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Emerging treatments for classical myeloproliferative neoplasms

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Take-home messages

- An accurate diagnosis is an essential first step in the management of MPN.
- Novel prognostic scores integrating molecular data are being developed.
- Initial data from comparator studies with IFN and HU demonstrate equivalence in their ability to control blood counts and that both agents may deliver molecular and histological responses.
- JAK inhibition is an important modality and data from phase III studies with second line JAK Pacritinib and Momelotinib is important. The management of cytopenia in MF remains challenging and novel agents such as PRM-151, Sotatercept and others are of interest. Telomerase inhibition is also being assessed.

Introduction

The myeloproliferative neoplasms essential thrombocythemia (ET), polycythemia vera (PV) and primary myelofibrosis (PMF, collectively termed MF) have overlapping clinical and biological features. However, an accurate diagnosis is important as increasingly management is nuanced to very specific features of the disease. The recent revision of the WHO diagnostic criteria further emphasizes the distinction between ET and PV and recognizes pre-fibrotic MF as a separate entity.[1] Furthermore, a decision regarding treatment intensity: watch and wait, vs aspirin; vs aspirin with cytoreductive therapy vs experimental therapy follows a risk adapted strategy for PV and ET. For PMF prognostic scoring is used for transplantation only and then a problem-based approach is employed. Currently available prognostic scores are summarized in Table 1. Gaps currently exist with regard to patients who have myelofibrosis following a prior diagnosis of ET or PV and in the integration of data regarding non-driver mutations.

Current state of the art

Survival for high-risk PV patients receiving contemporary care is 10.9 years;[2] in contrast for low-risk ET a standardized mortality ratio of 1 has been reported.[3] Despite current therapy there is an on-going risk of thrombosis, hemorrhage, impaired quality of life and risk of transformation. For example, in treated high-risk PV, residual thrombosis risk is 2.93 per 100 patient-years, with overall risk of PPV-MF (26%), and AML (10%) at 20 years, respectively.[4]

Aspects meriting specific consideration are changes in prognostic scores with CALR mutated ET potentially needing less intensive treatment, refinement of treatment targets and the emergent importance of the leucocyte count as a marker of disease risk. An on-going question has been the relative benefit of interferon alpha (IFN) *vs* hydroxycarbamide (HU). Results from PROUD PV[5] a study with peg-proline interferon alpha2b (PEGINVERA) *vs* HU and an interim analysis from the MPDRC-112 study comparing pegylated-interferon alpha-2a (PEGASYS) vs HU (in both ET and PV)[6] were recently presented. PROUD PV demonstrated better tolerability of PEGINVERA, however rates of hematological adverse events with HU were unexpectedly high. Hematological control was equivalent but 2 cases of acute leukemia, and 3 non-squamous cell skin malignancies occurred on the HU arm.[5] Interestingly the interim analysis from MPDRC-112 study also demonstrated equivalent outcomes, the striking finding from MPDRC-112 was that both arms were equivalent in achieving molecular and histological remission.[6] Further data is required from longer-term follow-up of these studies as at present both agents look equivalent. Stopping IFN has also been reviewed in some detail with data to suggest around 40% of patients who stop may remain off interferon for over 6 months, without further therapy.[7]

Experimental therapies for ET and PV include the JAK inhibitors, histone deacetylase inhibitors and imetelstat. Ruxolitinib has been evaluated in 3 phase III studies, RESPONSE, RESPONSE2 and RELIEF showing that in second line after HC failure/intolerance ruxolitinib effectively controls blood count, spleen size, symptoms and interestingly

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there may be molecular responses in some patients (reviewed in [4]). All of these agents are of interest for both ET and PV but further data is needed regarding long-term safety and efficacy regarding thrombosis and transformation to MF.

Future refinement of prognostic scores is also likely in MF with for several reasons: first *CALR* mutations, especially type1/type1-like, are associated with longer survival and so-called triple-negative (TN) disease much shorter,[8] lastly the presence of mutations in *ASXL1, EZH2, SRSF2, IDH1* or *IDH2* carries a poor prognosis.[9] How this might impact on therapeutic decisions relates mainly to stem cell transplant (SCT). For example, *ASXL1* or TN mutation status in a DIPSS intermediate-1 patient might make them a putative candidate for HSCT, and their absence in an intermediate-2 risk patient perhaps the opposite.

The JAK1/JAK2 inhibitor (JAKi) ruxolitinib as evaluated in

Table 1. Current prognostic scores for patients with PV, ET and PMF.

Polycythemia vera	Essential thrombocythemia	Primary myelofibrosis
Conventional Thrombosis score	**Conventional Thrombosis score**	**IPSS**
Age >60y Previous thrombosis Presence of either variables define a high-risk patient	Age >60y Previous thrombosis Presence of either variables define a high-risk patient	Age >65 Anemia (Hb <100g/L) Leukocytes >25x10^9/L Blood blasts >1% Constitutional symptoms Each variable= 1 point *Categories:* Low-risk= 0 point Intermediate-1 risk= 1 point Intermediate-2 risk= 2 points High risk= 3-5 points
Survival score	**IPSET score**	**DIPSS**
Age >67 (5 points) Age 55-66 (2 points) Leukocytes >15x10^9/L (1 point) Venous thrombosis (1 point) *Categories:* Low-risk= 0 Intermediate-risk= 1-2 High risk= ≥3	Age >60y (1 point) CV risk factors (1 point) Previous thrombosis (2 points) JAK2V617F mutation (2 points) *Categories:* Low-risk= 0 Intermediate-risk= 1-2 High risk= ≥3	Age >65 Anemia (Hb <100g/L) Leukocytes >25x10^9/L Blood blasts >1% Constitutional symptoms Each variable= 1 point, except anemia=2 points *Categories:* Low-risk= 0 point Intermediate-1 risk= 1-2 point Intermediate-2 risk= 3-4 points High risk= 5-6 points
		DIPSS-plus
		DIPSS score RBC transfusion dependency Platelets <100x10^9/L Unfavorable karyotype[§] DIPSS low= 0 point DIPPS int-1= 1 point DIPSS int-2= 2 points DIPSS high = 3 points Each additional variable = 1 point *Categories:* Low-risk= 0 point Intermediate-1 risk= 1 point Intermediate-2 risk= 2-3 points High risk= 4-6 points

CV= cardiovascular; [§]Unfavorable karyotype: complex karyotype or sole or two abnormalities that include +8, -7/7q-, i(17q), -5 /5q-, 12p-, inv(3), or 11q23 rearrangement.

the COMFORT studies delivers spleen volume reduction and improvement in quality of life; prolongation of survival has also been suggested. However, a Cochrane Review concluded that the evidence was insufficient to allow any conclusion regarding survival, mainly due to lack of statistical potency of the phase 3 trials to measure a possible survival gain. This review was conducted before mature data was available and indeed both studies recently reported updates.[10,11] Dose-limiting myelosuppression and an increased risk of infection ranging from common to rare severe infections such as progressive multifocal leucoencephalopathy (reviewed in [12]) can be problematic. A current question pertains to the earlier use of Ruxolitinib which has successfully been used in selected patients with intermediate-1 risk disease and the ReTHINK trial is currently underway for patients with lower risk disease and adverse mutational profile.[13] For higher risk patients a number of studies are assessing the benefit of combining Ruxolitinib with other drugs to either allow adequate dosing or to improve response (reviewed in [4]).

Concerning other JAKi; Pacritinib and Momelotinib are of interest, as is NS018[14] and INCB039110.[15] Pacritinib was evaluated in the PERSIST trials,[16,17] myelosuppression was not as marked as anticipated and 23% of transfusion dependent patients became transfusion independent. In January 2017 an FDA clinical hold due to safety concerns with Pacritinib was lifted. Momelotinib a JAK1/2i delivered anemia-related, spleen and symptom responses.[18] Peripheral neuropathy was reported and might impact its place in the therapeutic algorithm. Currently results of 2 phase III studies (SIMPLIFY-1 & -2), are expected.

Regarding non JAKi therapies Imetelstat, a telomerase inhibitor induced both molecular and fibrosis responses and is being assessed in the IMBARK study. PRM-151, a recombinant human pentraxin-2 (PTX-2) is also being assessed in a phase 2 study (PROMOTE). Sotatercept has shown some activity for anemia in a proportion of patients[19] and the SMAC mimetic (LCL161) is also being assessed in early phase studies.[20]

Future perspectives

Improvements in our understanding of basic biology in the MPNs has driven changes in diagnostic criteria, prognostic stratification and has now delivered important new therapeutic options for patients. Yet gaps persist; longer term data is lacking for most therapies used for PV and ET further data is to be expected regarding IFN and HU and is needed for Ruxolitinib. Concerning MF there is opportunity to deliver even more improvement for example myelosuppression is limiting for some patients with Ruxolitinib and studies with novel agents will deliver important information.

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