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INSIDE

Advancing Our Clinical Perspectives in Haematology: What Is Your Approach?

ADVANCING OUR CLINICAL PERSPECTIVES IN HAEMATOLOGY: WHAT IS YOUR APPROACH?

Summary of presentations from the 11th New Horizons in Haematology conference which took place on 11th March 2016 and was webcast live to moderated audiences in Hong Kong, Italy, Japan, Russia, South Africa, and Spain, and to individuals throughout the world

Moderator

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MEETING SUMMARY

The 11th New Horizons in Haematology (NHH11) conference was moderated by Dr Sarah Jarvis, healthcare reporter and television presenter, and was delivered in the format of a live, interactive, online meeting. Prof Gunnar Birgegård opened the conference with a presentation on the evolution of essential thrombocythaemia (ET) disease, Prof Sélim Aractingi described the incidence of skin lesions in myeloproliferative neoplasms (MPN), Prof Claire Harrison discussed key aspects in women's health

when managing ET including pregnancy, Prof Jean-Jacques Kiladjian covered the management of elderly patients with ET, and Dr Manuel Martínez-Sellés concluded the meeting by emphasising the importance of identifying and managing cardiovascular (CV) risk factors in ET. Dr Tamara Lado Cives, Prof Chiaki Nakaseko, Dr Melania Moreno Vega, and Dr Samah Alimam each shared a case study after the main presentations.

Introduction

Doctor Sarah Jarvis

Dr Jarvis welcomed the audiences in Hong Kong, Italy, Japan, Russia, South Africa, and Spain, and invited them to submit questions via their moderators. Individual participants were encouraged to submit questions via the NHH11 website or Twitter.

Evolution of Essential Thrombocythaemia Disease

Professor Gunnar Birgegård

The 2008 revision of the World Health Organization (WHO) classification of myeloid neoplasms and acute leukaemia marked an important milestone in ET care.[1] For the first time, it was acknowledged that ET and early/prefibrotic primary myelofibrosis (PMF) are different entities that require a bone marrow biopsy to differentiate between them. The importance of this distinction was highlighted by a retrospective study of 1,104 patients[2] with an initial diagnosis of ET using the Polycythaemia Vera Study Group (PVSG) criteria.[3] A retrospective reclassification using the 2008 WHO guidelines showed that while 81% (n=891) of patients had true ET, 16% (n=180) actually had PMF.[2] The importance of this diagnostic distinction became apparent when researchers examined the cumulative incidence of the transformation to leukaemia: patients with PMF had a higher incidence at each time point than patients with ET (Figure 1).[2] A similar pattern was seen for transformation to overt myelofibrosis (Figure 1) and overall survival (Figure 1).[2]

The WHO 2008 guidelines also emphasise the importance of blood counts, CV work-up, and mutation analysis as prognostic tools.[1] Approximately 50–60% of patients with ET or PMF have a mutation in the *Janus kinase 2* gene (*JAK2*), and a further 5–10% have activating mutations in the *thrombopoietin receptor* gene (*MPL*).[4] Among those patients with ET or PMF who do not carry *JAK2* or *MPL* mutations, 67% and 88% have a mutation in the *calreticulin* gene (*CALR*), respectively.[4] ET patients who carry the *CALR* mutation have fewer thromboses;[5,6] however, *CALR* mutation status has yet to be included in risk-score models owing to a paucity of data.

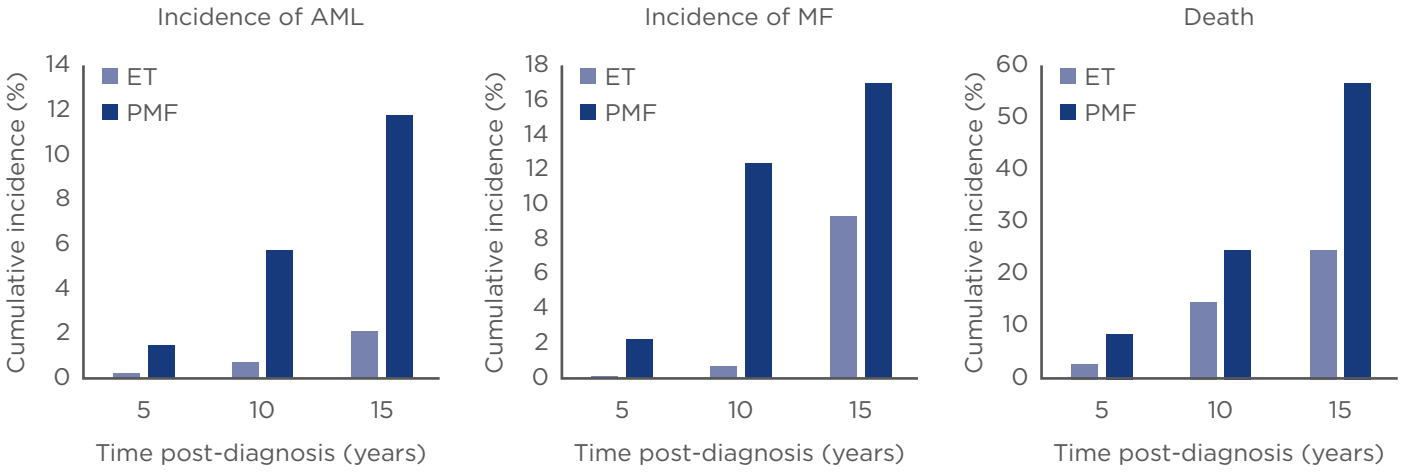

Figure 1: The impact of WHO-defined essential thrombocythaemia versus early primary myelofibrosis to predict events in 1,104 essential thrombocythaemia patients.[2]

AML: acute myeloid leukaemia; CI: cumulative incidence; ET: essential thrombocythaemia; MF: myelofibrosis; PMF: prefibrotic primary myelofibrosis; WHO: World Health Organization.

JAK2 mutation status, together with CV risk factors, age (>60 years), and previous thromboses has been included in a thrombosis risk-stratification model.[7] However, models that do not include *JAK2* mutation status, such as the Cardio-ET prognostic risk score that relies on CV risk factors and previous thromboses only,[8] produce similar odds for low, intermediate, and high-risk patients. Nevertheless, *JAK2* mutation status may be important when assessing individual patients.

Despite the advances in classification, risk stratification, and treatment of ET, there remain a number of unmet needs. These include a reliable marker of biological activity and disease progression, and drugs and targets that have a marked impact on the biology of the disease, for example, by inhibiting fibrosis. Finally, further research is required into so called 'triple-negative ET' patients who do not have *JAK2*, *MPL*, or *CALR* mutations.

An Unusual Presentation of Essential Thrombocythaemia Disease

Doctor Tamara Lado Cives

A 34-year-old woman presented with painful splenomegaly without additional clinical or laboratory findings. Non-haematological causes were ruled out and lymphoproliferative syndrome was suspected. Bone marrow aspiration revealed normocellular bone marrow with prominent megakaryocytes. There were no clonal cells detected by flow cytometry and cytogenetics were normal. Splenectomy was performed and histopathology showed congestion. A week after surgery the patient was re-admitted with daily headaches and abdominal pain. At admission, she presented with a severe paresis of the left hand with spontaneous resolution after a few hours. The patient also described a burning sensation in the palms and soles with a blushing appearance. Laboratory examination showed leukocytosis with a platelet count of 1,767x10^9/L and an increase in cholestasis enzymes (gamma glutamyltransferase 116 U/L). An abdominal computed tomography (CT) scan revealed a widespread portal thrombosis of the main veins and the splenic vein, and a partial thrombosis of the superior mesenteric vein. It also showed a small amount of ascites in the right hemiabdomen and in the pouch of Douglas, and a moderate right pleural effusion. A cerebral CT scan was normal. At this time, the suspected diagnosis was severe reactive thrombocytosis secondary to splenectomy with possible transient ischaemic attack. Treatment was initiated with anticoagulants and low-dose aspirin. At 1-month follow-up the platelet count was 3,244x10^9/L. Thrombapheresis was negative and a new bone marrow study was requested; aspiration showed megakaryocytic hyperplasia and biopsy showed megakaryocytes had increased with moderate reticulin fibrosis Grade 1 compatible with ET. The *JAK2* profile showed mutation in 23% of alleles. Owing to the history of thrombosis the patient was classified as high-risk and treatment was initiated with hydroxycarbamide and low-dose aspirin.

This case highlights that in the event of an unexplained splenomegaly, even if the haemogram is normal without thrombocytosis, it is important to suspect MPN and patients should be screened for *JAK2* mutations. Indolent lymphomas and MPN are the most prevalent haematological malignancies associated with splenomegaly and up to 35% of patients with ET present with splenomegaly.

Skin Lesions in Myeloproliferative Neoplasms

Professor Sélim Aractingi

Patients with MPN experience a number of cutaneous manifestations, mainly related to microvascular disorders. Pruritus is an important sign that may aid in the diagnosis of unrecognised disease and is found in 5–69% of polycythaemia vera (PV) patients,[9] 3–46% of ET patients,[10] and 16–54% of PMF patients.[11,12] Aquagenic pruritus is present in 30–50% of PV patients[9] and 30–65% of ET patients.[13] ET patients experience a range of microvascular lesions, including erythromelalgia (6%) and livedo reticularis (3%),[10] as well as spontaneous skin ulcers and superficial phlebitis.[10,14] Acrocyanosis, Raynaud's phenomenon, blue toes, digital gangrene, and vasculitis have also been reported, but remain rare.[10,14]

A Case of Treatment-Induced Skin Ulcer in a Patient with Essential Thrombocytosis

Professor Chiaki Nakaseko

A 59-year-old male presented with thrombocytosis (platelet count 900x10^9/L) and was diagnosed

with ET following several investigations including bone marrow aspiration. He was considered at low-risk of thrombosis and was treated with low-dose aspirin. A year later his platelet count had increased to 1,790x10^9/L and hydroxycarbamide 500 mg/day was prescribed, increasing to 1,000 mg/day. Three years later his platelet count was 1,580x10^9/L and hydroxycarbamide was increased to 1,500 mg/day. The patient's platelet count stabilised at 800–1,200x10^9/L. The following year, the patient received a small cut to his right heel which became ulcerated. Hydroxycarbamide was reduced to 1,000 mg/day and treatment with silver sulfadiazine was initiated. The skin ulcer healed but the platelet count rose to 2,000x10^9/L; as there was no increase in bleeding the dose of hydroxycarbamide was maintained. Two years later, hydroxycarbamide was discontinued and the patient was switched to anagrelide 1 mg/day. The platelet count decreased from 2,300x10^9/L to 620x10^9/L, and in the absence of adverse events the dose of anagrelide was increased to 1.5 mg/day, resulting in a platelet count that was maintained with the range of 400–600x10^9/L. In this case, an intractable skin ulcer developed after hydroxycarbamide dose increase for uncontrolled platelet count. Treatment with anagrelide enabled successful platelet count control, and can be considered as an option for patients with adverse reactions to hydroxycarbamide.[15]

Identifying Key Aspects in Women's Health When Managing Essential Thrombocythaemia

Professor Claire Harrison

The European Collaboration on Low-dose Aspirin in PV (ECLAP) study revealed a number of gender specific differences; women with PV were older at diagnosis, and more likely than men to have venous embolic events and microcirculatory disturbances, and men were more likely to have peripheral arterial disease and myocardial infarction.[16] Furthermore, splanchnic venous thrombosis occurred most typically in young women and five out of six cases of Budd–Chiari syndrome were female.[16] In a study of abdominal vein thrombosis in ET, 17 out of 19 cases were recorded in females[17] and in a study of cerebral venous thrombosis in MPN, 7 out of 9 documented cases were female.[18] Women are affected by MPN at all stages of life and physicians must therefore consider contraception, pregnancy, and menopause. The British Committee for Standards in Haematology (BCSH) guidelines on oestrogen therapy recommend that combined oral contraceptives (OC) be discouraged for women with ET/PV.[19] Ovarian stimulation therapy is associated with a risk of thrombosis, and each case should be individually assessed and offered thromboprophylaxis where appropriate.[19]

Table 1: Pregnancy outcomes in myeloproliferative neoplasms.[21-23]

	Essential thrombocythaemia[21]	Polycythaemia vera[22]	Idiopathic myelofibrosis[23]
Study type	Meta-analysis	Case series and historical reports	Case series and historical series
Pregnancies (n)	461	18 and 20	4 and 4
Live birth rate (%)	50–70	60	50
First trimester loss (%)	25–40	21 (n=8)	NR
Late loss (%)	10	18 (n=7)	NR
Placental abruption (%)	3.6	NR	NR
IUGR (%)	4.5	15 (n=6)	NR
Post-partum thrombosis (%)	5.2	NR	0
Ante/post-partum haemorrhage (%)	5.2	3 (n=1)	0
Premature delivery (%)	NR	15 (n=6)	NR

IUGR: intrauterine growth retardation; NR: not reported.

Hormone replacement therapy may pose a minor increase in venous thromboembolism (VTE) risk, and therefore should only be used in patients without additional risk factors for VTE and without a personal history of thrombosis.[19] There are three main issues surrounding pregnancy in MPN, namely, risks of: 1) poor pregnancy outcome; 2) thrombohaemorrhagic events; 3) teratogenicity.[20] Studies of pregnancy in ET include a meta-analysis of 461 pregnancies (Table 1).[21] There are fewer data on pregnancy outcomes in PV; data from a case series of 18 pregnancies combined with 20 historical reports are shown in Table 1.[22] There were three cases of maternal VTE, one case of post-partum haemorrhage, four cases of pre-eclampsia, and one maternal death (deep vein thrombosis, pulmonary emboli, sagittal sinus thrombosis, and disseminated intravascular coagulation).[22] In a case series of four pregnancies and four historical cases in patients with idiopathic myelofibrosis there was 50% fetal loss but no maternal thrombosis or haemorrhage (Table 1).[23] There are mixed data on whether obstetric complications can be predicted in ET.[24,25] Platelet counts decline and may correlate with improved outcome[24] but disease complications may not be predictive of pregnancy outcome[25] and past pregnancy outcome may not be predictive for subsequent events.[25] Thrombophilia testing and screening for acquired Von Willebrand's disease may be useful but should only be performed if there is an additional indication. An increased pulsatility index assessed by uterine artery Doppler ultrasonography at 20–24 weeks of gestation is the best predictor of placental dysfunction, with a mean pulsatility index >1.4 considered a positive result.[26]

When managing pregnancy in an MPN patient, a pre-conceptual meeting to advise the patient of the risks is recommended and patients wishing to become pregnant should be formally assessed to determine the level of risk.[20] Previous pregnancy complications potentially caused by MPN put a patient at high-risk and include: three pregnancy losses in <10 weeks; one pregnancy loss in >24 weeks; and intrauterine death or still birth (with no obvious other cause); intrauterine growth retardation or other evidence of placental dysfunction; significant ante or post-partum haemorrhage and severe pre-eclampsia (necessitating preterm delivery <7 weeks).[20] Finally, haematocrit levels will fall as pregnancy progresses and it is important to consider gestation-specific ranges and the risk of thrombosis.[20]

Case Study of Essential Thrombocythaemia in a 39-Year-Old Woman

Doctor Melania Moreno Vega

A 39-year-old woman presented with thrombocytosis in 2014. A review of her medical history revealed that she had experienced a high platelet count since 2008, spontaneous pneumothorax in resolution and endometriosis that required an oophorectomy. The patient used OC for 10 years until an incident of Budd–Chiari syndrome in 2012, following which acenocoumarol was initiated. The patient had presented at the emergency department with a 2-month history of oedema and increased abdominal perimeter; imaging and a liver biopsy revealed suprahepatic vein thrombosis. The patient was negative for most common thrombophilia mutations and *JAK2* so MPN was temporarily ruled out and OC use and smoking were considered the main cause of thrombosis. Further genotyping revealed a Type 1 variant, *CALR* positive mutation and, following bone marrow biopsy, the patient was diagnosed with *CALR* positive high-risk ET. Treatment was initiated with hydroxycarbamide but the patient developed skin lesions after 1 year and was switched to anagrelide. At follow-up, the patient requested *in vitro* fertilisation but, owing to the high thrombotic risk inherent with hormone therapy, this was advised against.

In terms of diagnosing MPN in Budd–Chiari syndrome patients, it is well established that PV is the most common form of MPN, followed by ET,[27] and that mutation analysis is an important diagnostic tool. However, the role of *CALR* mutations is not clear and there are conflicting reports.[28-30] Despite the low prevalence, analysis of *CALR* mutations in cases of thrombosis in unusual venous sites is a simple and inexpensive tool that may be useful for diagnosing young patients with MPN.

Management of Elderly Patients with Essential Thrombocythaemia

Professor Jean-Jacques Kiladjian

Data from a large Swedish registry study show that MPN is frequently diagnosed in patients >60 years of age (18–49 years, 11%; 50–59 years, 14%; 60–69 years, 24%; 70–79 years, 33%; >80 years, 18%) and the median age of ET diagnosis is 65 years.[31] Several studies have demonstrated that age is a clear risk factor for the development of ET.[7,31,32] Among the 3,598 high-risk patients with ET in the EXELS study, 395 were >80 years of age at registration.[33] In this registry study, 72% of patients (n=575) receiving anagrelide were aged <65 years, 17% (n=133) were aged 65–74 years, and 12% (n=96) were aged ≥75 years; whereas the use of other cytoreductive therapies (mainly hydroxycarbamide) in these age ranges was distributed equally (34% [n=913], 34% [n=897], and 32% [n=854], respectively).[34] These differences are likely due to the European Leukaemia Net (ELN) recommendation to use hydroxycarbamide with caution in younger patients[35] and concerns about the cardiac toxicity of anagrelide in elderly patients. However, in the EXELS study, the incidence of vascular events in patients aged ≥80 years such as stroke (1.3% [n=5], 95% confidence interval [CI]: 0.2–2.4) and venous thrombosis (1.8% [n=7], 95% CI: 0.5–3.1) was similar to the incidence in the total group (1.4% [n=49] and 1.2% [n=44], respectively). In conclusion, in the largest elderly ET patient cohort studied to date, management of elderly patients was homogeneous across the European Union and elderly patients' characteristics did not clearly differ from younger patients at presentation.[33] Haematological response to cytoreductive therapy was similar across age categories and there were no new safety concerns, particularly among elderly patients.[33]

Case Study

Doctor Samah Alimam

The patient was an 84-year-old female with a 40-year 1 pack-a-day history of smoking who was previously asymptomatic. During routine investigations, she was found to have a consistent platelet count over 1000x10^9/L with a slightly elevated white cell and neutrophil count. Blood film revealed platelet anisocytosis with no evidence of dysplasia. ET was suspected and mutational analysis revealed *CALR* mutation. On examination, the patient was well with no palpable splenomegaly. The patient had had a myocardial infarction at the age of 64 years and ongoing hypertension and high cholesterol were managed by her general practitioner. Aspirin 75 mg once daily was initiated, and smoking cessation, and antihypertensive and cholesterol management medications were optimised in conjunction with primary care together with hydroxycarbamide 500 mg once daily. This dose of hydroxycarbamide was well tolerated but there was no reduction in platelet count. The dose was escalated to 500 mg Monday to Friday and 1,000 mg at the weekend. The patient developed hair thinning and a fall in haemoglobin but there was no change in platelet count. The regimen was further adjusted to 1,000 mg Monday to Friday and 500 mg at the weekend, and platelet count was well controlled; however, the patient became increasingly intolerant with ongoing hair thinning, nausea, and weight loss, and her haemoglobin began to fall below 100 g/L. Despite the poor tolerability profile, the patient was concerned about having a stroke and wanted her platelet count managed. At this time, the patient's platelet count was below 400x10^9/L and, after discussing management options with the patient, treatment was suspended to assess response. Adverse effects improved but the platelet count doubled in a short space of time and the patient wanted to restart treatment. One option was to reduce the dose of hydroxycarbamide but the patient was against this. Anagrelide was briefly considered but ruled out in view of the patient's CV history. The dosing schedule of busulfan therapy appealed to the patient and we therefore initiated busulfan 400 mg daily for 14 days with repeated cycles every 28 days until the platelet count was below 400x10^9/L. The patient tolerated this regimen well, appreciated the breaks in treatment, and, importantly, showed a reduction in platelet count. This case demonstrates that individualising treatment to balance efficacy with quality of life is critical in elderly patients.

Identification and Management of Cardiovascular Risk Targets in Essential Thrombycthaemia

Doctor Manuel Martínez-Sellés

CV risk targets are important at any age: no tobacco; blood glucose <110 mg/dL; blood pressure <140/90 mmHg; cholesterol <190 mg/dL; low-density lipoprotein <115 mg/dL; and body mass index <25 kg/m^2,[36] and can be expressed simply as the American Heart Association (AHA)'s 'ABCs': Avoid tobacco; Become more active; Choose good nutrition.[37] Patients with comorbidities such as diabetes are likely to require medication to achieve these targets and should be treated aggressively.[38] Despite the omission of CV risk factors in the older, 'classical' risk calculations,[2] the role of CV risk factors in ET is now considered especially important in patients with ET, as demonstrated by the newer risk calculations.[7,8] For instance, having more than one CV risk factor will give the maximal risk according to the criteria of Lekovic et al.[8] This is particularly important in so called 'low-risk' patients with *JAK2* mutations and should be considered when deciding whether or not to initiate cytoreductive therapy.[39] CV risk factors are also important in 'high-risk' patients, however they are unlikely to influence the decision to initiate cytoreductive therapy as these patients are likely to be candidates already.[39] Therefore, all ET patients should be assessed for CV risk factors early on in their treatment pathway and these factors should be treated before commencing cytoreductive therapy.[40]

In conclusion, ET patients aged >60 years should be treated with cytoreductive therapy, whereas in younger patients, decisions should be primarily based on CV risk factors.[41] The most important predictor of thrombosis is the presence of CV risk factors.[8] Even in ET, the most likely pathogenic mechanism is always atherosclerosis, with coronary thrombosis caused by plaque rupture.[42]

Meeting Close

Doctor Sarah Jarvis

Sarah Jarvis thanked the speakers for their presentations and brought the meeting to a close by looking towards NHH12 next year.

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