2022

Asian Myeloid Malignancies Exchange Forum

By Asian Myeloid Working Group

Virtual Meeting
30 April 2022 (Saturday)

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Introduction

The 2022 Asian Myeloid Malignancies Exchange Forum, led by Prof. Yok Lam Kwong and Dr. Harry Gill, was held online on 30th April, 2022. Panel members from Hong Kong, Singapore and Taiwan were invited to share their thoughts on the clinical landscape of myeloid malignancy management in the Asian population.

2021 AP MPN Consensus by Asian Myeloid Working Group

Dr. Harry GILL

Dr. Gill introduced the Asian Myeloid Working Group (AMWG) as a co-founder and gave a presentation of the AP MPN Consensus drafted by the AMWG.

Myeloproliferative neoplasms (MPN) diagnosis and classification

Dr. Gill started the sharing by stating the required information for an accurate diagnosis of polycythemia vera (PV), essential thrombocythemia (ET) and primary myelofibrosis (PMF) including morphology, proof of clonality (driver mutations, myeloid gene panel), exclusion of chronic myeloid leukemia (CML) BCR-ABL1+ and other subtypes of myelodysplastic syndrome (MDS)/MPN, and exclusion of reactive causes (especially for ET/myelofibrosis (MF) without somatic mutations). He also stated the importance of regularly monitoring post-PV or post-ET MF, in order to look for signs of progression to secondary myelofibrosis (SMF), which has worse prognosis.

The minimum work-up and investigation for MPN included a bone marrow test, genetic tests (for *BCR-ABL1*, *JAK2 V617F*, *CALR*, *MPL*, and *JAK2* exon 12), human leukocyte antigen (HLA) typing for allogeneic hematopoietic stem cell transplant (allo-HSCT) candidates, a myeloid gene Next Generation Sequencing (NGS) panel for all patients with MF and all MPN patients who are "triple negative", as well as symptom assessment using MPN-10, because symptom improvement can be used to determine the efficacy of treatment.

The prognostic risk assessment of MPN, including cytogenic risk

Dr. Gill introduced prognostic tools for ET, PV and MF. He emphasized that the minimal prognostic scoring system that we would need is DIPSS-plus. The molecularly-inspired models including MIPSS70, MIPSS70-plus version 2.0, and GIPSS were also introduced as important prognostic tools since the most objective method to stratify risk and predict long-term survival was through genetic and cytogenetic features. High risk patients with a median overall survival (OS) ≤5 years may consider allo-HSCT, whereas those without the high risk cytogenetic changes only require adequate symptom management and cytoreduction. *ASXL1* and *SRSF2* are two mutations that are the most consistently associated with higher risk of progression and worse outcomes in MPN.[1] It is now possible to classify patients with MPN into genomic subgroups with varying phenotypic characteristics and outcomes. GIPSS would serve the same purpose for secondary MF.

Treatments of PV, ET and PMF

Treatments of PV and ET usually involve initiating low-dose aspirin, maintaining cardiovascular risk factors, monitoring thrombosis and bleeding, and evaluating indications of cytoreductive therapy.

Treatment algorithm of PMF without molecular markers relies on DIPSS-plus assessment. MPN Symptom Assessment Form (SAF) is used as the decisive tool for physicians to consider the necessity of performing cytoreduction. Both DIPSS-plus low risk and intermediate-1 (Int-1) risk patients might consider ruxolitinib for symptom control and splenomegaly, in order to improve quality of life (QoL). Those with high molecular risk mutations might consider allo-HSCT. Intermediate-2 (Int-2) and high risk patients should first be evaluated for allo-HSCT; suitable candidates would be given ruxolitinib before allo-HSCT to reduce spleen size. Non-transplant candidates should be treated with ruxolitinib or other Janus kinase 2 (JAK-2) inhibitors, along with the management of MF-associated problems and consideration of clinical trials. Transplant candidates with accelerated/blast phase MF ought to consider ruxolitinib to induce remission before allo-HSCT and manage MF-related symptoms.

Ruxolitinib dosing and precautions

The key treatment goal is to achieve symptom and spleen response. Dose increment every 2-4 weeks is recommended and any response in symptoms and spleen size may be meaningful. Dose adjustment for thrombocythemia and neutropenia (absolute neutrophil count $<0.75*10^9$/L) should be based on the degree of cytopenia, the benefits of ruxolitinib, and the exclusion of other causes. Ruxolitinib-related anemia may occur during dose optimization, but usually improves beyond 6 months, so transfusion support, erythropoiesis stimulating agents (ESA) or thalidomide can be considered within these 6 months. There are concerns regarding endemic infections in Southeast Asia, such as tuberculosis, hepatitis B and *Talaromyces marneffei*, as well as COVID-19 infections and vaccinations during the current pandemic.

Ruxolitinib failure and alternative treatment options

Ruxolitinib failure is most common due to disease progression into blast phase and the lack/loss of response. A minority of cases were caused by ruxolitinib-related adverse events. Baseline risk factors are predictive of ruxolitinib discontinuation, with higher-risk patients more likely to discontinue treatment. Compared with conventional treatment, ruxolitinib-failure patients achieve better overall OS when treated with novel agents. Patients experiencing adverse events tend to have a better OS than those with disease progression.[2] Dr. Gill believed that it is important to individualize therapy and go for combination therapy of novel agents in case of disease progression.

Panel discussion

Prof. Kwong invited panelists to share experiences from their local practices. Dr. Teo stated that the treatment of MPN in Singapore is very similar to that of Hong Kong. On the other hand, Prof. Hou highlighted the limited access to clinical trials and novel agents, such as second-generation JAK-2 inhibitors in Taiwan. Due to the lack of novel treatment, patients of high risk or intermediate risk with poor risk disease progression/mutation are usually transferred to allo-HSCT, despite HSCT-related morbidity and mortality.

Regarding the QoL of the disease treatment, Prof. Kwong noted the need for more data on patient satisfaction of treatment. Since novel agents for MPN are not curative, how well these treatments alleviate symptoms and improve QoL is significant. Dr. Gill supplemented that ruxolitinib is not commonly used in Asia, so patient response and efficacy of ruxolitinib treatment requires more data. He suggested supplementing the current MPN-10 questionnaire with other tools for QoL assessment. Dr. Ooi agreed that an Asian-specific questionnaire is needed and described that in the patients she treated in Singapore, the MPN-10 questionnaire was unable to differentiate them very well. A questionnaire with greater differentiation of symptoms could convince more Asian patients to be treated with ruxolitinib.

Prof. Hou raised the concern of patients being dishonest about their symptoms in the MPN-10 due to strict reimbursement policies and suggested that building an Asian-Pacific database of patient symptoms could improve the scoring system. The panelists agreed that better assessment tools for patient-reported outcomes (PRO) are necessary.

Dr. Leung raised a question about the increased risk of infection with ruxolitinib and asked for other panelists' opinion on antibiotics prophylaxis. Dr. Teo and Prof. Hou stated that antibiotic prophylaxis is not common practice in Singapore and Taiwan, but screening would be conducted. Prof. Kwong suggested the pooling of opportunistic infection data in ruxolitinib treatment after the meeting.

Case Sharing

A 55-year-old female from Mumbai, India was diagnosed with MF in 1997. She has received hydroxyurea (HU) and transfusion in the past. She tested negative for *JAK2* V617F mutation and *BCR-ABL* translocation in 2012. In 2013, she presented with easy fatigability and abdominal discomfort. She was found to have calreticulin (CALR) mutation (*5 base pair insertion).

PATIENT JOURNEY

SEP 2013	Presented for the 1st time	HU 500 mg/1000 mg alternate day	Anemia management: Lenalidomide 5 mg OD & Prednisolone 20 mg OD
FEB 2014	Continued anemia		
NOV 2014	No improvement in anemia and spleen size	Ruxolitinib 15 mg BD from 18th DEC 2014	• Well tolerated • Blood transfusion once in 6 months • Spleen size: 29 cm (2011) to 26 cm (MAY 2016) after 18 months of starting Ruxolitinib from 18th DEC 2014
NOV 2016	Platelet dropped to <100*10^9/L	Ruxolitinib 10 mg BD	-
JUN 2017	Increased fatigability and symptoms due to massive splenomegaly	-	-
JULY 2017	Splenectomy Thrombocytosis (>500*10^9/L)	HU 500 mg OD and Aspirin	-
OCT 2017	Peripheral smear blast (5%)	Decitabine (6 cycles)	No response, +blast, fatigue Liver: 10 cm below SCM
JULY 2018	Peripheral smear blast (10%)	Azacytidine (monthly cycle)	Patient is doing well
PRESENT*	Well with no symptoms	-	-

* At the time of the webinar

Panel discussion of case sharing

Dr. Gill pointed out that the use of lenalidomide and prednisolone for the management of anemia in this patient was unsuccessful. The patient also experienced disease progression during ruxolitinib treatment, but the use of hypomethylating agents (HMA) achieved treatment response. NGS could have been beneficial for predicting prognosis and determining whether allo-HSCT was a viable option.

Dr. Ooi agreed that allo-HSCT could be considered, because the patient is classified as DIPSS high risk. Other novel treatments, such as momelotinib and fedratinib, may not be readily available or may be too costly. Dr. Teo commented that ESA should be considered for the management of anemia.

Landscape of Asian Myelodysplastic Syndrome (MDS): Epidemiology, Clinical Features, Risk Stratification and Treatments

Professor Hsin-An HOU

In this presentation, Prof. Hou summarized the differences between the Western and Asian MDS populations.

The incidence of MDS in the Asian population is lower by 2- to 4-folds (Figure 1),[3] but the age of MDS onset is around 10 years earlier.[4-8] A higher percentage of Asian patients have greater risk, as defined by classifications by the World Health Organization (WHO) 2008/2016, the International Prognostic Scoring System (IPSS) and the Revised IPSS (IPSS-R).[3-4,6] *SF3B1*, *TET2*, *ASXL1*, *SRSF2*, *DNMT3A*, and *IDH1/2* mutations are frequently detected in Western MDS population compared to Asian patients, whereas *U2AF1* and *ETV6* mutations are more common in Asian MDS patients (Figure 2).[3] Prof. Hou emphasized that there were still unmet medical needs in terms of diagnostic accuracy, drug accessibility and enrolment in clinical trials.

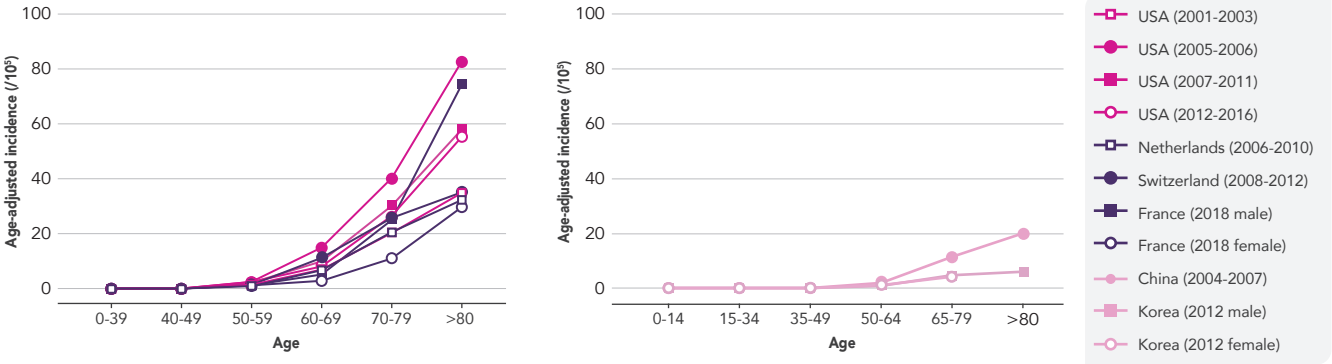


Figure 1: The age-adjusted incidence of MDS in Western and Asian countries.[3]

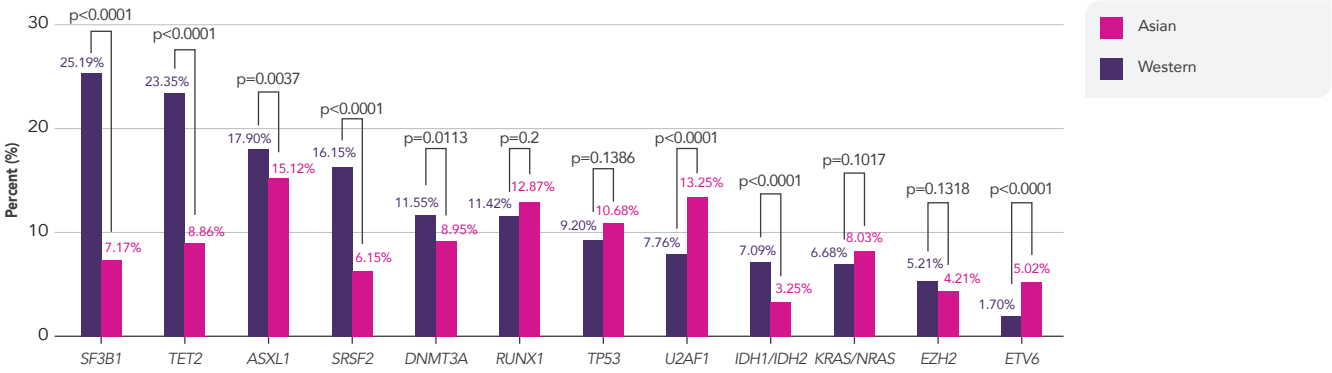


Figure 2: Frequency of common gene mutations in Western and Asian countries.[3]

Panel discussion

Both Dr. Gill and Dr. Teo agreed that there are local unmet needs regarding MDS treatment. Dr. Ooi stated that low risk MDS patients are often not officially diagnosed in Singapore, possibly due to clinicians and patients unwilling to undergo a bone marrow test when patients experienced mild cytopenia.

Prof. Kwong asked for the panel's opinion on conducting allo-HSCT in elderly patients aged 70 years or above and whether extending the age limit to 75 years is appropriate. Prof. Hou supported allo-HSCT in elderly aged between 70-75 years old, as long as the patient's organ function and disease status were fit for allo-HSCT. Dr. Ooi explained that patients above 60 years old in Singapore would receive geriatric assessment from the allo-HSCT team. She also pointed out that elderly patients nowadays tend to be fitter than those 10 years ago. Dr. Teo stated that the oldest patient she had seen receiving allo-HSCT was around 72 years old and she believed that extending the age limit to 70 years is already pushing the limits.

Another question that Prof. Kwong raised was the application of patient-reported outcomes (PRO) in treatment assessment. He explained that he would ask patients to provide a list of what improvements they would expect after treatment, and he would aim to check all the boxes on the list. The panel agreed that QoL and functional assessments are important parameters in assessing treatment outcomes.

Applications of molecular genetics and NGS in myeloid malignancies

Dr. Harry GILL

In his second presentation, Dr. Gill described how molecular genetics and NGS would benefit myeloid malignancy treatment. Here are some key messages from the sharing.

NGS and molecular minimal residual disease (MRD) in acute myeloid leukemia (AML)

NGS and MRD can be used for diagnosis, treatment selection, and improving allo-HSCT outcomes. Molecular combinations can result in varying levels of poor outcomes, such as *NPM1* mutation + *FLT3-ITD* + *DNMT3A* mutation producing a worse outcome than *DNMT3A* mutation in isolation or with *FLT3-ITD*.[9] Cryptic fusions, such as *NUP98-NSD1*, also result in worse outcomes.[10] Frontline induction can be personalized based on AML biology.

Treatment based on molecular genetics

Midostaurin + intensive chemotherapy produced survival benefits in *FLT3*-mutated AML patients across all three European LeukemiaNet (ELN) risk groups, with significant outcomes in the intermediate and adverse risk groups, whereas the benefit of reduction in cumulative incidence of relapse was seen mainly in ELN intermediate risk group.[11] Gemtuzumab ozogamicin displayed benefits in event-free survival (EFS) and OS in AML patients of ELN favorable/intermediate risk groups.[12,13] Response to venetoclax-azacitidine is phenotype-dependent, with *IDH2* and *NPM1* mutation showing OS benefit.[14] NGS should be performed for all patients because the presence of molecular markers may affect treatment approach for the disease.

Treatment based on MRD

MRD predicts the OS and relapse incidence after induction or chemotherapy in patients with *NPM1* mutation - lower peripheral blood MRD log reduction and MRD-positivity are related to poorer outcomes.[15,16] In AML with *RUNX1-RUNX1T1*, MRD-positivity is predictive of long-term/cumulative relapse, but patients with MRD transcript level ≤150 in bone marrow samples have a very low risk of relapse in the long term.[17] It is important to determine the risk of relapse based on the trend of MRD-positivity, *RUNX1-RUNX1T1* transcript levels, and MRD log reduction. Therapies such as gemtuzumab ozogamicin have a higher chance of inducing MRD negativity.

MRD and allo-HSCT

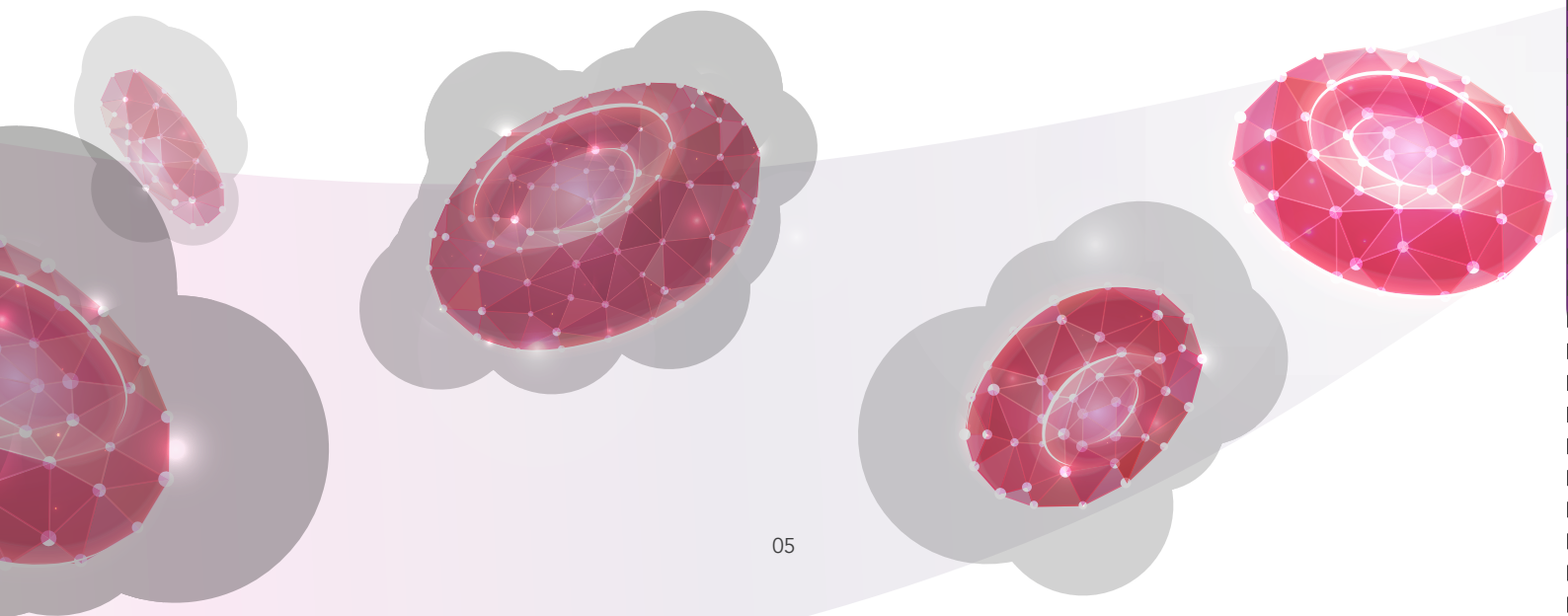
MRD positivity and high number of *NPM1* mutant copies are related to suboptimal post-HSCT outcomes.[18] Dr. Gill suggested the induction of MRD-negativity before allo-HSCT to achieve better OS, including the use of gemtuzumab ozogamicin or venetoclax-HMA. MDS patients with *TP53*, *EZH2*, *ETV6*, *RUNX1*, or *ASXL1* mutation tend to have worse outcome,[19] so using NGS to detect these mutations are necessary for MRD assessment.

Panel discussion

Prof. Hou asked for panelists' opinion on single-cell sequencing in clinical practice. The panel agreed that while single-cell myeloid panels are currently available for more accurate genetic information and individualized therapy, financial burden remained as a hurdle for it to become the main testing method for MRD.

Prof. Kwong raised the option of using cell-free deoxyribonucleic acid (DNA) for the testing of extramedullary diseases, such as core-binding leukemia, due to its homogeneity. Dr. Gill said that although there was no experience in Hong Kong, data of cell-free DNA predictive of relapse or leukemic progression after allo-HSCT in AML and MDS has been published. Furthermore, he suggested that cell-free DNA monitoring could be integrated into the post-HSCT assessment.

The panel discussed strategies to lower MRD before allo-HSCT. Gemtuzumab ozogamicin is an option, although it requires a washout period of 4-8 weeks before allo-HSCT. Venetoclax-HMA could be used as a bridging option before allo-HSCT in patients with *NPM1* mutation. For patients with concurrent *FLT3-ITD* and *NPM1* mutations, switching from midostaurin to a third-generation FLT3 inhibitor (e.g. gilteritinib) may improve *NPM1* MRD. However, Prof. Kwong questioned the improvement of MRD by upgrading the FLT3 inhibitor, as many cases of relapse were already FLT3-negative after chemotherapy or allo-HSCT.



Management strategies in early myelofibrosis

Dr. Eng Soo YAP

Dr. Yap joined this open discussion session to share his thoughts on the management of early MF.

Both Dr. Yap and Dr. Gill expressed their struggles with defining early MF, due to the heterogenic patient characteristics. Prefibrotic MF is often categorised as early MF. However, it is undecided that whether low risk MF with high molecular risk mutation and less symptomatic should be considered as early MF.

Dr. Yap believed that patients with early MF would require treatment if heavily symptomatic or showing spleen-related symptoms. He added that prophylaxis for vascular thrombotic event is necessary. In addition, patients that require cytoreduction should initiate the treatment regardless of their symptoms and spleen size according to Dr. Gill.

When discussing the treatment goal of early MF, Dr. Yap stated that preventing or delaying disease progression was more important than improving survival. Early MF is not a benign disease and progression is inevitable, so slowing down disease progression should be the main focus. While there is no current data proving so, he believed that slowing down disease progression could positively impact survival. Dr. Gill believed that disease modification, such as reducing the molecular driver gene burden and reversing the morphologic features, could theoretically reduce the risk of progression to overt MF.

Dr. Gill would consider patients' condition (such as age) and risk of progression as the priorities in deciding treatment. For example, elderly patients with prefibrotic MF or low risk PMF may opt for ruxolitinib treatment if they are experiencing appetite problems due to very large spleens. On the other hand, Dr. Yap pointed out that patients probably care more about symptom/treatment burden, so those with early MF that have no symptoms might be reluctant to receive treatment in the first place.

Furthermore, Dr. Gill and Dr. Yap shared their views on whether to use DIPSS/DIPSS-plus or GIPSS for risk stratification in early MF. GIPSS includes molecular and cytogenetics, whereas DIPSS/DIPSS-plus involve more clinical and symptom factors. The choice depends on whether molecular diagnostics are available, because even younger patients stratified as high risk with GIPSS could benefit from disease-modifying agents.

Panel discussion

The panel agreed that identifying patients with early MF is a major obstacle to overcome and more data has to be collected to better characterize these patients. The potential applications of biomarkers may help clinicians decide the appropriate time to initiate treatment. NGS should be routinely incorporated into diagnostic process, due to the possibility of certain patients carrying genetic mutations that result in increased risk. NGS may also help with diagnosing early MF, reducing the risk of misdiagnosis, and finding potential disease-related biomarkers.

Prof. Kwong wrapped up the discussion by stating that it was of vital importance to monitor disease progression due to the difficulty in predicting early MF progression. He strongly suggested using disease-modifying agents in patients with early MF only in the context of a clinical trial.

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