 1. Kubitza D, Becka M, Schwers S, et al. Investigation of Pharmacodynamic and Pharmacokinetic Interactions Between Rivaroxaban and Enoxaparin in Healthy Male Subjects. Clin Pharmacol Drug Dev. 2013; 2(3): 270-277 **2.** Xarelto® 15mg & 20mg Prescribing Information (BHC Hong Kong) Feb 2012 **3.** EINSTEIN Investigators. Oral rivaroxaban for symptomatic venous thromboembolism. N Engl J Med. 2010;363(26):2499-2510. **4.** EINSTEIN-PE Investigators. Oral rivaroxaban for the treatment of symptomatic pulmonary embolism. N Engl J Med. 2012;366(14):1287-1297. **5.** Prins MH, et al. Oral rivaroxaban versus standard therapy for the treatment of symptomatic venous thromboembolism: a pooled analysis of the EINSTEIN-DVT and PE randomized studies. Thrombosis Journal 2013; 11:21

DVTx=treatment of deep vein thrombosis; OAC=oral anticoagulant; PEx=treatment of pulmonary embolism.

LAE-11-2013-3424

Advances in the Management of Myelofibrosis

Dr Raymond SM Wong

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

Specialist in Haematology and Haematological Oncology
Consultant, Department of Medicine & Therapeutics, Prince of Wales Hospital, Hospital Authority

Dr Raymond SM Wong

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 1 CME credit under the programme upon returning the completed answer sheet to the Federation Secretariat on or before 31 October 2014.

Myelofibrosis (MF) is one of the classical Philadelphia-negative chronic myeloproliferative neoplasms (MPNs) occurring in the form of primary MF (PMF), post-polycythaemia vera (PV) or essential thrombocythaemia (ET) (post-PV or post-ET MF)[1]. The disease involves a clonal proliferation of a pluripotent haemopoietic stem cell. The abnormal cell population releases several cytokines and growth factors in the bone marrow that lead to the development of marrow fibrosis and colonises extramedullary organs such as the spleen and the liver. MF is characterised by marrow fibrosis, extramedullary haemopoiesis with splenomegaly, and leukoerythroblastosis in blood[2].

Molecular basis of MF

A hallmark of MPNs, including PMF, is aberrant myeloproliferation associated with dysregulated Janus kinase (JAK)-signal transducer and activator of transcription (STAT) signalling[3]. Patients with MPNs carry somatic mutations in haematopoietic stem cells that result in constitutive activation or over-activation of JAK-STAT pathways[4,5], which play an important role in the proliferation, differentiation, and survival of the haemopoietic cells, as well as in the immune function. A gain-of-function mutation in the gene encoding the JAK2 tyrosine kinase, at position V617F, is present in 50% to 65% of patients with MF and is seen in the other Philadelphia chromosome-negative MPNs (96% in PV and 55% in ET)[6]. In patients with MF, dysregulated JAK-STAT signalling not only is involved in the pathogenesis of myeloproliferation but also appears to be associated with secondary pathogenic phenomena, particularly the excess production of inflammatory cytokines, which are believed to be associated with MF-related symptoms and are sensitive to JAK inhibition[7,8].

More recently, new mutations shared by other myeloid neoplasias have been described in a small proportion of MF patients. Some of these mutations (e.g., CBL and LNK) result in a loss of function, while others (e.g., TET2, ASXL1, and EZH2) affect proteins involved in the epigenetic regulation of transcription[6,9]. Mutations in genes encoding for RNA splicing machinery (such as SF3B1 and SRSF2) have also been described in MF[10, 11]. These new findings of molecular pathogenesis of MF might provide insights to the development of new agents for the treatment of the disease.

Clinical presentation and natural history

The clinical presentation, natural history and symptom severity of MF vary widely from patient to patient. The clinical characteristics of advanced MF are massive splenomegaly due to extramedullary haematopoiesis and splenic sequestration of immature blood cells, severe anaemia due to insufficient haematopoiesis and debilitating symptoms caused by high circulating levels of inflammatory cytokines[12]. Common symptoms include fatigue, night sweats, pruritus, early satiety, abdominal and bone pain and severe weight loss[12]. Further complications of disease progression may include hepatomegaly (particularly in post-splenectomy patients), portal hypertension, splenic infarcts and thrombosis[13]. Patients with advanced MF have an increased risk of transforming to a blast phase (i.e. secondary acute myeloid leukaemia [sAML]). Although sAML is the single most common cause of death, the majority of patients die from MF-related complications[13].

Diagnosis and prognostic assessment

The diagnostic criteria of PMF were updated in 2008 and incorporated the new molecular findings of the disease (Table 1) [14].

Table 1. WHO 2008 Diagnostic Criteria for Primary Myelofibrosis [14]

Major criteria (all are required)	
1.	Presence of megakaryocyte proliferation and atypia, usually accompanied by either reticulin and/or collagen fibrosis, or in the absence of significant reticulin fibrosis the megakaryocyte changes must be accompanied by an increased bone marrow cellularity characterised by granulocytic proliferation and often decreased erythropoiesis (i.e. prefibrotic cellular-phase disease).
2.	Not meeting WHO criteria for polycythaemia vera, BCR-ABL1+ chronic myelogenous leukaemia, myelodysplastic syndromes, or other myeloid neoplasms.
3.	Demonstration of JAK2V617F or other clonal markers (e.g.MPLW515L/K), or in the absence of a clonal marker, no evidence that the bone marrow fibrosis or other changes are secondary to infection, autoimmune disorders or other chronic inflammatory conditions, hairy cell leukaemia or other lymphoid neoplasms, metastatic malignancy, or toxic (chronic) myelopathies.
Minor criteria (two are required)	
1.	Leukoerythroblastosis
2.	Increase in serum LDH level
3.	Anaemia
4.	Splenomegaly

The prognosis of MF patients is heterogeneous with survivals ranging from within 1 year to more than 20

years from diagnosis. Overall, patients with MF have a substantially reduced life expectancy, with a median survival time of only 6 years for those diagnosed with PMF [13]. The most important unfavourable prognostic factors are anaemia (Hb < 10 g/dL), age > 65 years, constitutional symptoms, white blood cell count higher than 25 x 10^9/L and peripheral blood blasts ≥ 1%. These five factors have been incorporated into an International Prognostic Scoring System (IPSS), which is used at disease diagnosis[13].

The IPSS has been complemented by a dynamic IPSS (DIPSS), useful anytime during the disease course[15], in which there is a stronger weight of the anaemia (if it is related to the disease and not caused by therapy), accounting for two points instead of one point in the IPSS and always if it is related to the disease, and has been further refined in a DIPSS-plus model, also including thrombocytopenia, transfusion need, and karyotypic information[16]. Table 2 summarises the current prognostic models of MF.

Table 2. Summary of current prognostic models for myelofibrosis.

Parameter	IPSS	DIPSS	DIPSS-plus
Age > 65 years	+	+	DIPSS high: 3 points DIPSS int-2: 2 points DIPSS int-1: 1 points
Constitutional symptoms	+	+	
Haemoglobin (Hb) < 10g/dL	+	+	
Leukocytes > 25 x 10^9/L	+	+	
Blood blast ≥ 1%	+	+	
Platelet < 100 x 10^9/L			+
Red blood cell transfusion need			+
Unfavourable karyotypes: +8, -7/7q-, -5/5q-, i17q, 12p-, 11q23 rearrangement			+
	1 point each	1 point each Hb: 2 points	Platelet, karyotype, transfusion need: 1 point each
Risk group	**Score / Median survival**		
Low	0 / 11.25 years	0 / NR	0 / 15.4 years
Intermediate-1	1 / 7.92 years	1-2 / 14.2 years	1/ 6.5 years
Intermediate-2	2 / 4.00 years	3-4 / 4 years	2-3 / 2.9 years
High	≥ 3 / 2.25 years	5-6 / 1.5 years	4-6 / 1.3 years

NR = not reached

Conventional therapies of MF

The majority of the traditional therapies are palliative and predominantly used for the management of splenomegaly or anaemia[17]. Hydroxyurea has commonly been used for the management of splenomegaly as well as leukocytosis and thrombocytosis. In one study, approximately 30% of patients receiving hydroxyurea achieved a reduction in spleen size and 12% of patients achieved improvements in haemoglobin levels[18]. However, the benefits of hydroxyurea are transient, with a median response of approximately 13 months. Adverse events associated with hydroxyurea include the development and/or worsening of anaemia and ulcers (e.g. oral and leg).

Splenectomy and irradiation have been used for the management of splenomegaly. Splenectom associated with significant mortality (~9%) and morbidity (30-40%)[19]. Post-splenectomy thrombocytosis which increases the risk of thrombosis as well as progressive and massive hepatomegaly may also occur. Irradiation provides a short-term alleviation of symptoms but is also associated with significant risks of severe and long-lasting cytopenias[19].

Symptomatic anaemia is typically managed by blood transfusion. The use of recombinant human erythropoietin in patients with inappropriately low levels of erythropoietin (<125 μ/l), androgen therapy with danazol, corticosteroids and immunomodulatory drugs (e.g. thalidomide and lenalidomide) have been used although formal efficacy data from randomised clinical trials are lacking[7, 20].

The only potential curative therapy is allogeneic stem cell transplantation (alloSCT). However, it is associated with high treatment-related mortality and relapse rate[21]. Ideal candidates should be young, without comorbidities, with a good performance status and without peripheral blood blasts[21]. Only a small proportion of MF patients are appropriate candidates for alloSCT.

Treatment of MF with JAK inhibitors

Ruxolitinib, a JAK1 and JAK2 inhibitor, demonstrated efficacy irrespective of mutation status in two large Phase III studies in patients with PMF, post-PV MF and post-ET MF and intermediate-2 or high-risk disease. It has been approved for the treatment of MF. Several other JAK inhibitors are in various phases of clinical trials.

COMFORT-I was a double-blind, placebo-controlled Phase III clinical study (N = 309) in which patients were randomised (1:1) to ruxolitinib or placebo[22]. Significantly, more patients in the ruxolitinib arm achieved at least a 35% reduction in spleen volume (assessed by MRI or CT) versus placebo at week 24 (41.9 vs 0.7%, p < 0.001)[22]. Improvements in MF-associated symptoms were also achieved with ruxolitinib therapy. In the ruxolitinib arm, 45.9% of patients achieved a 50% or greater improvement in total symptom score (assessed with the modified MFSAF v2.0) by week 24 versus 5.3% in the placebo group (p < 0.001). Individual symptoms improved in the ruxolitinib arm and worsened in the placebo arm. Patients also experienced improvements in fatigue and quality of life (QoL), as assessed by the PROMIS Fatigue scale and EORTC QLQ-C30, respectively. In a 3-year update of the study, spleen reductions and QoL improvements were sustained with longer-term ruxolitinib therapy[23].

In another open-label, randomised Phase III study (COMFORT-II; n = 219), patients were randomised (2:1) to ruxolitinib or best available therapy (BAT)[24]. Significantly, more patients in the ruxolitinib arm (28%) achieved at least a 35% reduction in spleen volume versus BAT (0%) (p < 0.001) at week 48. While most patients in the ruxolitinib arm had a reduction in spleen size, the majority of patients in the BAT arm had worsening splenomegaly. Patients treated with ruxolitinib experienced significant improvements in QoL, as measured by the European Organization for Research and Treatment of Cancer (EORTC-QLQ-C30) and the Functional Assessment of Cancer Therapy Lymphoma (FACT–Lym).

In a pooled analysis of the 3 years' data, patients who received ruxolitinib in the COMFORT studies had significantly prolonged survivals compared with patients who received placebo or BAT[25]. The most common adverse events with ruxolitinib therapy were anaemia and thrombocytopenia which were most common in the first three months after initiation of treatment[22-24]. In the COMFORT studies, the most common non-haematologic adverse events that occurred more frequently in the ruxolitinib group were ecchymosis, dizziness and headache.

Summary

MF is a heterogeneous disease with debilitating symptoms and splenomegaly. Until recently, treatments have been predominantly palliative and offered limited long term benefits, with only alloSCT as a potential cure. The discovery of the JAK-STAT pathway has improved our understanding of the pathogenesis of MF and led to the development of JAK inhibitors. Experience with ruxolitinib has been encouraging with significant improvements in MF-related symptoms and overall survival. A better knowledge of the mechanisms underlying MF will hopefully lead to the development of better treatment strategies.

References

1. Mesa, R.A., et al., Primary myelofibrosis (PMF), post polycythemia vera myelofibrosis (post-PV MF), post essential thrombocythemia myelofibrosis (post-ET MF), blast phase PMF (PMF-BP): Consensus on terminology by the international working group for myelofibrosis research and treatment (IWG-MRT). Leuk Res, 2007. 31(6): p. 737-40.
2. Barosi, G., Myelofibrosis with myeloid metaplasia: diagnostic definition and prognostic classification for clinical studies and treatment guidelines. J Clin Oncol, 1999. 17(9): p. 2954-70.
3. Quintas-Cardama, A., et al., Janus kinase inhibitors for the treatment of myeloproliferative neoplasias and beyond. Nat Rev Drug Discov, 2011. 10(2): p. 127-40.
4. Vainchenker, W., et al., New mutations and pathogenesis of myeloproliferative neoplasms. Blood, 2011. 118(7): p. 1723-35.
5. Cross, N.C., Genetic and epigenetic complexity in myeloproliferative neoplasms. Hematology Am Soc Hematol Educ Program, 2011. 2011: p. 208-14.
6. Tefferi, A. and W. Vainchenker, Myeloproliferative neoplasms: molecular pathophysiology, essential clinical understanding, and treatment strategies. J Clin Oncol, 2011. 29(5): p. 573-82.
7. Barbui, T., et al., Philadelphia-negative classical myeloproliferative neoplasms: critical concepts and management recommendations from European LeukemiaNet. J Clin Oncol, 2011. 29(6): p. 761-70.
8. Verstovsek, S., et al., Safety and efficacy of INCB018424, a JAK1 and JAK2 inhibitor, in myelofibrosis. N Engl J Med, 2010. 363(12): p. 1117-27.
9. Brecqueville, M., et al., Mutation analysis of ASXL1, CBL, DNMT3A, IDH1, IDH2, JAK2, MPL, NF1, SF3B1, SUZ12, and TET2 in myeloproliferative neoplasms. Genes Chromosomes Cancer, 2012. 51(8): p. 743-55.
10. Lasho, T.L., et al., SRSF2 mutations in primary myelofibrosis: significant clustering with IDH mutations and independent association with inferior overall and leukemia-free survival. Blood, 2012. 120(20): p. 4168-71.
11. Lasho, T.L., et al., SF3B1 mutations in primary myelofibrosis: clinical, histopathology and genetic correlates among 155 patients. Leukemia, 2012. 26(5): p. 1135-7.
12. Atallah, E. and S. Verstovsek, Emerging drugs for myelofibrosis. Expert Opin Emerg Drugs, 2012. 17(4): p. 555-70.
13. Cervantes, F., et al., New prognostic scoring system for primary myelofibrosis based on a study of the International Working Group for Myelofibrosis Research and Treatment. Blood, 2009. 113(13): p. 2895-901.
14. Tefferi, A. and J.W. Vardiman, Classification and diagnosis of myeloproliferative neoplasms: the 2008 World Health Organization criteria and point-of-care diagnostic algorithms. Leukemia, 2008. 22(1): p. 14-22.
15. Passamonti, F., et al., A dynamic prognostic model to predict survival in primary myelofibrosis: a study by the IWG-MRT (International Working Group for Myeloproliferative Neoplasms Research and Treatment). Blood, 2010. 115(9): p. 1703-8.
16. Gangat, N., et al., DIPSS plus: a refined Dynamic International Prognostic Scoring System for primary myelofibrosis that incorporates prognostic information from karyotype, platelet count, and transfusion status. J Clin Oncol, 2011. 29(4): p. 392-7.
17. Tefferi, A., Essential thrombocythemia, polycythemia vera, and myelofibrosis: current management and the prospect of targeted therapy. Am J Hematol, 2008. 83(6): p. 491-7.
18. Martinez-Trillos, A., et al., Efficacy and tolerability of hydroxyurea in the treatment of the hyperproliferative manifestations of myelofibrosis: results in 40 patients. Ann Hematol, 2010. 89(12): p. 1233-7.
19. Cervantes, F., Modern management of myelofibrosis. Br J Haematol, 2005. 128(5): p. 583-92.
20. Reilly, J.T., et al., Guideline for the diagnosis and management of myelofibrosis. Br J Haematol, 2012. 158(4): p. 453-71.
21. Ballen, K.K., et al., Outcome of transplantation for myelofibrosis. Biol Blood Marrow Transplant, 2010. 16(3): p. 358-67.
22. Verstovsek, S., Therapeutic potential of Janus-activated kinase-2 inhibitors for the management of myelofibrosis. Clin Cancer Res, 2010. 16(7): p. 1988-96.
23. Verstovsek, S., et al., Long-Term Outcomes Of Ruxolitinib Therapy In Patients With Myelofibrosis: 3-Year Update From COMFORT-I. Blood, 2013. 122(21): p. 396.
24. Harrison, C., et al., JAK inhibition with ruxolitinib versus best available therapy for myelofibrosis. N Engl J Med, 2012. 366(9): p. 787-98.
25. Vannucchi, A.M., et al., A Pooled Overall Survival Analysis of The COMFORT Studies: 2 Randomized Phase 3 Trials of Ruxolitinib For The Treatment of Myelofibrosis. Blood, 2013. 122(21): p. 2820.

MCHK CME Programme Self-assessment Questions

Please read the article entitled "Advances in the Management of Myelofibrosis" by Dr Raymond SM Wong 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 31 October 2014. 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. **Myelofibrosis can develop in patients with Polycythaemia vera or essential thrombocythaemia .**
2. **Increased tyrosine kinase activity is associated with Myelofibrosis.**
3. **Massive splenomegaly and leukoerythroblastosis in blood is common in patients with myelofibrosis.**
4. **The International Prognostic Scoring System (IPSS) is used in disease diagnosis.**
5. **The Dynamic International Prognostic Scoring System (DIPSS) is only useful at disease diagnosis.**
6. **Adverse events associated with hydroxyurea include pancytopenia and ulcers.**
7. **Ruxolitinib, a JAK1 and JAK2 inhibitor, is only useful if the patient has documented JAK-2 mutation.**
8. **Comfort-I and Comfort-II studies showed significant improvements in symptom score and reduction in spleen size in the group receiving ruxolitinib.**
9. **Ecchomyosis, dizziness and headache are some common non-haematologic adverse events associated with ruxolitinib.**
10. **Allogeneic stem cell transplantation remains the potential curative therapy in myelofibrosis in patients who are young and fit with an available donor.**

ANSWER SHEET FOR OCTOBER 2014

Please return the completed answer sheet to the Federation Secretariat on or before 31 October 2014 for documentation. 1 CME point will be awarded for answering the MCHK CME programme (for non-specialists) self-assessment questions.

Advances in the Management of Myelofibrosis

Dr Raymond SM Wong

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

Specialist in Haematology and Haematological Oncology
Consultant, Department of Medicine & Therapeutics, Prince of Wales Hospital, Hospital Authority

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

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

HKID No.: __ __ - __ __ __ __ X X (X) HKDU No.: _____ HKAM No.: _____

Contact Tel No.:_____ MCHK No.: _____ (for reference only)

Answers to September 2014 Issue

Inverting the Pyramid of Antenatal Care?

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

MediLink Square 美迪寧廣場

Tailored for the medical community

A premium venue, ideally located in

The Heart of Kowloon

and within 30 minutes reach of all private hospitals in Kowloon and New Territories

MediLink Square is adjacent to Yau Ma Tei MTR (Exit B1) and located at the intersection of Nathan Road and Waterloo Road within easy reach of major bus routes

MediLink Square was designed from the outset to accommodate exclusive private clinics, unlike other buildings which often create medical floors converted from general office facilities.

The top floor is reserved exclusively for private clinics as a 5-star medical treatment location.

SEMINAR ROOM AVAILABLE FOR MEDICAL MEETING & SEMINAR USE

Specially designed for medical tenants:

- *Size options ranging from 450 sq ft to 2,430 sq ft to fit your needs*
- *Similar concept to leading US and European medical centres*
- *High ceilings and a warm lighting system provide a comfortable and relaxing atmosphere for your visitors*
- *Multiple lifts and escalators reduce waiting time for you and your patients*
- *High standards of hygiene*
- *Large voltage electricity supply available in some units*

525 Nathan Road, Yau Ma Tei, Kowloon
(Yau Ma Tei MTR Station, Exit B1)

Leasing Enquiries: **2721 9388**
Email: info@medilink-hk.com *Website:* www.medilink-hk.com

Personalised Treatment for Acute Myeloid Leukaemia – Are We There Yet?

Prof Anskar YH LEUNG

BMedSc, MB, ChB (Hons), PhD(CUHK), MRCP (HK), FHKCP, FHKAM (Medicine), MD (HKU), FRCP (Glasgow, London, Edinburgh)

Assistant Dean (Platform Technologies)
Li Shu Fan Medical Foundation Professor in Haematology
Clinical Professor, Department of Medicine, the University of Hong Kong

Acute myeloid leukaemia – a disease with unmet clinical needs

Acute myeloid leukaemia (AML) is one of the most lethal cancers in Hong Kong, affecting more than 300 patients per year. It is a group of heterogeneous diseases with distinctive clinicopathologic, cytogenetic and genetic features, sharing in common an abnormal increase in myeloblasts. Induction chemotherapy comprising daunorubicin for 3 days and cytarabine for 7 day, the "7+3" regimen, is the mainstay of treatment, with a complete remission (CR) rate of about 60-80%.[1] Alternative chemotherapeutic regimens, based on low dose cytarabine in combination with idarubicin or mitoxantrone, have also been shown to achieve similar CR rates and comparable, if not superior survivals.[2,3] Patients with adverse prognostic factors based primarily on clinical, cytogenetic and more recently genetic factors and in whom donors are available will receive allogeneic haematopoietic stem cell transplantation (HSCT) as consolidation.[4] Patients with apparently favourable prognostic factors or in whom donors are unavailable will receive a high dose of cytarabine as consolidation. These treatment regimens were based on a series of randomised control trials of chemotherapeutic regimens conducted since the early 70s, when groups of patients were treated uniformly according to trial protocols without due consideration of their disease heterogeneity.[5] As a result, the treatment outcome has been unsatisfactory and despite an apparent remission after induction chemotherapy, most patients eventually relapse, with an overall cure rate of only 30-40%. Most patients die of progressive diseases or the toxicity of repeated but futile chemotherapy. There is an unmet clinic need for novel and effective therapeutic strategies that should address the two intertwined problems in AML viz. disease heterogeneity and drug resistance.

Disease heterogeneity of AML

Heterogeneity of AML has long been recognised and has formed the basis of the FAB (French-American-British) classification in the 1970s in which AML was classified into M0 to M7 based primarily on morphological grounds. Except acute promyelocytic leukaemia ("M3"), a subtype of AML that responds favourably to differentiating agents, the clinical and therapeutic implications of the FAB classification were poorly defined. On the other hand, an increasing number of recurrent cytogenetic (CG) aberrations in AML have been reported since its first description in the 1950s. To date, more than 100 CG abnormalities have been identified based on which patients were categorised into "good", "intermediate" and "poor" risks with long-term disease free survivals of about 60, 30 and 10% respectively.[6] While CG may guide the decision whether individual patients should receive HSCT as a means of consolidation, it has given limited insights to the therapeutic strategies for each group, especially in the chemorefractory state. Recently, next generation sequencing (NGS) has underpinned the heterogeneity of AML at the genetic level. In a cohort of 200 de novo AML, recurrent mutations were identified in 23 genes, notably Fms-like tyrosine kinase 3 (FLT3), nucleophosmin 1 (NPM1), DNA methyltransferase 3A (DMNT3A), isocitrate dehydrogenase 1/2 (IDH1/2) etc. and almost all AML had at least 1 non-synonymous mutations of pathogenetic significance.[7] Furthermore, cooperation and mutual exclusivity existed[8] and new genetic aberrations may be induced by exposure to genotoxic chemotherapy.[9] These observations supported the proposition that a personalised rather than regimental approach for AML patients should be adopted to improve the treatment outcome.

Relapse and drug resistance in AML

Despite an initial response to induction chemotherapy in most AML patients, a major clinical problem is the emergence of therapy-resistant leukaemic cells, leading to relapse and/or a chemorefractory state. As a result, most patients die either of their disease or the toxicity of repeated but ineffective treatments. The high relapse rate in AML may reflect two underlying biological features shared by most AML cases. One is an intrinsic therapy resistance of a rare subset of cells referred to as "leukaemia-initiating cells" (LICs) that are thought to be responsible for propagating the disease based on their ability to regenerate AML when transplanted into immunodeficient mice in experimental models.[10] Recent evidence has suggested that LICs may arise from specific driver mutations in normal haematopoietic stem cells (HSCs) or their downstream myeloid progenitors. During the process of transformation, genomic instability may occur that accelerates additional genetic and epigenetic changes and contributes to the eventual establishment of a full-blown leukaemic state and the continuing development of mutant subclones. Because most LICs are replicatively quiescent, they are less sensitive to the cytotoxic effects of chemotherapy than the bulk of the highly proliferative myeloblasts that they produce. As a result, some LICs may survive even when the bone marrow appears to be in morphological remission and, in time, lead to relapse. Moreover, some AML may have acquired additional mutations

or epigenetic changes that make all of their progeny resistant and these clones will then be selected during the course of treatment of relapses – thus serving as a second mechanism of treatment resistance. As a result, the targets for AML are constantly evolving and effective therapeutic strategies of AML should be determined in real time.

New strategies on the horizon

The intrinsic problems aforementioned have made it clear that further shuffling of chemotherapeutic agents or clinical trials ignoring the intrinsic heterogeneity of the disease will not bring out major improvement in the treatment of AML. A number of strategies could be developed in newly diagnosed or relapsed and/or refractory AML with particular reference to a personalised treatment and targeting of specific oncogenic pathways in AML.

Personalised treatment strategy for newly diagnosed AML

The heterogeneity of AML and the overall unsatisfactory treatment outcome of patients clearly indicate that the patient's treatment should be a personalised consideration. To accomplish this objective, reliable biomarkers are needed to select specific groups of patients who will benefit most from a particular treatment. A number of strategies have emerged. Based on cytogenetics, patients with core binding factor (CBF) AML including t(8;21) and inv(16) as well as those with normal karyotype carrying mutant NPM1/wild-type FLT3 and bi-allelic CEBPα have demonstrated the best treatment outcome to conventional induction and consolidation chemotherapy with long term leukaemia free survivals of over 60%. As a result, patients with these favourable clinicopathologic features, including those older than 60 years old, should receive standard chemotherapy.

On the other hand, patients with complex and/or monosomal (CK/MK) karyotype have dismal outcomes with conventional chemotherapy and allogeneic HSCT.[11,12] In this group of patients, an alternative treatment should be considered. Earlier studies have demonstrated the efficacy of hypomethylating agents azacitidine and decitabine in AML with less than 30% blasts in the bone marrow/blood, formerly RAEB-t (refractory anaemia with excess blasts in transformation). More recent studies that focused on newly diagnosed AML patients older than 60 years who were unfit for conventional chemotherapy, have shown that decitabine may be effective in AML with more than 30% blasts, particularly those with CK/MK with a CR rate of up to 50%.[13] A critical question is whether these agents could be used as an induction regimen in young patients with CK/MK AML to reduce the toxicity prior to curative allogeneic HSCT and whether this approach can be translated into a positive impact on their overall outcome.

The fact that DMNT3A regulates global methylation and IDH1/2 mutations results in elevation of 2 hydroxyglutarate (2HG) that suppresses TET2 activity in AML and has led to the hypothesis that hypomethylating agents may have preferential effects in AML carrying these mutations.[14] The rarity of these mutations and the relatively small number of patients in the reported cohorts have made it difficult to draw definitive conclusions although emerging data suggested that DMNT3A mutations may predict a better response to hypomethylating agents in both newly diagnosed MDS[15] and AML.[16]

Patients with FLT3-ITD relapsed/ refractory cases

FLT3-ITD occurs in about 30% AML and is particularly prevalent in patients with normal karyotype and t(6;9) as well as APL. In AML, FLT3-ITD is associated with an inferior clinical prognosis and although the initial response may not be significantly affected, this specific type of AML is notorious for high risk of relapse and subsequent drug resistance. ITD is thought to confer a gain-of-function to FLT3, leading to constitutive activation of FLT3 signalling including phosphoinositide-3-kinase/AKT and RAS/mitogen-activated protein kinase (MAPK) pathways as well as signal transducer and activator of transcription 5 (STAT5). FLT3 inhibitors have been tested in Phase II/III clinical trials either as monotherapy or in combination with conventional chemotherapy and their effects are largely seen in FLT3-ITD+ AML though recent data with quizartinib have also shown a modest effect in FLT3 wild-type AML.[17] As a single agent, FLT3 inhibitors including sorafenib and quizartinib could induce clearance of blasts in more than half of the patients.[18] However, response is at best transient, with a median progression free survival of 2-3 months and progression is associated with the emergence of resistant clones carrying D835 TKD mutation and activation of intracellular alkalisation machineries.[19,20] Strategies targeting these evolving leukaemogenic pathways have emerged.[20,21] A number of phase III clinical trials have evaluated the additional benefit of FLT3 inhibitors in combination to conventional chemotherapy[22] and hypomethylating agents.[23] The long term outcome of these patients should be evaluated to see if concomitant treatment with FLT3 inhibitors can prevent leukaemia relapse in the long term.

Conclusion

AML is a group of largely heterogeneous diseases that are susceptible to the development of drug resistance but ironically treatment in the past four decades have been regimental and unified and hence the outcome of the treatment has been disappointing. Recent advances in leukaemia and stem cell biology as well as the advent of next generation sequencing have provided us very important insights to the understanding of these diseases. Therapeutic strategies that recognise such heterogeneity and the unique subtypes of characteristic aberrant signalling profiles have emerged and their impact on the overall outcome in the long term would have to be evaluated.

References

1. Fernandez HF, Sun Z, Yao X et al. Anthracycline dose intensification in acute myeloid leukemia. N Engl J Med. 2009;361(13):1249-59.

2. Mandelli F, Vignetti M, Suciu S et al. Daunorubicin versus mitoxantrone versus idarubicin as induction and consolidation chemotherapy for adults with acute myeloid leukemia: the EORTC and GIMEMA Groups Study AML-10. J Clin Oncol. 2009;27(32):5397-403.
3. A systematic collaborative overview of randomized trials comparing idarubicin with daunorubicin (or other anthracyclines) as induction therapy for acute myeloid leukaemia. AML Collaborative Group. Br J Haematol. 1998;103(1):100-9.
4. Oran B, Weisdorf DJ. Allogeneic stem cell transplantation in first complete remission. Curr Opin Hematol. 2011;18(6):395-400.
5. Wiernik PH. Inching toward cure of acute myeloid leukemia: a summary of the progress made in the last 50 years. Med Oncol. 2014;31(8):136.
6. Grimwade D, Hills RK, Moorman AV et al; National Cancer Research Institute Adult Leukaemia Working Group. Refinement of cytogenetic classification in acute myeloid leukemia: determination of prognostic significance of rare recurring chromosomal abnormalities among 5876 younger adult patients treated in the United Kingdom Medical Research Council trials. Blood. 2010; 116(3):354-65.
7. Cancer Genome Atlas Research Network. Genomic and epigenomic landscapes of adult de novo acute myeloid leukemia. N Engl J Med. 2013; 368(22):2059-74.
8. Patel JP(1), Gönen M, Figueroa ME et al. Prognostic relevance of integrated genetic profiling in acute myeloid leukemia. N Engl J Med. 2012; 366(12):1079-89.
9. Ding L, Ley TJ, Larson DE et al. Clonal evolution in relapsed acute myeloid leukaemia revealed by whole-genome sequencing. Nature. 2012; 481(7382): 506-10.
10. Pollyea DA, Gutman JA, Gore L, Smith CA, Jordan CT. Targeting acute myeloid leukemia stem cells: a review and principles for the development of clinical trials. Haematologica. 2014;99(8):1277-1284.
11. Breems DA, Van Putten WL, De Greef GE et al. Monosomal karyotype in acute myeloid leukemia: a better indicator of poor prognosis than a complex karyotype. J Clin Oncol. 2008;26(29):4791-7.
12. Kayser S, Zucknick M, Döhner K et al; German-Austrian AML Study Group. Monosomal karyotype in adult acute myeloid leukemia: prognostic impact and outcome after different treatment strategies. Blood. 2012;119(2):551-8.
13. Blum W, Garzon R, Klisovic R et al. Clinical response and miR-29b predictive significance in older AML patients treated with a 10-day schedule of decitabine. Proc Natl Acad Sci U S A. 2010;107(16):7473-8.
14. Im AP, Sehgal AR, Carroll MP et al. DNMT3A and IDH mutations in acute myeloid leukemia and other myeloid malignancies: associations with prognosis and potential treatment strategies. Leukemia. 2014 Apr 4. [Epub ahead of print]
15. Traina F, Visconte V, Elson P et al. Impact of molecular mutations on treatment response to DNMT inhibitors in myelodysplasia and related neoplasms. Leukemia. 2014;28(1):78-87.
16. Metzeler KH, Walker A, Geyer S et al. DNMT3A mutations and response to the hypomethylating agent decitabine in acute myeloid leukemia. Leukemia. 2012;26(5):1106-7.
17. Cortes JE, Kantarjian H, Foran JM et al. Phase I study of quizartinib administered daily to patients with relapsed or refractory acute myeloid leukemia irrespective of FMS-like tyrosine kinase 3-internal tandem duplication status. J Clin Oncol. 2013;31(29):3681-7.
18. Leung AY, Man CH, Kwong YL. FLT3 inhibition: a moving and evolving target in acute myeloid leukaemia. Leukemia. 2013;27(2):260-8.
19. Man CH, Fung TK, Ho C et al. Sorafenib treatment of FLT3-ITD(+) acute myeloid leukemia: favorable initial outcome and mechanisms of subsequent nonresponsiveness associated with the emergence of a D835 mutation. Blood. 2012;119(22):5133-43.
20. Man CH, Lam SS, Sun MK et al. A novel tescalcin-sodium/hydrogen exchange axis underlying sorafenib resistance in FLT3-ITD+ AML. Blood. 2014;123(16):2530-9.
21. Galanis A, Ma H, Rajkhowa T et al. Crenolanib is a potent inhibitor of FLT3 with activity against resistance-conferring point mutants. Blood. 2014;123(1):94-100.
22. Ravandi F, Arana Yi C, Cortes JE et al. Final report of phase II study of sorafenib, cytarabine and idarubicin for initial therapy in younger patients with acute myeloid leukemia. Leukemia. 2014 ;28(7):1543-5.
23. Ravandi F, Alattar ML, Grunwald MR et al. Phase 2 study of azacytidine plus sorafenib in patients with acute myeloid leukemia and FLT-3 internal tandem duplication mutation. Blood. 2013;121(23):4655-62.

Certificate Course for General Practitioners, Nurses and Health Care Providers who are interested in Office Gynaecology

Course No. C248

CME/CNE/PEM Course

Jointly organised by

The Federation of Medical Societies of Hong Kong

The Obstetrical and Gynaecological Society of Hong Kong

Certificate Course on

Office Gynaecology

Objectives: This course is designed for general practitioners, nurses and health care providers. A series of lectures covering various aspects and updates of office gynaecology are provided in the course.

Date	Topics	Speakers
5 Nov	Medical management of Endometriosis	Dr. Alice Yuen-kwan WONG Specialist in Obstetrics & Gynaecology Private Practice
12 Nov	New Concept in the use of Hormonal Replacement Therapy	Dr. Dominic Fuk-him LI Specialist in Obstetrics & Gynaecology Private Practice
19 Nov	Management of Infertility & Assisted Reproductive Technology in the 2010s	Dr. Grace Wing-shan KONG Assistant Professor Department of Obstetrics and Gynaecology The Chinese University of Hong Kong
26 Nov	Screening of Cervical Cancer and the present view in the use of HPV vaccination	Dr. Karen Kar-loen CHAN Clinical Associate Professor Department of Obstetrics and Gynaecology The University of Hong Kong
3 Dec	Update in the Diagnosis and Management of Abnormal Uterine Bleeding	Dr. Vincent Yuk-tong CHEUNG Consultant and Honorary Clinical Associate Professor Department of Obstetrics and Gynaecology Queen Mary Hospital
10 Dec	Current Trend in the use of Emergency Contraception	Dr. Grace Ching-yin WONG Senior Doctor The Family Planning Association of Hong Kong

Date : 5 November 2014 - 10 December 2014 (Every Wednesday)
Time : 2pm - 3:30pm
Venue : Lecture Hall, 4/F., Duke of Windsor Social Service Building, 15 Hennessy Road, Wanchai, Hong Kong
Language Media : Cantonese (Supplemented with English)
Course Fee : HK$750 (6 sessions)
Certificate : Awarded to participants with a minimum attendance of 70%
Enquiry : The Secretariat of The Federation of Medical Societies of Hong Kong
Tel.: 2527 8898 Fax: 2865 0345 Email: info@fmshk.org

CME Accreditation in application

A total of 9 CNE/PEM points for the whole course and the points will be awarded according to the number of hours attended.
Application form can be downloaded from website: http://www.fmshk.org

Thrombocytopenia in Pregnancy

Dr Shek-ying LIN

FHKAM (Medicine), MRCP

Associate Consultant, Department of Medicine & Geriatrics, United Christian Hospital, Hong Kong

Dr Shek-ying LIN

Introduction

Thrombocytopenia is common in pregnancy with variable severities and occurs in approximately 10% of pregnancies. Most cases observed are due to normal physiological changes. The differential diagnoses will include entities that are unique to pregnant ladies. The treatment goal will be more on maintaining a safe platelet count during pregnancy and throughout the peri-partum period. Treatment must be safe both to the mother and the foetus. Thrombocytopenia may limit the choices of anaesthesia. The foetus is rarely severely affected at birth and the mode of delivery should be based on obstetric indications. A history of ITP is not a contraindication to future pregnancies but requires special monitoring and treatment.

Differential diagnoses of thrombocytopenia during pregnancy

Gestational thrombocytopenia

Gestational thrombocytopenia is the most common cause of pregnancy-associated thrombocytopenia, accounting for 65%-80% of cases[1]. Increases in the plasma volume, platelet activation and clearance contribute to a decrease in the platelet count in pregnancy. These changes cause a mild decrease in the platelet count, typically 10-15%. The onset of thrombocytopenia and the actual platelet count have a strong bearing on the diagnosis. Gestational thrombocytopenia is rare in the first trimester and commonly presents in the second or third trimester. The platelet count rarely drops below 70 x 10^9/L in gestational thrombocytopenia. Platelet counts < 70 x 10^9/L or occurring during the first or early in the second trimester suggest other aetiologies and require further evaluations[2]. Gestational thrombocytopenia is not associated with foetal thrombocytopenia[3] and if the infant is thrombocytopenic, then other causes such as infection, foetal and neonatal allo-immune thrombocytopenia should be considered. Maternal thrombocytopenia usually resolves within 2 months after delivery and a complete blood count at 2 months post-partum is recommended.

Immune Thrombocytopenia

Immune thrombocytopenic purpura (ITP) has a prevalence of 0.2-0.5 % in pregnancy and is the most common cause of thrombocytopenia in the first trimester. ITP is a diagnosis by exclusion, but in a young patient with isolated thrombocytopenia without atypical features, a bone marrow biopsy is not required. ITP and gestational thrombocytopenia sometimes cannot be differentiated with certainty until post- partum, especially when there is mild thrombocytopenia found in the second trimester.

Autoimmune disorders such as systemic lupus erythematosus may first appear or increase in severity during pregnancy and more frequent follow ups or titrations of the immuno-suppressant is required. The anti-phospholipid syndrome associated with thrombocytopenia should be considered because of its association with miscarriages and may require treatment with anticoagulation.

Disorders associated with thrombocytopenia in late pregnancy

Thrombocytopenia that presents near the end of pregnancy should raise the possibility of other diagnoses. Disorders that may first present at that time may include preeclampsia[4], the HELLP syndrome (Haemolysis, Elevated Liver enzymes, Low Platelets)[5], acute fatty liver of pregnancy, disseminated intravascular coagulation (DIC) related to pregnancy, thrombotic thrombocytopenic purpura (TTP), and haemolytic uraemic syndrome(HUS). Constitutional symptoms, oedema, hypertension, anaemia or an abnormal liver or renal function suggest something more than gestational thrombocytopenia.

Other causes of thrombocytopenia

Thrombocytopenia may be the presenting feature of viral infections such as HIV, viral hepatitis, and cytomegalovirus infection. Drug related thrombocytopenia should always be included in the differential diagnoses and a history of herbs or nutritional supplements intake should be sought. Women receiving low-molecular-weight or conventional un-fractionated heparin may have heparin-induced thrombocytopenia. The temporal relationship of thrombocytopenia and heparin use or the presence of thrombosis should prompt further testings.

History and physical examination

The history is important in establishing the onset of thrombocytopenia, any previous thrombocytopenia and any thrombocytopenia during previous pregnancy. Any thrombocytopenia in the immediate post-partum period of a sibling is the most predictive factor for thrombocytopenia in the coming newborn. We should also assess any bleeding problem and the severity of bleeding. Symptoms of fluid retention may suggest preeclampsia. Neurological symptoms, decreased urine output or fever may suggest thrombotic

microangiopathy. Joint pain, oedema, skin rash or oral ulcer may suggest auto-immune diseases. Herbs, over-the-counter drugs or nutritional supplements may rarely contain chemicals that can cause thrombocytopenia. A positive family history of thrombocytopenia may lead to the investigation of hereditary thrombocytopenia. A history of recurrent abortions or thrombosis may prompt the test for the anti-phospholipid syndrome.

The physical examination should include pallor, jaundice, oedema or skin rash. The blood pressure should always be checked. Petechiae or bruises should be assessed and recorded carefully. Stigmata of chronic liver disease may suggest pre-existing cirrhosis. Splenomegaly may signify portal hypertension or chronic lympho-proliferative or myelo-proliferative diseases.

Investigation

A complete blood count, reticulocyte count and a peripheral blood smear are essential in the evaluation of thrombocytopenia and to exclude spurious thrombocytopenia due to platelet clumping. Large platelets may be seen in ITP. Red cell fragments or schizocytes should be specially looked for to exclude microangiopathic haemolytic anaemia. Polychromasia or spherocytes may suggest auto-immune haemolytic anaemia(Evan's syndrome). Hypersegmentation of neutrophils may be seen in nutritional deficiencies. An abnormal liver or renal function test may be seen in preeclampsia, microangiopathic haemolytic anaemia, the HELLP syndrome, or acute fatty liver of pregnancy. A prolonged clotting time, decreased fibrinogen and raised D-Dimer may suggest DIC or acute fatty liver of pregnancy. Clotting times are usually normal in TTP or HUS. A Coomb's test may be ordered if ITP is the likely diagnosis. The anti-nuclear factor and anti-DS DNA should be included as in non-pregnant patients. A viral screen should include serology for HIV, Hepatitis B and C. Tests for EBV and CMV should be specially asked for if other investigations fail to achieve a reasonable diagnosis. The anti-platelet antibody is not indicated in the diagnosis of ITP[6]. An ultra-sonogram of abdomen may be helpful in patients with abnormal liver or renal function tests or there is a suggestion of chronic lymphoproliferative or myeloproliferative disorders. Bone marrow biopsy is rarely indicated unless there is a strong suggestion of primary marrow problem or a splenectomy is considered for ITP patients.

Management of ITP in pregnancy

Treatment

The treatment goal of ITP during pregnancy is to maintain a safe platelet count to prevent bleeding rather than achieving a normal count. Pregnancy is associated with a pro-coagulant state with increased levels of factor VIII, von Willebrand Factor and fibrinogen. Bleeding is rare unless the platelet count is less than 30 x 10^9/L. Treatment is not required if the platelet count is > 30 x 10^9/L and without bleeding. Low dose prednisolone of 10-20mg daily may be given for a short period of time to boost up the platelet count before invasive procedures.

The first line treatment for ITP should include steroids or intravenous immunoglobulins (IVIG) or a combination of the two. Generally, treatment response is similar to non-pregnant patients. Some centres prefer the first line use of IVIG as the side effects are minimal and the response is faster. But the effect of IVIG usually lasts for 3 weeks and the cost may be of a concern. Steroids may increase the blood pressure and blood sugar and cause weight gain. Mood disturbance effects of steroids should be noted, especially in the post-partum period.

Azathioprine has been safely administered during pregnancy[7] and may be added for steroid sparing if the maintenance dose of steroid is too high or the side effects of steroid are not acceptable. Cyclosporine A is safe to the mother or foetus during pregnancy when used for inflammatory bowel diseases and may be considered as a second line treatment. Danazol, a synthetic androgen, may cause virilisation of the foetus and may be teratogenic. The effect of the new thrombopoietin receptor agonists on foetuses is unknown and hence not recommended.

Cytotoxic drugs such as vincristine and cyclophosphamide are contra-indicated in pregnancy. Rituximab has been successfully used for refractory ITP in non-pregnant patients. However since it can cross the placenta and its use in pregnancy cannot be recommended unless the benefits definitely out-weigh the risks[8].

Splenectomy is effective but should be done in the second trimester for refractory cases[9].

Management of delivery

The incidence of neonatal thrombocytopenia is low[10]. ITP in the mother is not an indication for Caesarean Section, and the mode of delivery should be guided by obstetric indications. Foetal scalp blood sampling may result in a falsely low platelet count. The risks of foetal platelet count determination exceed that of foetal intracranial haemorrhage and hence a foetal platelet count measurement is not recommended[11]. The best predictor of thrombocytopenia at birth is the platelet count at birth of an older sibling[12]. Caesarean Section would be the choice if an older sibling has thrombocytopenia at birth.

Epidural anaesthesia

The risk of spinal haematoma is increased in patients with thrombocytopenia[13] and the current recommendations are to withhold spinal anaesthesia if the platelet count is less than 80 x 10^9/L[14]. For patients who have platelet counts below the limit and require epidural anaesthesia, short-term corticosteroids or IVIG may be considered. Platelet transfusion is not safe to prepare the mother for spinal anaesthesia because the platelet increment is short-lived.

Management of other causes of thrombocytopenia

Diagnoses other than ITP or gestational thrombocytopenia are much less common and their management is highly specialised. A close collaboration with the obstetrician is essential. Preeclampsia, the HELLP syndrome or acute fatty liver will resolve after delivery and Caesarean Section may be required if the maturity of the foetus allows. TTP or HUS requires urgent plasma exchange. Obstetric causes of DIC such as abruptio placentae,

amniotic fluid embolism or intra-uterine sepsis may pose a diagnostic challenge.

Conclusion

Gestational thrombocytopenia is the most common cause of thrombocytopenia in pregnancy and needs to be differentiated from other pathological causes. The management of ITP in pregnancy is similar to that in the non-pregnant counterpart, but the treatment choices must be safe to the foetus. The treatment goal is to maintain a safe platelet count, rather than inducing a remission.The mode of delivery must be guided by obstetrical indications. A history of ITP is not a contraindication to pregnancy, and the majority of patients deliver non-thrombocytopenic or only mildly thrombocytopenic infants. Rarer causes of thrombocytopenia may require early specialist care.

Table 1. Causes of thrombocytopenia in pregnancy

Gestational thrombocytopenia
Immune thrombocytopenic Purpura
Systemic lupus erythematosus
Anti-phospholipid syndrome
Preeclampsia
HELLP syndrome
Acute fatty liver of pregnancy
Thrombotic thrombocytopenic purpura
Haemolytic uraemic syndrome
Disseminated intravascular coagulation
Viral infection
Nutritional deficiency
Drug induced thrombocytopenia
Hereditary thrombocytopenia
Primary marrow disorders

References

1. Burrows RF, Kelton JG. Incidentally detected thrombocytopenia in healthy mothers and their infants. N Eng J Med. 1988;319(3):142-145
2. British Committee for Standards in Hematology General Hematology Task Force. Guidelines for the investigation and management of idiopathic thrombocytopenic purpura in adults, children and in pregnancy. Br J Haematol. 2003;120(4):574-596
3. Burrows RF, Kelton JG. Fetal thrombocytopenia and its relation to maternal thrombocytopenia. N Eng J Med 1993;329(20):1463
4. Sibai BM. Diagnosis and management of gestational hypertension and preeclampsia. Obstet Gynecol 2003;102(1):181
5. O'Brien JM, Barton JR. Controversies with the diagnosis and management of HELLP syndrome. Clin Obstet Gynecol 2005;48(2):460
6. Provan D, Stasi R, Newland AC, et al. International consensus report on the investigation and management of primary immune thrombocytopenia. Blood. 2010;115(2):168-186
7. Alstead EM, Ritchie JK, Lennard-Jones JE, et al. Safety of azathioprine in pregnancy in inflammatory bowel disease. Gastroenterology. 1990;99(2):443-446
8. Herold M, Schnohr S, Bittrich H. Efficacy and safety of a combined rituximab chemotherapy during pregnancy. J Clin Oncol. 2001;19(14):3439
9. Griffiths J, Sia W, Shapiro AM, et al. Laparoscopic splenectomy for the treatment of refractory immune thrombocytopenia in pregnancy. J Obstet Gynaecol Can 2005;27(8):771
10. Fujimura K, Harada Y, Fujimoto T, et al. Nationwide study of idiopathic thrombocytopenic purpura in pregnant women and the clinical influence on neonates. Int J Hematol 2002;75(4):426
11. Garmel SH, Craigo SD, Morin LM, et al. The role of percutaneous umbilical blood sampling in the management of immune thrombocytopenic purpura. Prenat Diagn 1995;15(5):439
12. Burrows RF, Kelton JG. Pregnancy in patients with idiopathic thrombocytopenic purpura: assessing the risks for the infant at delivery. Obstet Gynecol Surv 1993;48(12):781
13. van Veen JJ, Nokes TJ, Makris M. The risk of spinal hematoma following neuraxial anesthesia or lumbar puncture in thrombocytopenic individuals. Br J Haematol. 2010;148(1): 15-25
14. Beilin Y, Zahn J, Comerford M. Safe epidural analgesia in thirty parturient with platelet counts between 69,000 and 98,000 mm(-3). Anesth Analg 1997;85(2):385

Advances in the Treatment of Haemophilia: Long-Acting Coagulation Factors

Dr Howard HN WONG
MBBS, MRCP
Resident Trainee, Department of Medicine, Pamela Youde Nethersole Eastern Hospital, Hong Kong

Dr Bonnie CS KHO
MBChB (CUHK), MRCP (UK), FHKCP, FHKAM (Medicine)
Specialist in Haematology and Haematological Oncology
Associate Consultant, Department of Medicine, Pamela Youde Nethersole Eastern Hospital, Hong Kong

Dr Howard HN WONG Dr Bonnie CS KHO

Introduction

Haemophilia, a rare inherited X-linked recessive disorder, is due to deficiency in the coagulation factor VIII (in haemophilia A) or factor IX (in haemophilia B). Patients with haemophilia present with spontaneous bleeding in joints and muscles, or excessive bleeding due to trauma or surgery. Global data showed that the incidence of haemophilia A and B is approximately 1 per 10,000 and 50,000 births respectively.[1] A survey in Hong Kong in 2011 showed that there were around 222 haemophilia patients in Hong Kong, with a crude prevalence of 6.8/100,000 male inhabitants.[2] Similar to the global data, 43% of them had severe disease and 33% moderate.

Haemophilia is diagnosed by specific factor assays for factor VIII or IX, the levels of which indicate the severity of the disease. Haemophilia can lead to repetitive bleeds into joints, and without proper treatment can result in chronic arthropathy with loss of function and deformity. The goal of treatment is to prevent and treat bleeding episodes by the administration of specific coagulation factors. The use of continuous prophylaxis, defined as the intent of treating for 52 weeks per year for a minimum of 45 weeks during the year,1 results in significantly fewer bleeding episodes and chronic arthropathy compared with on-demand treatment. The frequency of dosing in continuous prophylaxis varies between countries, but is usually three times per week for haemophilia A and twice weekly for haemophilia B. The age at the start of prophylaxis was an independent predictor of chronic arthropathy, and the early use of prophylaxis before the second joint bleed (primary prophylaxis) or after two bleeds but before the development of arthropathy (secondary prophylaxis) is the mainstay of treatment, because a joint bleed predisposes to further joint bleeds by inducing synovial hypertrophy and increased vascularity in the presence of blood in the joint. Each subsequent joint bleed thus perpetuates a vicious cycle. Radioactive or surgical synovectomy may control further bleeds in such target joints.

The local survey in 2011 also showed that the proportion of patients with moderate or severe disease on prophylactic treatment was 34% in Hong Kong, which was far lower than the figure in Sweden which was 93%. Since then, the Hong Kong Government had provided additional funding to encourage the use of factor prophylaxis for haemophilia patients. A major barrier towards treatment adherence to continuous prophylaxis is the frequency of intravenous factor injections that is daunting to many patients.

Long-acting coagulation factors

The use of coagulation factors with longer half-lives and therefore longer dosing intervals may potentially improve the patients' quality of life and their treatment adherence. The major long-acting factors being developed with three main types of designs are shown in Table 1.[3]

Table 1.

Type	Examples	Mechanism of action
Fusion with Fc fragment of Ig	rFVIIIFc, rFIXFc	Neonatal Fc-mediated recycling (Fig. 1)
Pegylation / Glycopegylation	PEG-BDD-rFVIII, BAX 855 N8-GP, N9-GP	Interference in the interactions with clearance receptors and reduced renal clearance by increasing hydrodynamic size
Fusion with albumin	F-IX-FP	Neonatal Fc-mediated recycling

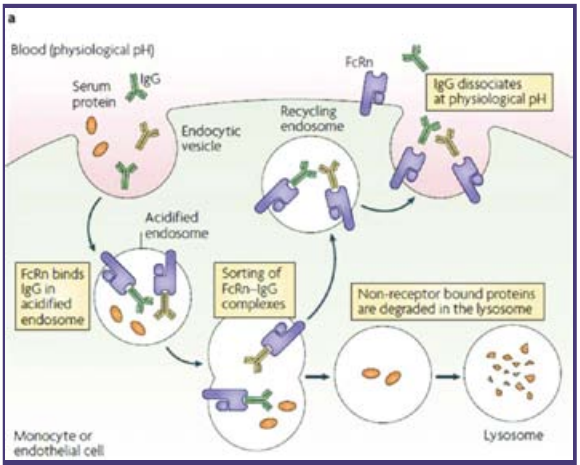


Fig 1.
IgG is taken up into the cell by pinocytosis; Fc domain of IgG binds to neonatal Fc receptors (FcRn) in the endosome at pH 6.0; IgG is protected whereas unprotected proteins are degraded by lysosomes; IgG is released into blood at physiological pH.

In March 2014, the Food and Drug Administration approved rFIXFc for the treatment of haemophilia B. In June 2014, rFVIIIFc for haemophilia A was also approved for the "control and prevention of bleeding episodes, perioperative management and routine

prophylaxis in adults and children". The approvals were based on the A-LONG and B-LONG studies which demonstrated efficacy and safety in the treatment of haemophilia A and B, in which the initial dosing intervals for prophylaxis were every 3 to 5 days for rVIIIFc in haemophilia A, and every 7-10 days for rFIXFc in haemophilia B.[4,5] In the last 3 months of the studies, the median dosing interval in the prophylaxis group in the A-LONG study was 3.5 days, which was similar to the initial dosing interval. On the other hand, in the B-LONG study, some patients had a dosing interval of 14 days or more, achieving a significant improvement over the usual twice weekly regimen in haemophilia B. In the treatment of bleeding episodes, both drugs were able to resolve bleeding with a single injection in about 90% of the cases.

Inhibitor formation is a concern in the use of coagulation factors in haemophilia, and no inhibitor titre was detected in the A-LONG or B-LONG study. Non-neutralising antibodies were detected in 14 out of 288 subjects (5%), in whom all were of low-titre and did not have clinical impact. The safety profiles were favourable with no serious adverse events noted.

Long-acting recombinant factors VIII and IX engineered with pegylation and albumin fusion are currently being studied in phase II/III trials.

Gene therapy

One of the major advances in the treatment of haemophilia is gene therapy, which is a potential curative treatment for haemophilia. The large FVIII gene represents a major hurdle to gene therapy, and the current research is concentrated on haemophilia B due to the relatively small size of the FIX gene. The intravenous infusion of adeno-associated virus 8 as a vector expressing factor IX gene was able to achieve a stable factor IX baseline level of 2% in human subjects with severe haemophilia, essentially converting severe haemophilia into moderate haemophilia. However, the response declined after a median of 15 months due to T-cell mediated attack on the transfected liver cells. Strategies to tackle the limited response duration are being studied, including immunosuppression, using an alternative vector serotype or an engineered viral capsid variant.

Summary

Long acting recombinant factors were shown to be safe and efficacious in both the treatment and prevention of bleeding episodes with the benefit of a less demanding injection frequency, especially in the case of rFIXFc which was able to prolong the typical dosing interval from every 3-4 days up to every 14 days or more. The long-term data on safety and efficacy, as well as the cost of the new drug, remain to be seen. There have been reports of hypersensitivity reactions to pegylated long-acting factors, but not in Fc or albumin fusion products.

Currently the use of continuous prophylaxis in adults is not a standardised practice but it is highly advocated for selected patients because in addition to the benefit of joint protection, prophylaxis allows an active leisure life in which sport activities can be enjoyed by patients with good joint condition, whereas patients with existing joint problems may undergo more intensive physical rehabilitation while on prophylaxis. There is physical and mental stress induced by the use of prophylaxis due to the associated pain and the need of strict adherence, but potentially the advent of long-acting coagulation factors can help alleviate such stress, leading to better physical and mental quality of life.

References

1. Makris M, Kasper C. The World Federation of Hemophilia guideline on management of haemophilia. Haemophilia: the official journal of the World Federation of Hemophilia 2013;19:1.
2. Au WY, Lee V, Kho B, et al. A synopsis of current haemophilia care in Hong Kong. Hong Kong medical journal 2011;17:189-94.
3. Shapiro AD. Long-lasting recombinant factor VIII proteins for hemophilia A. Hematology Am Soc Hematol Edu Program. 2013:37-43.
4. Mahlangu J. Phase 3 study of recombinant factor VIII Fc fusion protein in severe hemophilia A. Blood 2014;123(3):317-25.
5. Powell JS. Phase 3 Study of Recombinant Factor IX Fc Fusion Protein in Hemophilia B. The New England Journal of Medicine. 2013;369 :2313-23.

REVOLADE™
(eltrombopag olamine)

gsk

Compensated advanced liver disease with chronic hepatitis C

Rx REVOLADE to help patients with hepatitis C-associated thrombocytopenia achieve SVR with pIFN-based therapy[1,2]

Boost platelets[2]

- 95% of patients with low platelet counts were able to initiate pIFN-based therapy with REVOLADE[2]

Enable pIFN[1]

- REVOLADE enabled patients to maintain a platelet count* suitable for optimal pIFN-based therapy[1]

Enhance SVR opportunities[1,2]

- Significantly more patients treated with REVOLADE plus pIFN-based therapy achieved SVR compared with placebo[1,2]

*Platelet counts ≥50,000/μL.

REVOLADE™
(eltrombopag olamine)

REVOLADE Integrated Safety Information

Contraindications:
- Hypersensitivity to eltrombopag or to any of the excipients.

Warnings and Precautions:
- Eltrombopag administration can cause abnormal liver function. Increases in serum alanine aminotransferase (ALT), aspartate aminotransferase (AST) and bilirubin were observed
- Eltrombopag should be discontinued if ALT levels increase (≥ 3X ULN in patients with normal liver function or ≥ 3X baseline in patients with pre-treatment elevations in transaminases) and are: progressive, or persistent for ≥ 4 weeks, or accompanied by increased direct bilirubin, or accompanied by clinical symptoms of liver injury or evidence for hepatic decompensation
- Thrombotic/Thromboembolic complications might occur in patients with ITP and HCV receiving interferon-based therapy
- Eltrombopag should not be used in patients with hepatic impairment (Child-Pugh score ≥ 5) unless the expected benefit outweighs the identified risk of portal venous thrombosis
- Interactions are expected with pravastatin, simvastatin and lovastatin, however, clinically significant interactions are not expected between eltrombopag and atorvastatin or fluvastatin
- Concomitant administration of eltrombopag and OATP1B1 (e.g. methotrexate) and BCRP (e.g. topotecan and methotrexate) substrates should be undertaken with caution
- Antacids, dairy products and other products containing polyvalent cations, such as mineral supplements, must be administered at least four hours apart from eltrombopag dosing to avoid significant reduction in eltrombopag absorption due to chelation
- No dose adjustment is required for thrombocytopenic patients with chronic HCV and mild hepatic impairment (Child-Pugh score ≤ 6).

The following adverse events have been reported with a frequency of ≥1/100 to 1/10 (common) and ≥1/10 (very common)

ITP:

Very common: Headache

Common: Insomnia, Paraesthesia, Cataract, Dry eye, Nausea, Diarrhoea, Constipation, Abdominal pain upper, Alanine aminotransferase increased, Aspartate aminotransferase increased, Blood bilirubin increased, Hyperbilirubinaemia, Hepatic function abnormal, Rash, Pruritus, Alopecia, Arthralgia, Myalgia, Muscle spasm, Bone pain, Fatigue, Oedema peripheral

HCV (in combination with anti-viral interferon and ribavirin therapy):

Very common: Anaemia, Decreased appetite, Insomnia, Headache, Cough, Nausea, Diarrhoea, Pruritus, Alopecia, Myalgia, Pyrexia, Fatigue, Influenza like illness, Asthenia, Chills, Oedema peripheral

Common: Urinary tract infection, Upper respiratory tract infection, Bronchitis, Nasopharyngitis, Influenza, Oral herpes, Gastroenteritis, Pharyngitis, Hepatic neoplasm malignant, Lymphopenia, Haemolytic anaemia, Hyperglycaemia, Abnormal loss of weight, Depression, Anxiety, Sleep disorder, Dizziness, Disturbance in attention, Dysgeusia, Hepatic encephalopathy, Lethargy, Memory impairment, Paraesthesia Confusional state, Agitation, Cataract, Retinal exudates, Dry Eye, Ocular icterus, Retinal haemorrhage, Vertigo, Palpitations, Dyspnoea, Oropharyngeal pain, Dyspnoea exertional, Productive cough, Vomiting, Ascites, Abdominal pain, Abdominal pain upper, Dyspepsia, Dry mouth, Constipation, Abdominal distension, Toothache, Stomatitis, Gastrooesophageal reflux disease, Haemorrhoids, Abdominal discomfort, Gastritis, Varices oesophageal, Aphthous stomatitis, Oesophageal varices haemorrhage, Hyperbilirubinaemia, Jaundice, Portal vein thrombosis, Hepatic failure, Rash, Dry skin, Eczema, Rash pruritic, Erythema, Hyperhidrosis, Pruritus generalised, Night sweats, Skin lesion, Arthralgia, Muscle spasms, Back pain, Pain in extremity, Musculoskeletal pain, Bone pain, Irritability, Pain, Malaise, Injection site reaction, Non-cardiac chest pain, Oedema, Injection site rash, Chest discomfort, Injection site pruritus, Blood bilirubin increased, Weight decreased, White blood cell count decreased, Haemoglobin decreased, Neutrophil count decreased, International normalised ratio increased, Activated partial thromboplastin time prolonged, Blood glucose increased, Blood albumin decreased, Electrocardiogram QT prolonged

Please refer to the full prescribing information for further information and prior to administration.

REVOLADE™ 利復凝™ Abbreviated Prescribing Information

Indications For adult chronic immune (idiopathic) thrombocytopenic purpura (ITP) splenectomised patients who are refractory to other treatments (e.g. corticosteroids, immunoglobulins); Second line treatment for adult non-splenectomised patients where surgery is contraindicated. For adult patients with chronic hepatitis C virus (HCV) infection for the treatment of thrombocytopenia, where the degree of thrombocytopenia is the main factor preventing the initiation or limiting the ability to maintain optimal interferon-based therapy. **Dosage and administration** ITP: Revolade dosing must be individualised based on the patient's platelet counts. The objective of treatment with Revolade should not be to normalise platelet counts but to maintain platelet counts above the level for haemorrhagic risk. Measurable elevations in platelet counts take 1-2 weeks. *Adults* Recommended starting dose: 50 mg once daily. Patients of East Asian ancestry: initiate at 25 mg once daily. Adjust the dose to achieve and maintain a platelet count ≥ 50,000/μl as necessary to reduce the risk for bleeding. Do not exceed 75 mg daily. Clinical haematology and liver tests should be monitored regularly throughout therapy with Revolade and the dose regimen of Revolade modified based on platelet counts. CBCs should be assessed weekly until a stable platelet count (at least 4 weeks) is achieved and monthly thereafter. The lowest effective dosing regimen to maintain platelet counts should be used as clinically indicated. Discontinue treatment if the platelet count does not increase to a level sufficient to avoid clinically important bleeding after 4 weeks of Revolade 75 mg once daily. If the use of Revolade is deemed necessary in patients with moderate to severe hepatic impairment, the starting dose must be 25 mg once daily, wait 3 weeks before increasing the dose. HCV: Revolade treatment should be initiated and remain under the supervision of a physician who is experienced in the treatment of haematological diseases or the management of chronic hepatitis C and its complications. *Adults* Recommended starting dose: 25 mg once daily. No dosage adjustment is necessary for HCV patients of East Asian ancestry or patients with mild hepatic impairment. The dose of eltrombopag should be adjusted in 25 mg increments every 2 weeks as necessary to achieve the target platelet count required to initiate anti-viral therapy. Platelet counts should be monitored every week prior to starting antiviral therapy. On initiation of antiviral therapy the platelet count may fall, so immediate eltrombopag dose adjustments should be avoided. During antiviral therapy, the dose of eltrombopag should be adjusted as necessary to avoid dose reductions of peginterferon due to decreasing platelet counts that may put patients at risk of bleeding. Platelet counts should be monitored weekly during antiviral therapy until a stable platelet count is achieved, normally around 50,000-75,000/μl. CBCs including platelet counts and peripheral blood smears should be obtained monthly thereafter. Dose reductions on the daily dose by 25 mg should be considered if platelet counts exceed the required target. Wait 2 weeks to assess the effects of this and any subsequent dose adjustments. Do not exceed a dose of 100 mg eltrombopag once daily. Not recommended for children and adolescents below age 18. Revolade should be taken at least 4 hours before or after any products such as antacids, dairy products, or mineral supplements containing polyvalent cations. **Contraindications** Hypersensitivity to eltrombopag or to any of the excipients. **Warnings and precautions** Hepatic decompensation (use with interferon). Risk of hepatotoxicity. Thrombotic/ Thromboembolic complications. Bleeding following discontinuation of eltrombopag. Bone marrow reticulin formation and risk of bone marrow fibrosis. Progression of existing Myelodysplastic Syndromes (MDS). Ocular changes. QT/QTc prolongation. Loss of response to eltrombopag. Use a lower starting dose and monitor closely for patients with hepatic impairment. **Interactions** HMG CoA reductase inhibitors. OATP1B1 and BCRP substrates. Cytochrome P450 substrates. CYP1A2 and CYP2C8 inhibitors and inducers. HCV Protease Inhibitors, polyvalent cations. Food interactions. Lopinavir/ ritonavir. Platelet counts should be monitored when combining eltrombopag with other medicinal products for the treatment of ITP in order to avoid platelet counts outside of the recommended range. **Pregnancy and lactation** Revolade is not recommended during pregnancy and in women of childbearing potential not using contraception. It is not known whether eltrombopag / metabolites are excreted in human milk. **Adverse reactions ITP or HCV:** headache, anaemia, decreased appetite, insomnia, cough, nausea, diarrhoea, alopecia, pruritus, myalgia, pyrexia, fatigue, influenza like illness, asthenia, chills and peripheral oedema. **ITP:** Paraesthesia, Cataract, Dry eye, constipation, abdominal pain upper, Alanine aminotransferase increased*, Aspartate aminotransferase increased*, rash, arthralgia, muscle spasm, bone pain. **HCV** (in combination with anti-viral interferon and ribavirin therapy): Urinary tract infection, upper respiratory tract infection, bronchitis, nasopharyngitis, oral herpes, gastroenteritis, pharyngitis, hepatic neoplasm malignant, lymphopenia, haemolytic anaemia, hyperglycaemia, abnormal loss of weight, depression, anxiety, sleep disorder, confusional state, agitation, dizziness, disturbance in attention, dysgeusia, hepatic encephalopathy, lethargy, memory impairment, paraesthesia, cataract, retinal exudates, dry eyes, ocular icterus, retinal haemorrhage, vertigo, palpitations, dyspnoea, oropharyngeal pain, dyspnoea exertional, productive cough, Vomiting, Ascites, Abdominal pain, Abdominal pain upper, Dyspepsia, Dry mouth, Constipation, Abdominal distension, Toothache, Stomatitis, Gastrooesophageal reflux disease, Haemorrhoids, Abdominal discomfort, Gastritis, Varices oesophageal, Aphthous stomatitis, Oesophageal varices haemorrhage, Hyperbilirubinaemia, Jaundice, Portal vein thrombosis, Hepatic failure, Rash, Dry skin, Eczema, Rash pruritic, Erythema, Hyperhidrosis, Pruritus generalised, Night sweats, Skin lesion, Arthralgia, Muscle spasms, Back pain, Pain in extremity, Musculoskeletal pain, Bone pain, Irritability, Pain, Malaise, Injection site reaction, Non-cardiac chest pain, Oedema, Injection site rash, Chest discomfort, Injection site pruritus, Blood bilirubin increased, Weight decreased, White blood cell count decreased, Haemoglobin decreased, Neutrophil count decreased, International normalised ratio increased, Activated partial thromboplastin time prolonged, Blood glucose increased, Blood albumin decreased, Electrocardiogram QT prolonged. *Increase of alanine aminotransferase and aspartate aminotransferase may occur simultaneously, although at a lower frequency. **Overdose** In clinical trials there was one report of overdose where the subject ingested 5000mg of eltrombopag. Reported adverse events included mild rash, transient bradycardia, fatigue and elevated transaminases. Because eltrombopag is not significantly renally excreted and is highly bound to plasma proteins, haemodialysis would not be expected to be an effective method to enhance the elimination of eltrombopag. Please refer to the full prescribing information before prescribing. Full prescribing information is available upon request. Abbreviated PI (06 EMEA/H/C/1110/X/0012/G)

Please read the full prescribing information prior to administration, available from GlaxoSmithKline Limited.
Full Prescribing Information is available upon request.
For adverse event reporting, please call GlaxoSmithKline Limited at (852) 9046 2498.
Revolade and 利復凝 are trade marks of the GSK group of companies.
The material is for the reference and use by healthcare professionals only.

References:
1. Giannini EG et al. Expert Opin Pharmacother 2013;14:669-678.
2. REVOLADE Hong Kong Prescribing Information 2013

GlaxoSmithKline Limited
23/F, Tower 6, The Gateway, 9 Canton Road, Tsimshatsui, Kowloon, Hong Kong

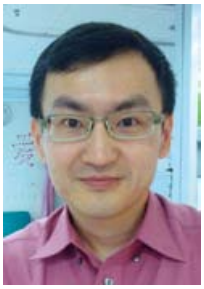
HKRXELT/0013/14(IN/2014)

Platelet Transfusion – Is it the Answer?

Dr Chung-yin HA

MBBS, FRCP, FHKAM (Medicine)

Resident Specialist, Department of Medicine and Geriatrics, Tuen Mun Hospital



Dr Chung-yin HA

Case 1

A 22-year-old woman was admitted for recurrent epistaxis and gum bleeding in the past few days; her last menses 2 weeks ago was also reported to be heavier than usual. Her first CBC showed severe thrombocytopenia with a platelet count of 5 x 10^9/L. Platelet transfusion was arranged; but her platelet count failed to rise after repeated transfusions and her bleeding symptoms persisted after 2 days. What went wrong?

Case 2

A 59-year-old man was admitted for fever and mild jaundice for 2 days. He did not have any abdominal pain. His CBC showed a normochromic normocytic anaemia with Hb 9.0g/dL and severe thrombocytopenia with a platelet count of 5 x 10^9/L; his liver function test showed elevated bilirubin but normal ALP/ALT. He was given platelet transfusion but developed generalized tonic clonic seizure shortly afterwards. What went wrong?

Approach to thrombocytopenia

Platelets are produced from megakaryocytes in the bone marrow. They circulate in the peripheral blood with an average life span of 7 days, and play an important role in haemostasis by forming the initial platelet plug at the sites of blood vessel injury, releasing several important mediators of clotting, and providing the surface for coagulation factors in the formation of a fibrin clot. The reference range for normal platelet count differs slightly among laboratories. Generally, a level of less than 150 x 10^9/L would be reported as thrombocytopenia; but usually a significant bleeding tendency would not be observed unless the count drops below 50 x 10^9/L.

Thrombocytopenia is a commonly encountered clinical condition, which may occur in isolation or in combination with anaemia and/or leucopenia. Aside from the concern of bleeding complications, it adds to the complexity of patient care in conditions such as planning for a major operation or in pregnancy. The management strategy would depend largely on the cause and the severity of thrombocytopenia; therefore every effort should be made to work out the underlying cause as soon as possible, which can usually be achieved by a detailed history-taking, thorough physical examination and the use of various investigation procedures. Major causes of thrombocytopenia is given in Table 1.

Table 1 – Causes of thrombocytopenia

Decreased production of platelets
- Bone marrow failure syndromes
  - Congenital (e.g. Fanconi's anaemia, amegakaryocytic thrombocytopenia, thrombocytopenia-absent radii syndrome, Wiskott-Aldrich Syndrome)
  - Acquired (e.g. aplastic anaemia)
- Myelodysplastic syndrome
- Bone marrow infiltration (neoplastic, infectious)
- Chemotherapy-induced
- Radiation-induced
- Alcoholism
- Severe vitamin B12 or iron deficiency

Increased clearance of platelets
- Immune thrombocytopenic purpura
- Heparin-induced thrombocytopenia
- Thrombotic thrombocytopenic purpura / haemolytic uraemic syndrome
- Disseminated intravascular coagulation
- Post-transfusion purpura
- Von Willebrand disease, type IIB
- Mechanical destruction (e.g. heart valve dysfunction, extracorporeal bypass)

Increased sequestration of platelets
- Hypersplenism

Other conditions
- Artefactual (pseudothrombocytopenia)
- Drug-induced thrombocytopenia
- Gestational thrombocytopenia
- Haemophagocytosis

Bleeding in thrombocytopenia is typically "mucocutaneous" (skin petechiae / ecchymoses, epistaxis, gingival and conjunctival bleeding), whereas internal organ involvement such as gastrointestinal or central nervous system (CNS) bleeding is uncommon unless with severe thrombocytopenia. The type and extent of bleeding, rate of onset and duration of symptoms should be noted. The past medical and social history may reveal the presence of liver disease or HIV infection, while symptoms such as unexplained skin rash or recurrent arthritis may indicate systemic autoimmune diseases as the cause of the thrombocytopenia. A history of blood or platelet transfusion may not only suggest the chronic or recurrent nature of cytopenia, but also the more remote possibility of blood-transmitted infections such as hepatitis or HIV acquired in the distant past. The presence of constitutional symptoms would be a hint to a system cause or process such as infection, malignancy or inflammatory disorders. The presence of neurological symptoms such as confusion or seizure should raise the suspicion of thrombotic thrombocytopenic purpura (TTP) in addition to the differential diagnosis of CNS bleeding. In paediatric or younger patients with a chronic history of bleeding, congenital bone marrow failure

syndromes have to be considered. The family history has to be noted. Moreover, many drugs have been reported to cause thrombocytopenia through various mechanisms (Table 2); a drug history has to be taken to see if they have a role in causing the thrombocytopenia.

Table 2 – Drugs commonly reported to cause thrombocytopenia

Antimicrobials
- Beta-lactams
  - Penicillin
  - Ampicillin
  - Piperacillin
  - Ceftazidime
- Sulphamethoxazole
- Anti-mycobacterial drugs
  - Rifampicin
  - Isoniazid
- Vancomycin
- Linezolid
- Quinine

Anticonvulsants
- Valproic acid
- Phenytoin
- Carbamazepine

Non-steroidal anti-inflammatory drugs
- Diclofenac
- Ibuprofen
- Indomethacin
- Mefanamic acid
- Sulindac
- Piroxicam

Others
- Gold salts
- Furosemide
- Amitriptyline
- Ranitidine
- Diazepam
- Iodinated contrast agent

The physical examination should focus on determining the extent of bleeding as well as looking for any feature of associated diseases. All petechial skin rash or bruises should be clearly documented. System reviews should be performed to look for features of internal bleeding. In severe thrombocytopenia the optic fundi should be examined as retinal haemorrhage reflects the risk of CNS bleeding. The presence of stigmata of chronic liver disease, skin rash, arthritis, lymphadenopathy or hepatosplenomegaly might suggest the cause of the thrombocytopenia and directs further investigations.

Initial investigations for thrombocytopenia would include a complete blood count (CBC) with white cell differentials. A blood smear is important to exclude pseudothrombocytopenia due to in-vitro platelet clump formation, and to assess for blood cell features that would suggest the cause of the thrombocytopenia (e.g. schistocytes or red cell fragments in TTP; hypersegmented neutrophils in vitamin B12 deficiency; large platelets in certain thrombocytopathies) or the presence of abnormal cells (e.g. blasts in acute leukaemia). Baseline liver and renal function tests should be done. Additional blood tests such as hepatitis serology, autoimmune markers, HIV testing and vitamin B12 / folate assays should be performed according to the history and clinical findings. A bone marrow examination is indicated when marrow pathology (e.g. myelodysplastic syndrome; aplastic anaemia; haematological malignancy or other malignant infiltration) is suspected. Although a bone marrow biopsy is generally not required for the diagnosis of idiopathic thrombocytopenia (ITP), it is recommended in cases of poor treatment responses to initial ITP therapy or before splenectomy.

General considerations in platelet transfusion

Advances in modern medical technology have undoubtedly made platelet transfusions more easily accessible, which in turn have supported the development of intensive chemotherapy regimes and bone marrow transplantation for haematoligical and various malignancies. Globally a slow and progressive increase in platelet concentrate consumption is observed. However, the use of platelet transfusion is not without risks or costs. Risks associated with platelet transfusion include allergic reactions, febrile non-haemolytic transfusion reactions, HLA-alloimmunisation with subsequent platelet refractoriness, post-transfusion purpura, transmission of blood-borne infections, transfusion-related acute lung injury, immunomodulation and sepsis caused by bacterial contamination. Since platelet products are stored at room temperature to preserve their function, bacterial contamination and overgrowth has been a serious and common problem before the introduction of bacterial surveillance in the blood donation process. Yet, the risk is not completely eliminated. Like in many countries, the blood donation programme in Hong Kong is on a non-remunerated basis; but heavy expenses are incurred in the collection, processing, storage and distribution of blood products. Since platelet units have a shelf life of only 5 days, the increase in platelet consumption caused by the ageing population has overstressed the supply worldwide. For all these reasons, the indication for platelet transfusion should be justified similar to all other medical therapies and evidence based transfusion practices should be promoted. Liberal prescription without balancing its risks and benefits should be discouraged.

Platelet transfusion can be prophylactic (for prevention of bleeding) or therapeutic (for treatment of bleeding) in patients with thrombocytopenia. One should always note that not every thrombocytopenic patient requires platelet transfusion support. Transfusion should never replace the workup for and treatment of the underlying cause of thrombocytopenia.

In general it is agreed that in the therapeutic setting, platelet transfusion can be given together with other measures to aim at a platelet count of above 50 x 10^9/L in thrombocytopenic patients with significant bleeding, such as gastrointestinal or post-operative bleeding. The target should be raised to above 100 x 10^9/L in cases of CNS bleeding. Thrombotic thrombocytopenia purpura (TTP) and heparin-induced thrombocytopenia (HIT) are the two conditions in which platelet transfusion is contra-indicated except in life threatening haemorrhages. Despite the thrombocytopenia, these two conditions are associated with an increased risk of thrombotic complications; studies have shown that platelet transfusions in these patients were associated with increased mortality by thrombotic events such as myocardial infarction and ischaemic stroke. In the rare patients with TTP or HIT with severe bleeding, an

expert opinion should be sought and the management should be individualised.

On the other hand, there are many debates surrounding the clinical value and use of prophylactic platelet transfusion in thrombocytopenic yet non-bleeding patients due to the scarcity of large-scale randomised studies. Studies have only demonstrated the value of prophylactic platelet transfusion in the setting of haematological malignancy and bone marrow transplantation. As a result, many recommendations in the currently available guidelines are based on clinical observation and consensus opinions. Over many decades a threshold for prophylactic platelet transfusion at 20 x 10^9/L has been recommended; however later studies suggested that spontaneous bleeding due to thrombocytopenia alone was unlikely to occur at platelet counts above 10 x 10^9/L. Recent data revealed that it was probably safe to further reduce the threshold to 5 x 10^9/L, but this would very much depend on the accuracy of the automated cell counters at such low platelet levels. Despite this, the value of prophylactic platelet transfusion over therapeutic transfusion in other thrombocytopenic conditions has never been proven. In cases of thrombocytopenia due to enhanced peripheral consumption, prophylactic platelet transfusion is unlikely to be useful and can be harmful in conditions such as TTP and HIT as discussed above. The recommended "trigger level" for prophylactic platelet transfusion in several specific conditions would be discussed below.

Prophylactic platelet transfusion in specific conditions

1. Bone marrow failure

In acute leukaemia, thrombocytopenia is related to marrow failure, or therapy such as chemotherapy or irradiation. Except in acute promyelocytic leukaemia (APML), it is generally recommended that prophylactic transfusion should be given to maintain a platelet count above 10 x 10^9/L; or a higher target above 20 x 10^9/L if there is fever or sepsis. In APML the bleeding risk is higher due to the frequent co-existence of coagulopathy. Therefore a threshold of 20 x 10^9/L is recommended by many experts, while some centres recommend an even higher level of 50 x 10^9/L because of concomitant disseminated intravascular coagulation (DIC).

On the other hand, in conditions of chronic failure in platelet production (e.g. in myelodysplastic syndrome or aplastic anaemia), many patients could remain free of haemorrhage even with severe thrombocytopenia. For these patients, it is reasonable to withhold prophylactic platelet transfusion and monitor the patients and adopt therapeutic platelet transfusion strategy for minimising the risk of HLA-alloimmunisation and development of platelet transfusion refractoriness.

2. Immune thrombocytopenia

Because of the enhanced platelet destruction, platelet transfusion alone would unlikely lead to a sustained platelet count increment, and is therefore generally not recommended. Instead, the use of drugs to suppress the abnormal immune destructive process (e.g. corticosteroids, intravenous immunoglobulin) should be considered in patients with a platelet count less than 30 x 10^9/L or with bleeding. Prophylactic platelet transfusion has essentially no role and therapeutic platelet transfusion in adjunct to drug treatment is indicated in major bleedings.

3. Prophylaxis for surgery

Because of the difficulty in carrying out an objective clinical study, suggestions in this area are mainly based on expert opinions. Platelet support is generally not required in bone marrow biopsy even in severe thrombocytopenia given that sufficient surface pressure is applied. For lumbar puncture, epidural anaesthesia, insertion of central lines, endoscopy with anticipated biopsy, liver biopsy, laparotomy and similar procedures, the BCSH guideline recommends that the platelet count should be increased to at least 50 x 10^9/L. For operations involving the brain or eyes, a target platelet level of 100 x 10^9/L is suggested.

4. Disseminated intravascular coagulation (DIC)

In the absence of bleeding, platelet transfusion is not indicated. It is indicated for patients with bleeding for whom a target level of 50 x 10^9/L is encouraged, the same level as recommended in other bleeding conditions. Correcting the underlying cause of DIC (e.g. severe sepsis) should be considered more important than just correcting the numerical count.

5. Platelet function disorder

Patients with platelet function disorders, inherited or acquired, usually do not have thrombocytopenia and a target platelet level cannot be recommended. Considering the fact that even patients with Glanzmann's thrombasthenia (a type of inherited disorder with severe impaired platelet function) seldom have severe bleeding tendency, the routine use of platelet transfusion in not justified except for bleeding. In patients taking anti-platelet agents, such as aspirin or clopidogrel, the use of these agents should be reviewed or withheld before invasive procedures. In uraemic patients, the correction of a low haematocrit to > 0.35 or the use of Desmopressin (DDAVP) can improve the platelet function.

Going back to our cases…

Case 1 Investigations including blood smear, autoimmune markers, hepatitis and HIV serology were all normal. She was treated as idiopathic thrombocytopenia purpura (ITP) with oral corticosteroids. Her platelet count increased to > 50 x 10^9/L after 5 days with gradual improvement in bleeding symptoms.

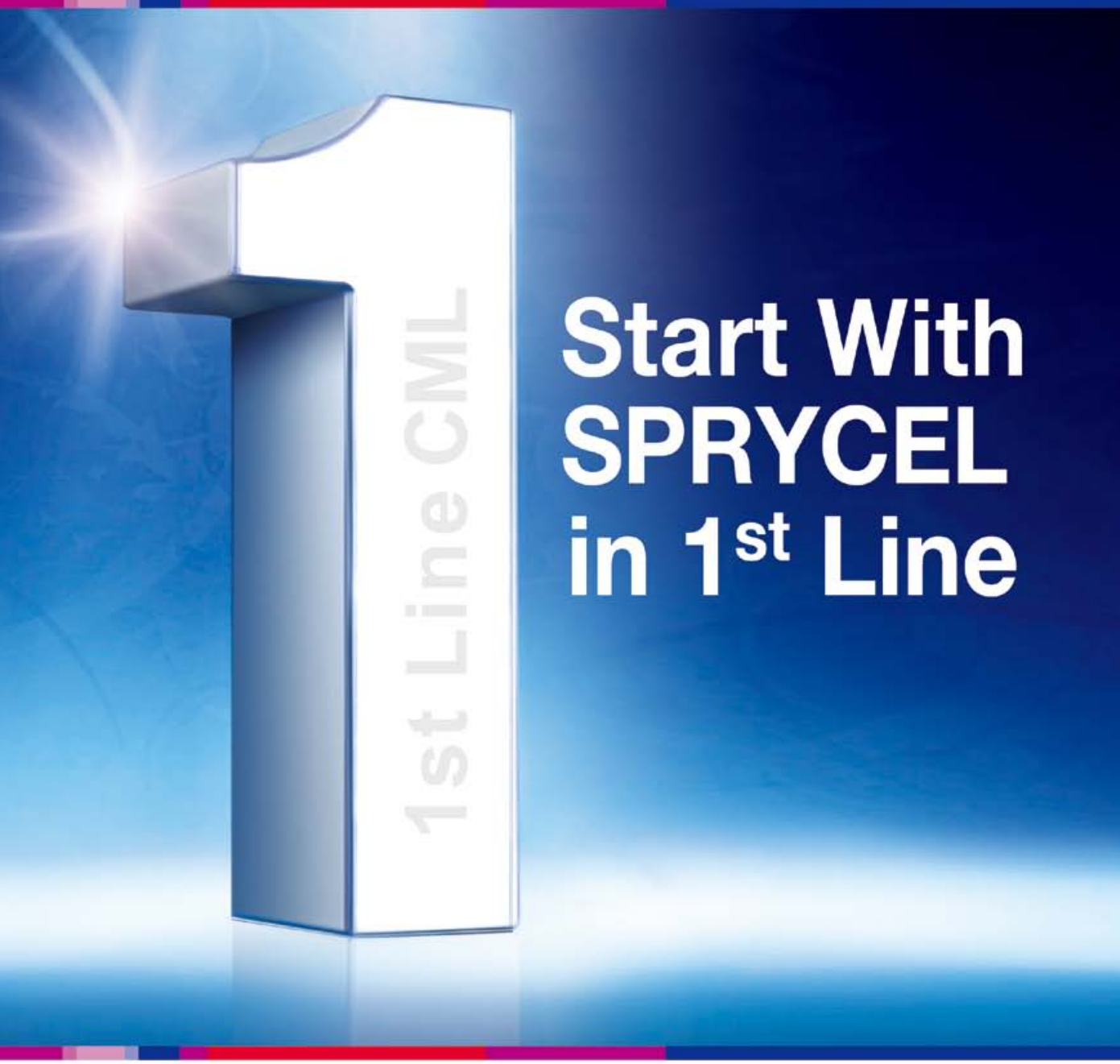
Case 2 Blood smear revealed abundant schistocytes. The diagnosis of thrombotic thrombocytopenic purpura was confirmed by the demonstration of low ADAMTS-13 antigen level and the presence of antibodies in subsequent blood tests. Plasmapheresis was immediately started and he made a slow but steady recovery.

References

1. Guidelines for the use of platelet transfusions. British Journal of Haematology, 2003, 122, 10-23.
2. Platelet transfusion for patients with cancer: clinical practice guidelines for the American Society of Clinical Oncology. Journal of Clinical Oncology, Vol 19, No 5, 2001: pp 1519-1538.
3. Evidence-based platelet transfusion guidelines. American Society of Haematology.
4. The platelet prophylactic transfusion trigger: when expectations meet reality. Transfusion, Vol 47, Feb 2007.

An Option for Adults With Newly Diagnosed Ph+ CML in Chronic Phase

Achieve Superior CCyR and MMR Rates at 12 Months vs Imatinib With the Convenient Once-Daily Dosing of SPRYCEL



Bristol-Myers Squibb Pharma (HK) Ltd.
Room 3001-3002, 30/F., Windsor House,
311 Gloucester Road, Causeway Bay, Hong Kong.
Tel: (852) 2510 6188 Fax: (852) 2510 6199

SPRYCEL™ dasatinib

SP-AD-HK140909-1409

Italian Wines

Dr Edmond SK MA

Specialist in Haematology

Dr Edmond SK MA

Drinking wine to a medical doctor is perhaps a guilty pleasure since the prevailing opinion of our profession is that alcohol consumption should be curtailed and the risk outweighs the meagre benefits if any. I however approach wine appreciation from an academic angle as pursuit of knowledge. The study of land, soil and weather (or the terroir in French) is geography, the study of viticulture is agriculture and the study of vinification process is chemistry and biology. And is there any link between molecular biology and wine? The answer I can think of is Benjamin Lewin, who is the founder of the journal *Cell* and the sole author of Genes to Genes IX (now in its eleventh edition and renamed as Lewin's Genes XI), the standard textbook in molecular biology. He has now become a Master of Wine and equally prolific, having written 'What Price Bordeaux?', 'Wine Myths and Realities' and 'In Search of Pinot Noir'. The study of wine is at least as vast as molecular biology.

Pinot Noir grapes at the Champagne region (the skin will turn red only close to harvest)

Like many other wine lovers, I started off with Bordeaux. After sometime they tasted rather similar be it the left bank or right bank and the excitement was gone, except for the occasional bottle of grand wine that caused much damage to the pocket. My interest in Italian red wines began when I read the articles by James Suckling and at that time he was still writing for Wine Spectator. The Sangiovese grape caught my attention. The grape on its own is associated with several styles of wine in the Tuscany region, namely Chianti, Brunello di Montalcino and Vino Nobile de Montepulciano, although it can also be blended with other grapes. I became fascinated by Brunello. Among the Sangiovese family, the Brunello di Montalcino shows the most complexity combined with power, concentration and personality. The wine needs time for airing. A nice bottle of Brunello shows a pleasant nose, medium body full of cherries and other fruits, and a long finish. My favourite producers are Altesino (especially Montosoli), Casanova di Neri (top cru Cerretalto), Biondi Santi, Pieve Santa Restituta (made by the Piedmont genius Angelo Gaja, both Sugarille and Rennina are excellent), Castelgiocondo (made by the famous Frescobaldi family) and Valdicava (top cru Madonna del Piano). My favourite vintage is 1997, which is now drinking very well but challenging to find and those who have patience are rewarded. In the recent past, two stories about Brunello di Montalcino hit international news. The first one was that in 2012 the cellars of cult Brunello producer Gianfranco Soldera was broken into and every litre of his wines from 2007 to 2012 were drained. It was thought to be a mafia styled personal attack on the producer himself. The second one was in 2008 when allegedly several producers were blending other grapes into Brunello that violated the DOCG regulation of 100% Sangiovese. In fact people who do not like to follow the regulations are producing pure Sangiovese as IGT wines without contravening the regulations, with successful examples such as Percalo and Fontalloro.

Tuscany is also home to the Super Tuscan red wines that I have the good opportunity of tasting extensively. It refers to the wine produced from international grape varieties such as Cabernet Sauvignon, Merlot and Syrah, either single grape or as Bordeaux styled blends, or even blending with the traditional grape of the region Sangiovese. Many of them are Cabernet Sauvignon based with a character in-between the complexity of Bordeaux and the fruitiness of Napa Valley red wines. The Super Tuscans came to fame in 1972 when Sassicaia emerged victorious in a tasting of clarets organised by Hugh Johnson for the Decanter magazine. Sassicaia, a blend of around 85% Cabernet Sauvignon and 15% Cabernet Franc, is popular in Hong Kong and the 1985 vintage that scores perfect Parker points is probably

the most expensive Italian wine. The Super Tuscan revolution owes a lot to the Antinori family. The elder brother Piero is the first one to blend Sangiovese (80%) with Cabernet (20%) to produce Tignanello, to follow with a mirror image of Tignanello in terms of grape proportion to produce the even more successful wine Solaia. The younger brother Lodovico produces Ornellaia but the real queen of his estate is a pure Merlot called Masseto, which now features regularly in wine auctions. Since Masseto is beyond approach by persons without deep pockets like me, I started to search for other Merlot wines of Tuscany. Outstanding examples are found in Redigaffi of Tua Rita, Messorio of Le Macchiole, Galatrona of Petrolo and l'Apparita of Castello di Ama. These Pomerol styled Italian wines shows soft tannins and a grassy to earthy flavour that is distinctive.

Vineyards at the Rheingau region along the picturesque river Rhine

My favourite Super Tuscans are too many to name. I used to like the Luce, which started off as a joint venture between the Frescobaldi family and Robert Mondavi, but recent vintages cannot keep up with the initial strong effort. Two cult Super Tuscan wines are worth trying. One is Tenuta di Trinoro located south of Montepulciano, especially the 2001 vintage. It is a blend of Cabernet Franc with Cabernet Sauvignon and a small amount of Petit Verdot. The other is Vigna d'Alceo of Castello dei Rampolla, a blend of Cabernet Sauvignon and Petit Verdot, especially the 1999 vintage.

Italy has a lot to offer for dessert wines, from passito wines such as vino santo, Passito di Pantelleria (e.g. Ben Rye of Donnafugata, Sicily) and recioto to Barolo Chinato. The most amazing bottle of Italian dessert wine I have had is the Solaria Jonica 1959, drank at Aimo and Nadia restaurant Milan in 2012. The year 1959 was the hottest year of the century in Puglia and the Primitivo grapes were overripe and dehydrated. The Piedmont merchant Antonio Ferrari harvested the grapes and expected to make a big alcoholic wine. However a sudden drop in temperature halted the fermentation at 14% alcohol, leaving high residual sugar. With a change in vision from producing a red wine to a sweet wine, Ferrari placed the juice for 10 years in the best Slovenian casks he could find before leaving it for another 35 years in a cement cask. Ferrari passed away and his daughter completed the journey. After 45 years, the wine boosts aromas of berries and espresso, and displays flavours of raisins and chocolate on the palate.

Having said so much about Italian wine, I have not yet touched upon the Piedmont region and the Nebbiolo grape. This will need another article to talk about. Italy as a country is the largest producer of wine in terms of volume and Sicily as a region is the largest producer within the country. However the reputation of Italian wine is somewhat tainted by the mediocre quality of most wines and the uneven performance of some of the top producers. Therefore to be able to select enjoyable wine is a matter of knowledge and experience. In general, to study wine properly and to travel to wine regions would need a lot of time and commitment and to me is an ideal pastime after retirement.

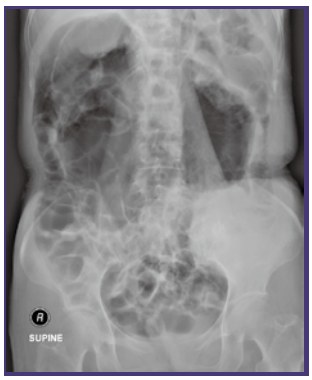
Solaria Jonica 1959

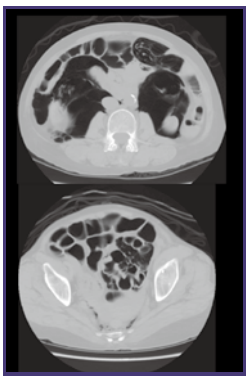
Joseph Phelps Vineyard in Napa Valley

A Patient with Acute Abdominal and Loin Pain after Workup for Anaemia

Dr Alan CS LAM

MBBS, FRCR
Department of Radiology, Queen Mary Hospital, Hong Kong





A 63 years old lady with a history of end stage renal failure and renal transplant was admitted for investigation of anaemia. After workup, she presented with acute abdominal pain.

Questions:

1. What were the X-ray and CT findings?
2. What was the most likely diagnosis?
3. Discussion.

(See P.36 for answers)

MOZOBIL®
(plerixafor injection)

Release their potential

Raise your expectations for apheresis success in NHL and MM patients with Mozobil® + G-CSF vs G-CSF alone[1,2]

Presentation: Plerixafor single-use vial solution.
Indications: In combination with granulocyte-colony stimulating factor to mobilize hematopoietic stem cells to the peripheral blood for collection and subsequent autologous transplantation in patient with non-Hodgkin's lymphoma and multiple myeloma. **Dosage:** Recommended dose 0.24 mg/kg body weight by subcutaneous injection. For dosing in renal impairment patient, please refer to full prescribing information. **Contraindications:** None **Precautions:** Tumor cell mobilization in leukemia patients. Increased circulating leukocytes and thrombocytopenia – monitor white blood cell and platelet counts during treatment. Evaluate patients who report left upper abdominal pain and/or scapular or shoulder pain for splenic integrity. Pregnancy, nursing mothers, pediatric, geriatric and renal impaired patients. **Interactions:** Not likely to have drug interactions. **Undesirable effects:** Diarrhea, nausea, fatigue, injection site reactions, headache, arthralgia, dizziness and vomiting. For uncommon, rare and very rare undesirable effects, please refer to the full prescribing information. **Preparation:** Vial 20mg/mL x 1.2 mL x 1's.
Full prescribing information is available upon request.

AP-HK-MOZ-11.08

References: 1. DiPersio JF, et al. J Clin Oncol. 2009;27(28):4767-4773. **2.** DiPersio JF, et al. Blood. 2009;113(23):5720-5726.

sanofi-aventis Hong Kong Limited
Units 706-710, Level 7, Core C, Cyberport 3, 100 Cyberport Rd, H.K.
Tel: (852) 2056 8333 Fax: (852) 2915 7760

HK-PE 14.08.01

SANOFI ONCOLOGY

HealthBaby
生寶臍帶血庫

Most Professional Accreditations
Most Recommended by O&G Doctors[1]
No.1 Cord Blood Bank[2]

HealthBaby's Cord Service Patented Technology

- **Obtained U.S. Patent**
- **Exclusively extracts the whole cord tissue**
- **Unique processing, storage and culturing techniques**
- **Enchances the cells' quantity and viability after thawing**

U.S. PATENTED

Source: 1. IMS 2010 Cord Blood Bank Market Research in Hong Kong (with Private O&G physicians) 2. Ipsos Healthcare 2009-2014 Cord Blood Bank Survey

Sunday	Monday	Tuesday	Wednesday	Thursday	Friday	Saturday
			1	2	3	★ The 8th Hong Kong Allergy Convention (HKAC 2014) – Novel Revelations in Allergies 4
★ The 8th Hong Kong Allergy Convention (HKAC 2014) – Novel Revelations in Allergies ★ RSCP Snooker Tournament 5	6	★ HKMA Yau Tsim Mong Community Network - Management of Benign Prostatic Hyperplasia in 2014 ★ HKMA New Territories West Community Network - BPH Treatment Options and Management ★ HKMA Tai Po Community Network - New Era for COPD Management - Dual Bronchodilation ★ FMSHK Officers' Meeting ★ HKMA Council Meeting 7	★ Hong Kong Neurosurgical Society Monthly Academic Meeting –Update on management of complex AVM ★ HKMA Central, Western & Southern Community Network - Certificate Course on Psychiatry (Session 3) - Management of Somatic Symptom and Related Disorders ★ HKMA Shatin Doctors Network - Common Foot and Ankle Problems 8	★ HKMA Kowloon East Community Network - The Management of Diabetes Mellitus for Geriatric Patients ★ The Hong Kong Medical Association Community Network Exercise Prescription Certificate Courses ★ HKMA Structured CME Programme with Hong Kong Sanatorium & Hospital Year 2014 - Updates on Surgical Management of Gastrointestinal Stromal Tumour 9	10	★ Refresher Course for Health Care Providers 2014/2015- Surgical minor procedures in primary care 11
★ HKMA Swimming Gala 2014 12	13	★ HKMA Kowloon West Community Network - New Era for COPF Management - Dual Bronchodilation 14	★ HKMA Shatin Doctors Network - Common Orthopaedic Conditions in Hand and Elbow 15	★ HKMA Hong Kong East Community Network - New Update for Family Doctors on Hypertension Management - JNC 8 Guideline and More ★ HKMA Kowloon East Community Netowrk - Management in Obstructive Airway Diseases: an Update ★ The Hong Kong Medical Association Community Network Exercise Prescription Certificate Courses ★ FMSHK Executive Committee Meeting 16	17	18
19	20	21	★ HKMA Central, Western & Southern Community Network - Certificate Course on Psychiatry (Session 4) - Practical Approach and Update on Management of Mood Disorder 22	★ The Hong Kong Medical Association Community Network Exercise Prescription Certificate Courses ★ FMSHK Foundation Meeting 23	24	★ OSHK A to Z symposia series: "G" – symposium Glucocorticoids, Geriatrics and Gender Specific Issues ★ KECN / HKCEP / UCH - CME Course for Health Personnel 2014 - Management of Low Back Pain 25
★ Lantau Hiking Yeam (Shek Pik to Mui Wo) 26	★ The 2014 East-West Alliance Global Symposia 27	★ The 2014 East-West Alliance Global Symposia ★ HKMA Kowloon West Community Network - Advances in the Management of Chronic Pain 28	★ HKMA Shatin Doctors Network - The Critical Impact of Dietary Protein Quality on Growth of Infants 29	★ HKMA Hong Kong East Community Network - Suggestions for Diabetic Patients with Renal Impairment ★ The Hong Kong Medical Association Community Network Exercise Prescription Certificate Courses 30	31	

Date / Time	Function	Enquiry / Remarks
4 SAT 11:45am-6:10pm	**The 8th Hong Kong Allergy Convention (HKAC 2014) – Novel Revelations in Allergies** Organiser: Hong Kong Institute of Allergy, Chairman: Dr Robert Tseng Venue: Hong Kong Convention and Exhibition Centre, Wan Chai	HKAC 2014 Secretariat Tel: 2559 9973 Fax: 2547 9528 CME points application in progress
5 SUN 8:30am-10:00pm	**The 8th Hong Kong Allergy Convention (HKAC 2014) – Novel Revelations in Allergies** Organiser: Hong Kong Institute of Allergy, Chairman: Dr Robert Tseng Venue: Hong Kong Convention and Exhibition Centre, Wan Chai	HKAC 2014 Secretariat Tel: 2559 9973 Fax: 2547 9528 CME points application in progress
12:00pm	**RSCP Snooker Tournament** Organiser:Recreation & Sports Club for Hong Kong Professional Bodies, Venue:Youth Billiard Club, Houston Centre, 63 Mody Road, Tsim Sha Tsui East, Kowloon	Mr. Andie HO Tel: 2527 8285
7 TUE 1:00pm	**HKMA Yau Tsim Mong Community Network - Management of Benign Prostatic Hyperplasia in 2014** Organiser:HKMA Yau Tsim Mong Community Network, Chairman:Dr. FONG Chun Yan, Julian, Speaker:Dr. YUNG Yee Ping, Max, Venue:Eaton, Hong Kong, 380 Nathan Road, Kowloon	Ms. Candice TONG Tel: 2527 8285 1 CME Point
1:00pm	**HKMA New Territories West Community Network - BPH Treatment Options and Management** Organiser:HKMA New Territories West Community Network, Chairman:Dr. CHEUNG Kwok Wai, Alvin, Speaker:Dr. MAN Chi Wai, Venue:Gold Coast Yacht and Country Club (黃金海岸鄉村俱樂部 – 遊艇會), 1 Castle Peak Road, Castle Peak Bay, Hong Kong	Miss Hana YEUNG Tel: 2527 8285 1 CME Point
1:45pm	**HKMA Tai Po Community Network - New Era for COPD Management - Dual Bronchodilation** Organiser:HKMA Tai Po Community Network, Speaker:Dr. CHAN Hok Sum, Venue:Chiuchow Garden Restaurant (潮江春), Shop 001-003, 1/F, Uptown Plaza (新達廣場), No. 9 Nam Wan Road, Tai Po	Ms. Iris POON Tel: 2577 0274 1 CME Point
8:00pm	**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
8:00pm	**HKMA Council Meeting** Organiser:The Hong Kong Medical Association, Chairman:Dr. SHIH Tai Cho, Louis,Venue:HKMA Head Office, 5/F, Duke of Windsor Social Service Building, 15 Hennessy Road, Hong Kong	Ms. Christine WONG Tel: 2527 8285
8 WED 7:30am	**Hong Kong Neurosurgical Society Monthly Academic Meeting –Update on management of complex AVM** Organiser: Hong Kong Neurosurgical Society, Chairman: Dr WONG Sui To, Speaker: Dr CHAN Ngo Lun, Allan, Venue: Seminar Room, Ground Floor, Block A, Queen Elizabeth Hospital	Dr. LEE Wing Yan, Michael Tel: 2595 6456 1.5 CME Points
1:00pm	**HKMA Central, Western & Southern Community Network - Certificate Course on Psychiatry (Session 3) - Management of Somatic Symptom and Related Disorders** Organisers:HKMA Central, Western & Southern Community Network, Chairman:Dr. TSANG Chun Au, Speaker:Dr. TSANG Suk Kwan, Jenny, Venue:HKMA Central Premises, Dr. Li Shu Pui Professional Education Centre, 2/F, Chinese Club Building, 21-22 Connaught Road Central, Hong Kong	Miss Hana YEUNG Tel: 2527 8285 1 CME Point
1:00pm	**HKMA Shatin Doctors Network - Common Foot and Ankle Problems** Organiser:HKMA Shatin Doctors Network, Chairman:Dr. MAK Wing Kin, Speaker:Dr. CHAN Wai Fu, Venue:Suite 710, One Grand Tower, 639 Nathan Road, Mongkok, Kowloon	Ms. Sandy CHUNG Tel: 3971 2930
9 THU 1:00pm	**HKMA Kowloon East Community Network - The Management of Diabetes Mellitus for Geriatric Patients** Organiser:HKMA Kowloon East Community Network, Chairman:Dr. MA Ping Kwan, Danny, Speaker:Dr. YIM Ting Kwan, Venue:East Ocean Seafood Restaurant (東海海鮮酒家), Shop 137, 1/F, Metro City Plaza 3, 8 Mau Yip Road, Tseung Kwan O, Kowloon	Miss Hana YEUNG Tel: 2527 8285 1 CME Point
1:30pm	**The Hong Kong Medical Association Community Network Exercise Prescription Certificate Courses** Organisers:The Hong Kong Medical Association;Department of Health, Speaker:Prof. IP Wing Yuk, Venue:Plentiful Delight Banquet, 1/F, Ho Shun Tai Building, 10 Sai Ching Street, Yuen Long	Miss Joey LEE Tel: 2527 8452 2 CME Points
2:00pm	**HKMA Structured CME Programme with Hong Kong Sanatorium & Hospital Year 2014 - Updates on Surgical Management of Gastrointestinal Stromal Tumour** Organisers:Hong Kong Medical Association and Hong Kong Sanatorium & Hospital, Speaker:Dr. Chan Chi Wai, Angus, Venue:Function Room A, HKMA Dr. Li Shu Pui Professional Education Centre, 2/F, Chinese Club Building, 21-22 Connaught Road Central, Hong Kong	HKMA CME Dept. Tel: 2527 8452 1 CME Point
11 SAT 2:15pm	**Refresher Course for Health Care Providers 2014/2015-** **Surgical minor procedures in primary care** Organisers:Hong Kong Medical Association, HK College of Family Physicians & HA-Our Lady of Maryknoll Hospital, Speaker:Dr. Chiu Ying Wah, Venue:Training Room II, 1/F, OPD Block, Our Lady of Maryknoll Hospital, 118 Shatin Pass Road, Wong Tai Sin, Kowloon	Ms. Clara Tsang Tel: 2354 2440 2 CME Points
12 SUN 2:00pm	**HKMA Swimming Gala 2014** Organiser:The Hong Kong Medical Association, Chairman:Dr. IP Man Ho, Venue:Hong Kong Polytechnic University Swimming Pool, Hung Hom	Mr. Ian KWA Tel: 2527 8285
14 TUE 1:00pm	**HKMA Kowloon West Community Network - New Era for COPF Management - Dual Bronchodilation** Organiser:HKMA Kowloon West Community Network, Chairman:Dr. LAM Ngam, Raymond, Speaker:Dr. CHAN Ka Wing, Joseph, Venue:Crystal Room I-III, 30/F, Panda Hotel, 3 Tsuen Wah Street, Tsuen Wan, N.T.	Miss Hana YEUNG Tel: 2527 8285 1 CME Point
15 WED 1:00pm	**HKMA Shatin Doctors Network - Common Orthopaedic Conditions in Hand and Elbow** Organiser:HKMA Shatin Doctors Network, Chairman:Dr. MAK Wing Kin, Speaker:Dr. TIO Man Kwun, Peter, Venue:Suite 710, One Grand Tower, 639 Nathan Road, Mongkok, Kowloon	Ms. Sandy CHUNG Tel: 3971 2930
16 THU 1:00pm	**HKMA Hong Kong East Community Network - New Update for Family Doctors on Hypertension Management - JNC 8 Guideline and More** Organiser:HKMA Hong Kong East Community Network, Speaker:Dr. WONG Bun Lap, Bernard, Venue:HKMA Wanchai Premises, 5/F, Duke of Windsor Social Service Building, 15 Hennessy Road, Wanchai	Ms. Candice TONG Tel: 2527 8285

Date / Time	Function	Enquiry / Remarks
16 THU 1:00pm	**HKMA Kowloon East Community Netowrk - Management in Obstructive Airway Diseases: an Update** Organiser:HKMA Kowloon East Community Network, Chairman:Dr. MA Ping Kwan, Danny, Speaker:Dr. CHAN Chio Ho, Michael, Venue:East Ocean Seafood Restaurant (東海海鮮酒家), Shop 137, 1/F, Metro City Plaza 3, 8 Mau Yip Road, Tseung Kwan O, Kowloon	Miss Hana YEUNG Tel: 2527 8285 1 CME Point
1:30pm	**The Hong Kong Medical Association Community Network Exercise Prescription Certificate Courses** Organisers:The Hong Kong Medical Association;Department of Health, Speakers:Prof. HUI Stanley S. C. HUI / Mr. WONG Sam W. S., Venue:Plentiful Delight Banquet, 1/F, Ho Shun Tai Building, 10 Sai Ching Street, Yuen Long	Miss Joey LEE Tel: 2527 8452 2 CME Points
8:00pm	**FMSHK Executive Committee Meeting** Organiser: The Federation of Medical Societies of Hong Kong, Veune: Council Chamber, 4/F, Duke of Windor Social Service Building, 15 Hennessy Road, Wanchai, Hong Kong	Ms. Nancy CHAN Tel: 2527 8898
22 WED 1:00pm	**HKMA Central, Western & Southern Community Network - Certificate Course on Psychiatry (Session 4) - Practical Approach and Update on Management of Mood Disorder** Organisers:HKMA Central, Western & Southern Community Network, Chairman:Dr. YIK Ping Yin, Speaker:Dr. MAK Ki Yan, BBS, JP, Venue:HKMA Central Premises, Dr. Li Shu Pui Professional Education Centre, 2/F, Chinese Club Building, 21-22 Connaught Road Central, Hong Kong	Miss Hana YEUNG Tel: 2527 8285 1 CME Point
23 THU 1:30pm	**The Hong Kong Medical Association Community Network Exercise Prescription Certificate Courses** Organisers:The Hong Kong Medical Association; Department of Health, Speakers:Mr. WONG Sam W. S. and PFA (Physical Fitness Association of Hong Kong, China) instructors, Venue:Plentiful Delight Banquet, 1/F, Ho Shun Tai Building, 10 Sai Ching Street, Yuen Long	Miss Joey LEE Tel: 2527 8452 2 CME Points
8:00pm	**FMSHK Foundation Meeting** Organiser: The Federation of Medical Societies of Hong Kong, Veune: Council Chamber, 4/F, Duke of Windor Social Service Building, 15 Hennessy Road, Wanchai, Hong Kong	Ms. Nancy CHAN Tel: 2527 8898
25 SAT 12:30pm-5:00pm	**OSHK A to Z symposia series: "G" – symposium Glucocorticoids, Geriatrics and Gender Specific Issues** Organiser: The Osteoporosis Society of Hong Kong, Chairpersons: Dr. Carmen Tze-kwan HO & Dr. Andrew Yiu-yan HO, Speakers: Dr. Lai-shan TAM, Dr. Chung-tai SY, Dr. Tai-pang IP, Venue: Grand Ballroom, 3/F Sheraton Hotel, 20 Nathan Road, Tsimshatsui, Kowloon	Ms. Cherie LI Tel: 29094802 Fax: 28905703 CME accreditation: (Pending)
1:30pm	**KECN / HKCEP / UCH - CME Course for Health Personnel 2014 - Management of Low Back Pain** Organisers:HKMA Kowloon East Community Network;Hong Kong College of Family Physicians; United christian Hospital, Chairman:Dr. David CHAO, Speakers:Dr. CHAN Wai Leung; Mr. CHOW Hon Yuen, chris;Mr. WONG Mei Fung, Agnes, Venue:Lecture Theatre, G/F, Block P, United Christian Hospital, 130 Hip Wo Street, Kwun Tong, Kowloon	Ms. Polly TAI Tel: 3513 3430 Ms. Cordy WONG Tel: 3513 3087 Fax: 3513 5505 1.5 CME Points
26 SUN 10:00am	**Lantau Hiking Yeam (Shek Pik to Mui Wo)** Chairman:Dr. SIN Pui Yee, Helena, Venue:Lantau Island	Mr. Benjamin CHAN Tel: 2527 8285
27 MON 8:00am-6:00pm (28)	**The 2014 East-West Alliance Global Symposia** Organiser: The University of Hong Kong Li Ka Shing Faculty of Medicine, Co-organisers: London School of Hygiene and Tropical Medicine and China Medical Board, Speakers: local and overseas speakers, Venue: Lecture Theatre(s), Cheung Kung Hai Conference Centre, Li Ka Shing Faculty of Medicine	Secretariat of the University of Hong Kong Li Ka Shing Faculty of Medicine Tel: 3917 9839 / 3917 9333
28 TUE 1:00pm	**HKMA Kowloon West Community Network - Advances in the Management of Chronic Pain** Organiser:HKMA Kowloon West Community Network, Chairman:Dr. CHAN Siu Man, Bernard, Speaker:Dr. Bernard LEE, Venue:Crystal Room I-III, 30/F, Panda Hotel, 3 Tsuen Wah Street, Tsuen Wan, N.T.	Miss Hana YEUNG Tel: 2527 8285 1 CME Point
29 WED 1:00pm	**HKMA Shatin Doctors Network - The Critical Impact of Dietary Protein Quality on Growth of Infants** Organiser:HKMA Shatin Doctors Network, Chairman:Dr. MAK Wing Kin, Speaker:Dr. CHENG Ling Ling, Venue:Jasmine Room, Level 2, Royal Park Hotel, 8 Pak Hok Ting Street, Shatin	Ms. Joey CHAN Tel: 2599 8895 1 CME Point
30 THU 1:00pm	**HKMA Hong Kong East Community Network - Suggestions for Diabetic Patients with Renal Impairment** Organiser:HKMA Hong Kong East Community Network, Chairman:Dr. AU YEUNG Shiu Hing, Speaker:Dr. LAM Man Fai, Venue:HKMA Wanchai Premises, 5/F, Duke of Windsor Social Service Building, 15 Hennessy Road, Wanchai	Ms. Candice TONG Tel: 2527 8285 1 CME Point
1:30pm	**The Hong Kong Medical Association Community Network Exercise Prescription Certificate Courses** Organisers:The Hong Kong Medical Association;Department of Health, Speaker:Ms. Joey CHENG, Venue:Plentiful Delight Banquet, 1/F, Ho Shun Tai Building, 10 Sai Ching Street, Yuen Long	Miss Joey LEE Tel: 2527 8452 2 CME Points

CME/CNE Course | Certificate Course for Medical, Nursing & Allied Health Professionals | Course No. C254

Certificate Course on

PET-CT Imaging in Daily Clinical Practice

Objectives:

PET-CT is one of the most widely used imaging modalities especially in clinical oncology. It is also useful in assessing various myocardial and neuro-psychiatric diseases. The course will give an overview of PET-CT status in Hong Kong, its basic principles, clinical application and recent advances. The attendees will learn how to apply PET-CT findings in daily clinical practice.

Jointly organised by

The Federation of Medical Societies of Hong Kong

Hong Kong Society of Nuclear Medicine

Date	Topics	Speakers
21 Nov	Overview of PET-CT	Dr. LOK Chiu Ming Director Nuclear Medicine & PET Centre Hong Kong Baptist Hospital
25 Nov	PET-CT in Oncology I: Head & Neck Malignancy	Dr. CHOI Pak Tat, Frankie Consultant i/c Department of Nuclear Medicine Pamela Youde Nethersole Eastern Hospital
2 Dec	PET-CT in Oncology II: Thoracic Malignancy	Dr. AU YONG Ting Kun Consultant Nuclear Medicine Unit Queen Elizabeth Hospital
9 Dec	PET-CT in Oncology III: Abdominal Malignancy	Dr. NGAI Wai Tat Consultant Department of Nuclear Medicine Pamela Youde Nethersole Eastern Hospital
16 Dec	PET-CT in Dementia	Dr. LEUNG Yim Lung Deputy Director Department of Nuclear Medicine & PET Hong Kong Sanatorium & Hospital
23 Dec	PET-CT in Lymphoma PET-CT in Cardiovascular Disease	Dr. WONG Kwong Kuen Consultant Nuclear Medicine & PET Centre Hong Kong Baptist Hospital Dr. John KUNG Associate Consultant Nuclear Medicine Unit Queen Elizabeth Hospital

Date : 21, 25 November 2014 and 2, 9, 16, 23 December, 2014
Time : 7:00 p.m. – 8:30 p.m.
Venue : Lecture Hall, 4/F., Duke of Windsor Social Service Building, 15 Hennessy Road, Wanchai, Hong Kong
Language Media : Cantonese (Supplemented with English)
Course Fee : HK$750 (6 sessions)
Certificate : Awarded to participants with a minimum attendance of 70%
Enquiry : The Secretariat of The Federation of Medical Societies of Hong Kong
Tel.: 2527 8898 Fax: 2865 0345 Email: info@fmshk.org

CME / CNE / CPD Accreditation in application

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

Hong Kong Disaster Medicine Association Ltd

The Hong Kong Disaster Medicine Association Ltd (HKDMA), established in 2004, is a charitable organisation aimed to promote disaster medicine among pre-hospital care providers, rescuers, volunteers and the public, through educational and academic activities. The HKDMA also promotes experience sharing and academic exchange in the field of disaster medicine both locally and overseas. Members are from the medical, nursing, and allied health professions.

HKDMA has arranged for visits to emergency response units, organised courses and drills, and participated in conferences in mainland China to share experiences. Locally, HKDMA has also organised symposiums and workshops to enhance knowledge exchange and hands on experience. In 2012, HKDMA organised a symposium-cum-workshop "Pre-hospital care – Training by Simulation" and will organise a symposium on "Our Preparedness and Response in Marine Disasters" at the Lecture Theatre, Hospital Authority Building on 6 December 2014.

You are welcome to visit the HKDMA website to learn more about the Association and support the development and promotion of knowledge in the discipline.

The Osteoporosis Society of Hong Kong

The Osteoporosis Society of Hong Kong (OSHK) was founded in 2002 by specialists with multidisciplinary representation including physicians, gynaecologists, orthopaedic surgeons and nuclear medicine specialists with Prof Annie Kung as the Founding President. With over 300 active members ranging from clinicians, scientists, technologists and allied health professionals, the major objective of OSHK is to promote professional education on osteoporosis. The Society has active representation in the International Osteoporosis Foundation (IOF) and the Asian Federation of Osteoporosis Societies (AFOS).

In terms of professional education, OSHK organizes an annual Regional Osteoporosis Conference (ROC) in May each year. We also organise densitometry training courses once every 2-3 years. This year the first Joint ISCD and IOF international Densitometry Course in Asia will be held before the ROC on 24-25 May 2013 with an optional attestation examination. Two upcoming meetings of interest are AFOS 3rd meeting in Seoul, Korea on 6-8 September 2013 and the IOF Regionals 4th Asia Pacific Osteoporosis Meeting on 12-15 Dec 2013. Our Society also regularly organizes scientific seminars and meetings, the A-Z Symposia series being a highlight every October in line with the World Osteoporosis Day.

To support training and research, OSHK provides sponsorship to members to attend osteoporosis-related conferences or courses. The OSHK Guideline for Clinical Management of Postmenopausal Osteoporosis in Hong Kong will be published as a supplement in the April issue of the Hong Kong Medical Journal. With this new set of guideline with clarifications on some current controversies, it serves as a reference guide for the local practitioners in the management of postmenopausal osteoporosis.

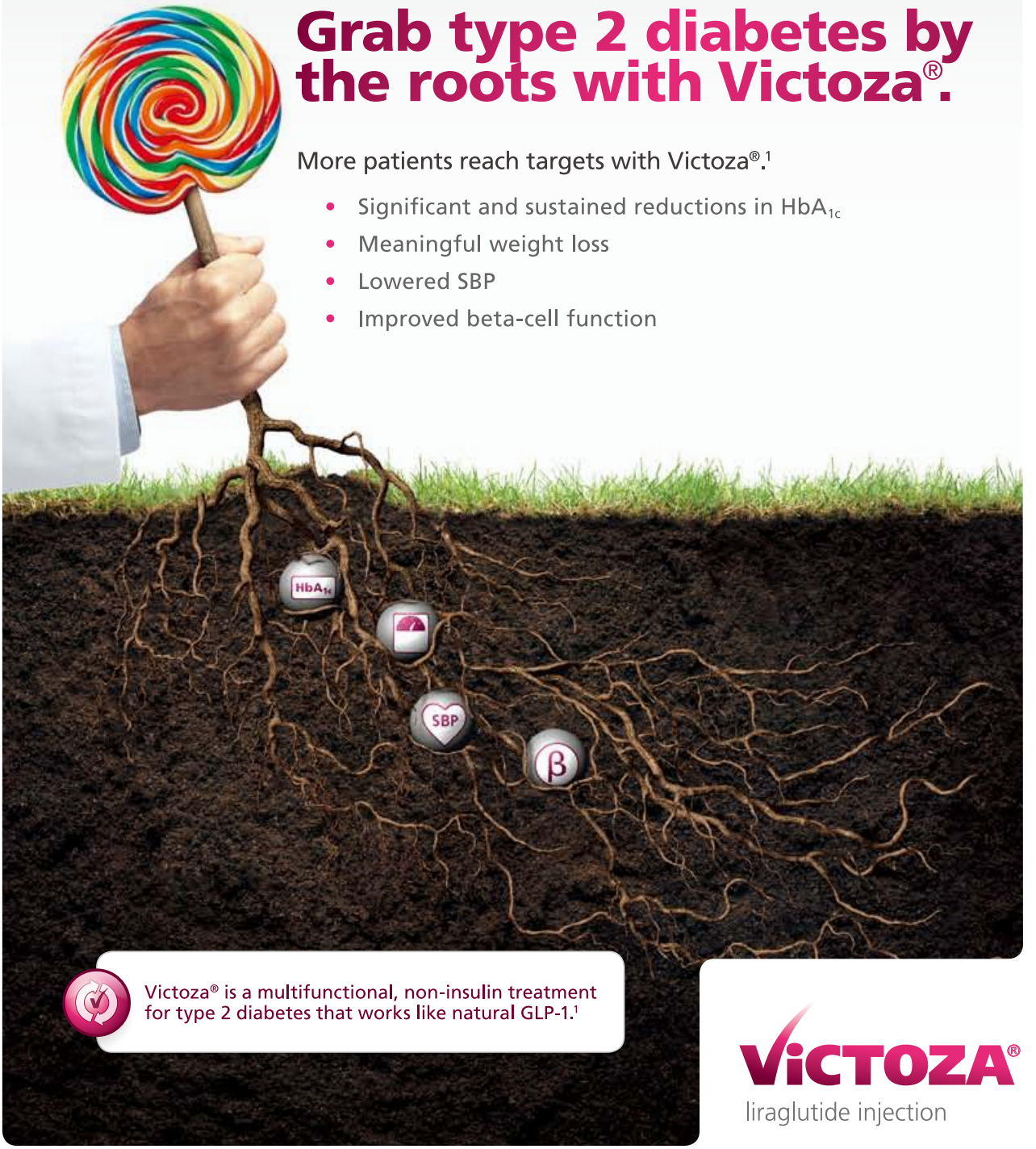
The Society is also very active in public education, with regular contributions to in the media including newspaper columns, TVB, RTHK and the NOW health programs.

For more information about the society, please visit www.oshk.org.hk

Grab type 2 diabetes by the roots with Victoza®.

More patients reach targets with Victoza®.[1]

- Significant and sustained reductions in HbA_{1c}
- Meaningful weight loss
- Lowered SBP
- Improved beta-cell function



Victoza® is a multifunctional, non-insulin treatment for type 2 diabetes that works like natural GLP-1.[1]

VICTOZA®
liraglutide injection

Reference: 1. Victoza® [summary of product characteristics]. Bagsværd, Denmark: Novo Nordisk A/S; 2011.

The Summary of Product Characteristics (SPC) is available at novonordisk.com.

changing diabetes®

Novo Nordisk Hong Kong Ltd
Tel: (852) 2387 8555 Fax: (852) 2386 0800 www.novonordisk.com

Novo Nordisk is changing diabetes. We provide innovative treatment solutions that empower people to achieve and maintain good control of their diabetes.

novo nordisk®

LIRA-D-20121001

CERTIFICATE COURSE FOR MEDICAL AND HEALTH PROFESSIONALS

Course No. C243 **CME/CNE Course**

Certificate Course on

Renal Medicine 2014

Jointly organised by

The Federation of Medical Societies of Hong Kong

Hong Kong Society of Nephrology

Objectives:

To update the participants on new advances in renal medicine and clinical practice of common renal problems, and to help the participants to interpret results of common renal investigations

Date	Topics	Speakers
5 Nov	Common investigation tests for renal disease including approach to proteinuria & haematuria Update and management of primary glomerulonephritis	Dr. Chi-kwan WONG Associate Consultant Department of Medicine Pamela Youde Nethersole Eastern Hospital Dr. Kai-ming CHOW Associate Consultant Department of Medicine and Therapeutics Prince of Wales Hospital
19 Nov	Update and management of hypertension Update on diabetic nephropathy	Dr. Bonnie Ching-ha KWAN Clinical Professional Consultant Department of Medicine and Therapeutics The Chinese University of Hong Kong Prince of Wales Hospital Dr. Kin-yee LO Associate Consultant Department of Medicine and Geriatrics Kwong Wah Hospital
26 Nov	Update and management of acute kidney injury Renal protective strategy for chronic kidney disease	Dr. Terence Pok-siu YIP Associate Consultant Department of Medicine Tung Wah Hospital Dr. Tsz-ling HO Associate Consultant Department of Medicine Tseung Kwan O Hospital
3 Dec	Drug prescribing in renal failure Introduction to palliative care in end-stage renal failure	Dr. Kai-ching HAU Associate Consultant Department of Medicine and Geriatrics Tuen Mun Hospital Dr. Hoi-wong CHAN Associate Consultant Department of Medicine Queen Elizabeth Hospital
10 Dec	ABC of peritoneal dialysis therapy ABC of hemodialysis therapy	Dr. Man-fai LAM Private Nephrologist Dr. Kwok-hong CHU Resident Specialist St Teresa's Hospital
17 Dec	ABC of kidney donation ABC of renal transplantation	Dr. Sunny Sze-ho WONG Consultant Department of Medicine and Geriatrics United Christian Hospital Dr. William LEE Associate Consultant Department of Medicine and Geriatrics Princess Margaret Hospital

Date : 5 November 2014 – 17 December 2014 (Every Wednesday, skip 12 November)
Time : 7:00 pm – 8:30 pm
Venue : Lecture Hall, 4/F., Duke of Windsor Social Service Building, 15 Hennessy Road, Wanchai, Hong Kong
Language Media : Cantonese (Supplemented with English)
Course Fee : HK$750 (6 sessions)
Certificate : Awarded to participants with a minimum attendance of 70%
Enquiry : The Secretariat of The Federation of Medical Societies of Hong Kong
Tel.: 2527 8898 Fax: 2865 0345 Email: info@fmshk.org

CNE / CME / CPD Accreditation in application

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

Answers to Radiology Quiz

1. X-ray Findings:

- Abnormal gaseous radiolucency was noted at bilateral abdomen outlining bilateral psoas margins, as well as the walls of the distal ascending colon and hepatic flexure. Findings were in keeping with pneumoretroperitoneum.

CT Findings:

- CT confirmed the presence of massive pneumoretroperitoneum, with gas at the bilateral pararenal spaces around the end stage atrophic kidneys. A mural defect was seen at the anterior distal sigmoid colon (arrowed) communicating with the retroperitoneal gas, suggestive of colonic perforation.

2. Diagnosis:

- Perforated sigmoid colon during colonoscopy causing pneumoretroperitoneum.
- Urgent laparoscopy was performed confirming presence of the perforation at the distal sigmoid colon.

3. Discussion:

- Pneumoretroperitoneum is defined as gas within the retroperitoneal space. It is most commonly due to perforation of a hollow retroperitoneal viscus including the duodenum, ascending/descending colon and rectum, which can be related to iatrogenic causes (i.e. endoscopy), peptic ulcer disease, diverticulitis, ischaemic colitis, colorectal cancer or abdominal trauma. Other causes include infection in the retroperitoneal organs such as a perinephric abscess or complicating pancreatitis
- Location of the gas can help narrow down the differential diagnoses:
  - Gas in the perirenal space is most likely due to renal infection.
  - Gas in the right anterior pararenal space is most commonly due to perforation of the 2nd part of the duodenum.
  - Gas in the left anterior pararenal space is most commonly due to perforation of the descending or sigmoid colon.
  - Gas in the bilateral anterior pararenal spaces can be due to rectal perforation or necrotising pancreatitis
  - Gas in the bilateral posterior pararenal spaces can be due to rectal perforation or dissecting gas from above the diaphragm.
- Perforation of the sigmoid colon usually gives rise to pneumoperitoneum rather than pneumoretroperitoneum. However, since the perforation in this patient was covered by paracolic fat, there was tracking of the gas backwards along the mesentery into the retroperitoneum resulting in massive pneumoretroperitoneum.

Dr Alan CS LAM
MBBS, FRCR
Department of Radiology, Queen Mary Hospital, Hong Kong

For patients with myelofibrosis

Improve quality of life. Improve survival.
Choose JAKAVI.

With JAKAVI, you can help patients by improving splenomegaly, symptoms, and survival[1,2]

- In COMFORT-II, there was a 52% reduction in the risk of death in the JAKAVI arm compared with the best available therapy arm (HR=0.48; 95% CI: 0.28-0.85; P=0.009)[1]

References: 1. Cervantes F, Vannucchi AM, Kiladjian J-J, et al; for the COMFORT-II investigators. Three-year efficacy, safety, and survival findings from COMFORT-II, a phase 3 study comparing ruxolitinib with best available therapy for myelofibrosis. Blood. 2013;122(25):4047-4053. **2.** JAKAVI® (Ruxolitinib) Hong Kong packing insert (version date: EMA Oct 2012+ CDS November 2013).

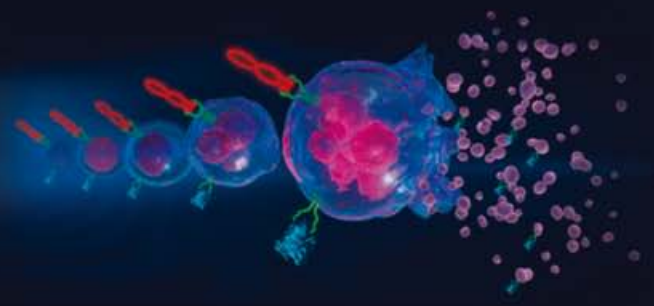
Prescribing Information: Important note: Before prescribing, consult full prescribing information. **Presentation:** tablets containing 5 mg, 15 mg, and 20 mg ruxolitinib. **Indications:** Jakavi is indicated for the treatment of disease related splenomegaly or symptoms in adult patients with primary myelofibrosis (also known as chronic idiopathic myelofibrosis), post polycythaemia vera myelofibrosis or post essential thrombocythaemia myelofibrosis. **Dosage:** •Perform blood cell count before initiating Jakavi therapy. Monitor complete blood counts every 2 to 4 weeks until optimal dose is reached. •Recommended starting dose for adults: 15 mg (platelet count between 100,000 and 200,000/mm^3) and 20 mg (platelet count >200,000/ mm^3) twice daily at the same time every day, with or without food. Maximum starting dose of 5 mg twice daily in patients with a platelet count between 50,000/ mm^3 and <100,000/ mm^3, caution in this patient population. •Discontinue treatment if platelet counts <50,000/ mm^3 or ANC <500/ mm^3. •Dose adjustment may be required due to thrombocytopenia or when used with strong CYP3A4 inhibitors. •4 weeks after initiating therapy dose may be increased at intervals of greater than 2 weeks to ensure adequate response. •Maximum dose is 25 mg twice daily •Treatment to be continued as long as the benefits outweigh the risks for the patient. •Recommend to reduce the starting dose by approximately 50% in patients with renal impairment (Clcr <30 mL/min) or with hepatic impairment. Monitor patients diagnosed with renal or hepatic impairment and reduce the dose as appropriate. •No dosage adjustment required for elderly patients. **Contraindications:** Hypersensitivity to ruxolitinib or to any of the excipients. Pregnancy and lactation. **Warnings/Precautions: •Decrease in blood cell count:** hematologic adverse reactions, including thrombocytopenia, anemia and neutropenia have been reported with Jakavi treatment. Complete blood counts monitoring recommended. Dose reduction or interruption may be required in patients developing thrombocytopenia, anemia and neutropenia. **•Infections:** Treat active serious infections prior to initiating Jakavi therapy. Monitor patients for signs and symptoms of infections during Jakavi treatment, and initiate appropriate treatment for infections. Tuberculosis cases have been reported. Progressive multifocal leukoencephalopathy (PML) has been reported. Physicians should be alert for neuropsychiatric symptoms suggestive of PML. **•Hepatic and severe renal impairment:** Due to increased Jakavi exposure, dose reduction is required. **•Pregnancy:** use in pregnancy not recommended. Avoid becoming pregnant during Jakavi therapy. **•Breast-feeding:** Women taking Jakavi should not breast feed. **Interactions:** •Caution with CYP3A4 inhibitors, dose reduction recommended when co-administered with strong CYP3A4 inhibitors. **Adverse reactions: •Very common (>10%):** Urinary tract infections, anemia, thrombocytopenia, neutropenia, hypercholesterolaemia, dizziness, headache, alanine aminotransaminase increased, aspartate aminotransferase increased, bruising. **•Common (1 to 10%):** Herpes zoster, tuberculosis, weight gain, flatulence. **Packs:** Ruxolitinib 5mg (56 tablets), Ruxolitinib 15mg (56 tablets), Ruxolitinib 20mg (56 tablets) **Legal classification:** P1S1S3

NOVARTIS ONCOLOGY

Novartis Pharmaceuticals (HK) Ltd
27/F, 1063 King's Road, Quarry Bay, H.K.
Tel: 2882 5222 Fax: 2577 0274

JAKAVI™ ruxolitinib

HK1408238375



Nplate®
romiplostim

Early Treatment
Early Results

Boosting Platelet Production with Once-Weekly Romiplostim

- Single-use 250 mcg/vial[a]
- First TPO-receptor agonist approved by FDA[b,c]
- Safe and effective for long-term treatment of chronic ITP[d-f]
- Without Black Box Warning for the risk of hepatotoxicity[a]
- Improving patients' health-related quality of life[g-j]

Clinical References:

a. Packing insert of Nplate. **b**. http://www.news-medical.net/news/2008/08/24/40859.aspx. **c**. http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ 2008/ucm116938.htm. **d**. Mehdi K. *et. al. Romiplostim safety and efficacy for immune thrombocytopenia in clinical practive: 2-year results of 72 adults in a romiplostim compassionate-use program, Blood doi:10.1182/blood-2011-03-340166.* **e**. *James B. Bussel, David J. Kuter et. al. Safety and efficacy of long-term treatment with romiplostim in thrombocytopenic patients with chronic ITP, Blood doi:10.1182/blood-2008-04-150078.* **f**. *Y. Shirasugi et.al. An open-label extension study evaluating the safety and efficacy of romiplostim for up to 3.5 years in thrombocytopenic Japanese patients with immune thromcytompenic purpura (ITP), Int J Hematol doi: 10.1007/s12185.012-1065-2.* **g**. *J.N. George et. al. Imroved quality of life for romiplostim-treated patients with chronic immune thrombocytopenic purpura: results from two randomized, placebo-controlled trials, British Journal of Haematology (2008) 144, 409-415.* **h**. *R. Deuson et. al. The burden of immune thrombocytopenia in adults: Evaluation of the thrombopoietin receptor agonist romiplostim, Journal of Medical Economics 2012, 1-21.* **i**. *D. J. Kuter et.al. Health-related quality of life in nonsplenectomized immune thrombocytopenia patients receiving romiplostim or medical standard of care, American Journal of Haematology 2012 Letter.* **j**. *D.J. Kuter et. al. Romiplostim or standard of care in patients with immune thrombocytopenia, The New England Journal of Medicine 2010 Vol. 363 (20)."*

KYOWA KIRIN

Kyowa Hakko Kirin (Hong Kong) Co., Ltd.
Unit B, 13/F., 169 Electric Road, North Point, Hong Kong
Tel: (852) 2956-0828
Fax: (852) 2956-1627
www.kyowa-kirin.com/hk