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Ruxolitinib for the Treatment of Essential Thrombocythemia

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Abstract

Deregulated Janus Kinase 2 (JAK2) activation is central to the pathogenesis of most myeloproliferative neoplasms (MPNs), of which essential thrombocythemia (ET) is the most common entity. Patients with ET are risk-stratified according to their risk of thrombo-hemorrhagic complications. High-risk patients are offered treatments to reduce their platelet count using cytoreductive therapy. The disease course is often long and therapy intolerance is not infrequent. Ruxolitinib, a Janus Kinase (JAK) 1/JAK2 inhibitor, has demonstrated efficacy in patients with both myelofibrosis (MF) and polycythemia vera and is well tolerated. Side effects include predictable cytopenias and an augmented risk of infections. Ruxolitinib has been investigated in a small group of ET patients who were refractory/intolerant to hydroxycarbamide (HC) and demonstrated improvements in both symptoms and splenomegaly. Of note, a proportion of treated patients (13.2%) also had a significant reduction in platelet counts. However, these results require further validation in comparison with conventional therapy. Recently, a randomized-controlled phase 2 study (MAJIC-ET) assessed the role of Ruxolitinib in patients refractory or intolerant to HC. This study revealed that Ruxolitinib demonstrated some clinical efficacy but was only superior in terms of symptom control. In clinical practice, some individuals with ET do exhaust all potential treatment options and there may well be a role for Ruxolitinib in such patients or those with a significant symptom burden. However, in the wider context the goal of therapy with the use of JAK inhibitor therapy in ET needs to be defined carefully and we explore this within this timely review article.

Introduction

Essential thrombocythemia (ET), an acquired clonal hemopoietic stem cell disorder, is classified as a *BCR-ABL1*-negative myeloproliferative neoplasm (MPN).[1] Other disorders may present with a thrombocytosis and must be carefully excluded at the time of diagnosis.[2]

Deregulated Janus Kinase 2 (JAK2) activation is central to the pathogenesis of most MPNs, including ET. A number of genetic mutations are contributory to JAK-STAT pathway activation. An acquired single point mutation in *JAK2* (valine to phenylalanine at position 617) (*JAK2* V617F), present in 50% to 60% of ET patients, leads to a constitutively active tyrosine kinase.[3] Activating mutations in exon 10 of the thrombopoietin receptor (*MPL*) have been described in between 8% and 10% of ET patients.[4] Lastly, Calreticulin (*CALR*) mutations affecting exon 9 were described by 2 groups in both ET and myelofibrosis (MF) patients lacking *JAK2*/*MPL* mutations and are present in approximately 25% of cases.[5,6] This translates that up to 20% of patients with ET have an as yet unidentified genetic aberration, the so-called "triple negative ET" cohort, which consists of a heterogeneous group of patients with varying clinical outcomes.[7–9] These patients may have other mutations within either JAK2 or MPL genes and it is widely assumed that deregulated JAK-STAT activation is also important in these individuals.[8,9]

ET is generally regarded as a benign disease but carries an inherent risk of progression to post-ET MF, myelodysplasia, or indeed acute myeloid leukemia (AML). Moreover, patients with ET have a shorter than normal life expectancy with an estimated median survival between 20 and 33 years,[10] though this is perhaps likely to be inaccurate due to a lack of long-term robust data. Most complications are related to arterial or venous thrombosis.[11] Bleeding due to platelet dysfunction or acquired von Willebrand syndrome occurs especially with high platelet counts.[12,13] Constitutional symptoms are common and often inadequately recognized and managed.[14,15] A unique clinical assessment tool called the MPN Symptom Assessment Form Total Symptom Score had been devised and validated in MPN patients.[16]

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Some conditions can resemble ET in the clinical setting; the recent World Health Organization (WHO) revision has particularly highlighted the entity prefibrotic-MF (pre-MF).[17] Pre-MF is defined by the presence of megakaryocytic proliferation and atypia with reticulin fibrosis grade 0 to 1 on bone marrow; a driver molecular mutation (*JAK2V617F*, *CALR*, or *MPL*), and one of anemia, leukocytosis, splenomegaly and an elevated LDH. Several studies have reviewed patients previously classified as ET and re-stratified a considerable proportion of patients as pre-MF (180/1071: 16.8%)[18] and also with patients reported as diagnosed with MF patients.[19] ET, pre-MF, and indeed as also highlighted by the WHO, polycythemia vera (PV), share similar characteristics, for instance, all affect young patients (<60 years) but the pre-MF population presents more frequently with splenomegaly, extreme leukocytosis and thrombocytosis than ET.[18,20] Regarding nondrivers mutations, it seems the mutational landscape and distribution of *ASXL1*, *SRSF2*, *U2AF1*, *SF3B1*, *EZH2* or *IDH1/2*[21] are comparable to that seen in overt-MF. Treatment for pre-MF has not been well defined. Several studies have suggested that the incidence of transformation to MF and AML is higher compared with ET. While in comparison with overt-MF population, the incidence of leukemia is lower and overall survival higher for pre-MF. Therefore, it is very important that in studies evaluating pathogenesis or therapeutics of ET that these other entities are excluded.

ET patients are traditionally risk-stratified based upon their age and/or history of vascular complications.[18] A more recent risk scoring system entitled the International Prognostic Score of thrombosis (IPSET-thrombosis) utilized age, thrombosis history, cardiovascular risk factors, and *JAK2* mutation status, resulting in 3 distinct risk groups. This system defined the risk of thrombosis better than the traditional 2-tiered model.[22] However, limitations of the IPSET-thrombosis system are a lack of prospective validation and the large intermediate-risk group for which the optimal management strategy is uncertain.

Ruxolitinib (Novartis, Basel, Switzerland), a selective JAK 1/2 inhibitor, is currently approved for treatment of MF,[23–25] and moreover recently received approval for patients with PV who are refractory/intolerant to hydroxycarbamide (HC).[26] Here we discuss the rationale of the potential use of Ruxolitinib in ET.

Current treatment of ET

Treatment for patients with ET varies according to individual risk stratification, and ranges from aspirin alone to the use of cytoreductive therapy as shown in Table 1.[10] Treatments in ET are not intended to be curative but rather directed at reducing the thrombo-hemorrhagic risk. Unless contra-indicated, most patients should be started on aspirin. A retrospective analysis showed that aspirin for low-risk ET reduced venous thromboembolism in those with the *JAK2* mutation and arterial thrombosis in patients with cardiac risk factors.[27] Although recently the benefit of aspirin in patients with CALR mutations was questioned our own practice is to use this agent unless bleeding occurs or there is another contra-indication.[28] Patients in the high-risk group require cytoreductive therapy to reduce the augmented risk of thrombosis.[10]

A landmark trial that investigated the efficacy of HC in high-risk ET was published in 1995.[29] Patients were randomized into receiving HC to keep the platelet count $<600 \times 10^9$/L or received no myelosuppression. Antiplatelet agents were permitted but not mandated. This trial demonstrated that HC treatment resulted in significantly less thrombosis compared with no cytoreduction (3.6% vs 24%).[29]

Anagrelide (Agrylin/Xagrid, Shire Pharmaceuticals, UK), an inhibitor of cyclic AMP phosphodiesterase III, was initially designed as an antiplatelet agent, and was subsequently found to inhibit both megakaryocyte differentiation and proliferation.[30] It is approved for second-line therapy for ET in the EU, and for therapy of MPN by the Food and Drug Administration (FDA).

Table 1

Previous Clinical Trials in High-Risk ET

	Cortelazzo et al[29]	PT-1[31]	ANAHYDRET[32]	EXELS[33]	MAJIC-ET[63]
Design	HC vs control	ANA + aspirin vs HC + aspirin	ANA vs HC	ANA vs other CRT (mostly HC) Nonrandomized	RUX vs BAT
Year of primary report	1995	2005	2013	2016	2017
Patient group	High risk	High risk	High risk	High risk	High risk
Number of participants	114– 56 HC 58 Control	809– 404 HC + aspirin 405 ANA + aspirin	259– ANA 122 HC 137	3649– ANA 804 Other CRT 2666 ANA + other CRT 141	110– 58 RUX 52 BAT
Primary end point/s	Risk of thrombosis	Composite endpoint of thrombosis, hemorrhage, death from vascular event	Reduction in platelets, hemoglobin, WCC, and total number of ET related events Planned for noninferiority	Safety and pregnancy outcomes	Reduction in platelets, WCC, and spleen size, ie, complete hematological response per ELN criteria
Outcome	HC superior to control	HC + aspirin superior to ANA + aspirin Higher rates of arterial events, hemorrhage, and MF transformation with ANA. Lower rates of venous thrombosis with ANA	ANA noninferior to HC	Higher rates of transformation to MF with ANA, higher rates of transformation to AML with HC	RUX noninferior to BAT

AML = acute myeloid leukemia, ANA = anagrelide, BAT = best available therapy, CRT = cytoreductive therapy, EXELS = Evaluation of Xagrid Efficacy and Long-term Study, ET = essential thrombocythemia, HC = hydroxycarbamide, MF = myelofibrosis, RUX = Ruxolitinib, WCC = white cell count.

Two randomized studies, primary thrombocythemia-1 (PT-1)[31] and ANAHYDRET,[32] compared the efficacy and safety of HC versus anagrelide in combination with aspirin for PT-1 and no aspirin in ANAHYDRET.[31,32] Both confirmed the efficacy and tolerability of anagrelide as a second-line agent, PT-1 demonstrating that anagrelide was inferior to HC and ANAHYDRET was a noninferiority study that met its primary endpoint. The efficacy and safety of anagrelide in ET was further clarified with the results of the Evaluation of Xagrid Efficacy and Long-term Study (EXELS) study (NCT00567502). This large phase 4 study demonstrated that anagrelide was most frequently prescribed for young patients and confirmed the results from the PT-1 study.[33]

Interferon-α may lead to up to 80% hematological responses as defined by reduction of hematocrit, white blood cell (WBC), and platelet count.[34] However, it can cause significant side effects leading to discontinuation in up to 25% of cases. Hence, it is usually reserved for younger patients or those who are pregnant.[34] The efficacy of HC and interferon-α therapy has not yet been compared, however, the results of the MPD-RC 112 trial investigating the efficacy of pegylated interferon-α against HC as a first-line treatment in high-risk ET and PV is awaited.

Other potential therapies for ET include alkylating agents such as Pipobroman and Busulfan. Pipobroman is effective in achieving hematological response but is clearly leukemogenic.[35,36] On the other hand, the leukemia-risk of Busulfan was modest when it was used as a short single course.[37] The use of these alkylating agents has been reserved for patients with no other option or limited life expectancy. Particular caution should be observed on sequential use of HC and Busulfan that can certainly result in higher leukemia risk.[38]

Recent therapeutic advances in MPN utilize the knowledge of the deregulated JAK/STAT pathway, which is targetable with JAK inhibitors and other agents.[24,25] This review focuses on Ruxolitinib in ET but other JAK inhibitors exist with good efficacy in MF, such as Pacritinib,[39] Momelotinib,[39–41] and Fedratinib.[42,43]

Other novel agents are currently being investigated in MPNs including ET. These agents usually target pathways downstream of JAK/STAT activation, such as the phosphatydylinositol-3'-kinase pathway. Targeting the telomere has additionally emerged as an area of interest in myeloid disorders. Imetelstat is a telomerase inhibitor that exhibited good efficacy in both MF and ET and was also observed to cause molecular responses in some patients who had clonality markers, such as JAK2 V617F mutation.[44,45] Moreover, Givinostat and Vorinostat, both histone-deacetylase inhibitors, have demonstrated improvements in splenomegaly, symptomatology, and allele burden in phase II studies of patients with ET.[46,47]

Despite the multiple agents available or undergoing exploration in ET, there is still a significant unmet medical need. In particular, there are only limited treatment options for patients who develop resistance or intolerance to first-line therapy. This group of patients requires a novel agent or combination therapy to control their symptoms and reduce complication risks. In a recent report, the Landmark survey identified that a further treatment aspiration for patients was to reduce risk of transformation although no current therapies have been shown to achieve this.[48]

Pharmacology of Ruxolitinib

Ruxolitinib (INCB18424) has a molecular weight of 306.4 g/mol. Its chemical name is (R)-3-(4-(7H-pyrrolo[2,3d-]pyrimidin-4-yl)-1H-pyrazol-1-yl)-3-cyclopentylpropanenitrile phosphate, with a molecular formula of $C_{17}H_{18}N_6$. In vitro, Ruxolitinib reduced proliferation of the *JAK2* V617F Ba/F3 cell line and interleukin-6 signaling. These findings were replicated in primary PV samples.[49,50] In a *JAK2 V617F* murine model, Ruxolitinib improved survival, splenomegaly, and normalized the cytokine profile. The half maximal inhibitory concentration (IC_{50}) values of Ruxolitinib for JAK1 and JAK2 are 3.3 and 2.8 nM, respectively.[49]Table 2 summarizes the characteristics of Ruxolitinib.

Oral Ruxolitinib is rapidly absorbed. Maximal plasma concentration was achieved within 1 to 2 hours in fasted subjects, coinciding with maximal inhibition of STAT3 phosphorylation.[51] Metabolism is predominantly by CYP3A4 and to a minor degree by CYP2C9 resulting in a less potent metabolite, M18. Inducers or inhibitors of CYP3A4 significantly affect Ruxolitinib metabolism.[52] Ruxolitinib is mostly excreted in the urine and to a small extent in the feces.[53] The half-life of Ruxolitinib and metabolites is about 6 hours. A phase 1/2 trial established the tolerated starting dose of Ruxolitinib in MF to be 15 mg twice a day followed by individualized titration.[54]

Clinical efficacy of Ruxolitinib

Phase 3 studies, COMFORT-1 and COMFORT-2, led to approval of Ruxolitinib for the management of symptoms and splenomegaly in MF. COMFORT-1 (NCT00952289) included 309 patients randomized 1:1 to either Ruxolitinib or placebo; 41.9% in the Ruxolitinib group had a 35% spleen volume reduction compared with 0.7% in the placebo group. Symptom improvement of more than 50% was observed in 45.9% of Ruxolitinib group and 5.3% of the placebo group. These benefits were seen regardless of *JAK2* mutation status.[24] A survival advantage was subsequently demonstrated in the Ruxolitinib arm but may have even been underestimated by the crossover design of the trial.[55] COMFORT-2 (NCT00934544) included 219 patients randomized in a 2:1 fashion to Ruxolitinib or best available therapy (BAT). The primary end point, a 35% reduction of spleen volume at 48 weeks, was attained by 28% of the Ruxolitinib group. Patients in the Ruxolitinib-treated group also reported significant symptom improvement.[25] At 144 weeks, splenomegaly response was sustained and improved survival compared with BAT was additionally demonstrated.[23]

Two studies investigating the role of Ruxolitinib in PV have been recently reported. The first was a phase 2 trial in high-risk PV/ET patients who were refractory or intolerant to HC (NCT00726232). Thirty-four PV patients received Ruxolitinib for a median of 35.0 months, 97% achieving a hematocrit <45% without phlebotomy by week 24. Moreover, spleen size reduction was observed in 63% of patients by week 144. Maintained symptom improvement was observed as early as week 4.[56] This study established a starting dose of 10 mg twice daily. The second,

Table 2

Characteristics of Ruxolitinib

Drug name	Ruxolitinib
Phase	Phase 2 studies for ET
Indication	Complications and symptoms management in patients with high-risk ET who are intolerant or resistant to HC
Pharmacology	Selective JAK1/JAK2 inhibitor
Route of administration	Oral
Chemical structure	$C_{17}H_{18}N_6$
Pivotal trials	NCT00726232 trial and MAJIC trial

Table 3

Current Clinical Trials Assessing Ruxolitinib in ET

Trial	Identifier	Design	Eligibility Criteria	Primary Outcome Measure
RESET 272	NCT03123588	ANA	High-risk ET—resistant or intolerant to HC	Control of platelets and WBC
Ruxobeat	NCT02577926	BAT	High-risk ET—including treatment naïve patients	Control of platelets, WBC, spleen size, and reduction in symptoms
RUXBETA	NCT02962388	ANA or IFN-α	High-risk ET—resistant or intolerant to HC	Avoidance of treatment failure

WBC = white blood cell.

RESPONSE (NCT01243944), was a phase 3 study in PV patients demonstrating resistance/intolerance to HC. Here patients were randomized 1:1 to receive either Ruxolitinib or BAT. Crossover occurred at week 32 if primary endpoints were not met or later. A total of 222 patients were randomized. The composite primary endpoints, hematocrit control and 35% spleen volume reduction, were reached in 20.9% of Ruxolitinib and only 0.9% of BAT groups, respectively. A 50% reduction in the MPN-SAF total symptom score occurred in 49% of the Ruxolitinib group but only 0.9% in the BAT group.[57] Recent 80-week follow-up data from the RESPONSE study were presented during 2015, these data were reassuring for prolonged maintenance of responses.[58]

Although these studies demonstrate a possible role of Ruxolitinib in PV and led to its approval for this indication by the FDA and European Medicines Agency, the relevance of the primary end points in this disorder, particularly spleen size reduction might be questioned. Certainly the limited therapy options for such patients are also demonstrated by the fact that over 50% of BAT patients went back to receive HC. Currently, there is no evidence that Ruxolitinib reduces the risk of PV transforming to MF and AML. Nonetheless, Ruxolitinib appeared useful in maintaining adequate hematocrit control in patients with high-risk PV who are refractory to HC. This and control of leukocytes and inflammation may have translated to a lower than expected risk of thromboembolic events in patients who received Ruxolitinib in the RESPONSE trial (1.2 events per 100 patient years).[57] This may well be due, at least in part, to the effect of Ruxolitinib on reducing both the WBC count and other cells involve in moderating inflammation and immune response like natural killers and T regulatory cells; and inflammatory markers (eg, IL6, TNF-α, or C-reactive protein) which may be responsible patient's constitutional symptoms.[59] However, this was not prespecified as an endpoint in the study and due to the crossover aspect of the trial cannot be evaluated further. Two other studies have evaluated the efficacy of Ruxolitinib in PV: RELIEF,[60] and RESPONSE 2[61] demonstrating similar results. In the real-world setting, data from the MAJIC-PV trial are awaited.

Safety and tolerability of Ruxolitinib in MF and PV

The safety profile of Ruxolitinib in MPN was primarily established in the COMFORT trials. Discontinuation rates were low in these 2 studies, ranging from 8% to 11% within study periods. Grade 3 to 4 nonhematological malignancies were uncommon. Common adverse events included fatigue, diarrhea, weight gain, and dyspnea.[24,25]

Hematological toxicity was noted to be more prevalent in the Ruxolitinib arm as compared to BAT in COMFORT-2. Anemia was mostly managed with dose modifications (5%), transfusions, or both. More patients in the Ruxolitinib arm required at least 1 unit of packed red cells (51% vs 38% in BAT arm) though the mean number of transfusions per month was not significantly different.[25] Thrombocytopenia usually led to dose modification or interruption in both studies. In COMFORT-1, grade 3 to 4 bleeding episodes took place with similar rate in both Ruxolitinib and placebo arms. Bruising occurred more often in patients on Ruxolitinib but was grade 3 in only 1 patient.[24] Progression to AML was similar in both arms of these studies.[24,25]

In the phase 1/2 PV/ET study, grade 3/4 leukopenia was observed in 3 patients (7.7%) while grade 3 anemia was observed in 1 patient only (2.6%). Two patients had more than grade 3 infections, both involving the respiratory tract. Nonhematological adverse events included weight gain, diarrhea, cough, and headache.[62] Similar data are available from the RESPONSE trial, both the initial report and the 80-week follow-up data.[58] In MAJIC-ET, hematological toxicity was again notably more common in the Ruxolitinib group with grade 3/4 anemia occurring in 21% compared with 0% in the BAT group, and 2 patients discontinued Ruxolitinib treatment because of anemia.[63] Grade 3 infections were also more frequent with Ruxolitinib occurring in 15.5%, compared with 3.5% of those treated with BAT, although no grade 4 infections were reported.

There is increasing evidence that Ruxolitinib is potently immunosuppressive as higher incidences of herpes infections, urinary and respiratory infections have occurred in Ruxolitinib-treated patients across all the phase 3 trials reported to date. Increased risk of basal-cell and squamous-cell carcinomas was demonstrated in the RESPONSE trial but did not result in interruption of therapy. However, it was noted that more patients with a prior history of these conditions were assigned to the Ruxolitinib and these patients had higher exposure previously to HC.[57] Case reports of *Cryptococcus neoformans* pneumonia,[64] *Pneumocystis jiroveci* pneumonitis,[65] bilateral toxoplasmosis retinitis,[66] and hepatitis B reactivation[67] among others have been described as complications in patients receiving Ruxolitinib as discussed in a recent review.[68] Significant morbidity involving Ruxolitinib and infection have also been reported, for example, an Epstein-Barr virus-driven lymphoproliferative disorder[69] and a case of progressive multifocal leukoencephalopathy (PML) associated with JC-Virus 40[70] resulted in permanent disability. Well-described effects on T cell subsets,[71] natural killer cells,[72] and dendritic cell function and migration[73] have also been described and may contribute to the higher rate of atypical infectious complications occurring in a number of patients.[68]

Ruxolitinib in ET

Table 3 summarizes the current studies investigating the use of Ruxolitinib in ET. An open label, phase 2 study investigating the efficacy and safety of Ruxolitinib in patients with high-risk PV and ET who are refractory or intolerant to HC has been reported. The PV aspect of the study was discussed above. There were 39 high-risk ET patients resistant to HC who were treated with Ruxolitinib within this trial for a median exposure of 205.6

weeks. All patients were followed up for a period of 48 months. At the time of data cut off, 61.5% of patients were still receiving Ruxolitinib.[62] Efficacy was as follows: 13.2% of those with platelet $>400 \times 10^9$/L had reduction to $<400 \times 10^9$/L; 72.7% with WBC count $>10 \times 10^9$/L had a WBC $<10 \times 10^9$/L at 48 months. These data suggest more than modest efficacy and the median exposure period is actually long for a phase II study though it is appropriate for a disease with a protracted course such as ET. All of the ET patients with a palpable spleen had >50% reduction; improvement in symptoms were also reported.

In a recent publication of a cohort of patients from this study, Pieri et al's report that 3 patients (2 ET and 1 PV) achieved and maintained a complete molecular response (CMR) with Ruxolitinib at 5-year review.[56] At the time of CMR, the patient with PV also had complete hematological remission while the patients with ET had partial hematological remission, although their bone marrows displayed persistent morphological features of MPN. Furthermore, the patient with PV had a persistent *TET2* Y867H mutation at 5 years. These findings, if replicated, could be of significant importance and it will also be essential to look at molecular responses for other "nondriver mutations" in addition, such as *ASXL1*. The only other therapies reported to induce molecular responses in ET are interferon alpha and imetelstat as discussed above. Data for effects on clones such as *TET2* as discussed above suggest interferon may not be comprehensively effective[74] and there was also an admixed clonal response for imetelstat where clonal emergence with therapy was identified.[75]

MAJIC-ET, a phase 2 trial in which 110 patients with high-risk ET either intolerant or resistant to HC, were randomized on a 1:1 basis between Ruxolitinib and BAT, has recently reported initial results.[63] BAT consisted predominantly of HC (71.1%), anagrelide (48.1%), and interferon (40.4%), with many patients in this group receiving more than 1 line of therapy at different time points. The primary outcome was achievement of a CR as defined by a platelet count of $<400 \times 10^9$/L, white cell count $<10 \times 10^9$/L, and a normal spleen size. Ruxolitinib was shown to be noninferior to BAT with 46.5% achieving CR compared with 44.2% in the BAT group. Similarly, PR was largely equivalent in the 2 groups, occurring in 46.5% treated with Ruxolitinib compared with 51.9% of those receiving BAT. There was no evidence of a difference in the duration of overall response between Ruxolitinib and BAT, and OS and PFS at 1 year were also similar. Safety and tolerability were similar to that reported in PV and MF.

Molecular analysis was also performed in MAJIC-ET, with the overall mean allele burden for JAK2, MPL, and CALR mutations not reduced after 1 year of treatment with Ruxolitinib. Interestingly, a single CMR was seen in a *JAK2* V617F positive patient and 2 occurred in *CALR*-mutated patients treated with Ruxolitinib. With regard to disease transformation, there were no statistically significant differences between the 2 groups. Importantly the validity of CMR was called into question as a consequence of one of these patients attaining a CMR and then progressing to PET-MF. Thrombosis was seen in the Ruxolitinib group on 11 occasions in 10 patients, compared with 5 events in 3 patients in the BAT group; however, thrombosis-free probability between the 2 groups, although borderline, was not statistically significant ($P = 0.09$).

Overall 85 patients completed a symptom burden questionnaire at baseline and at least once during treatment. The maximum total symptom score reduction taken from any point during the first 12 months of treatment was significantly greater in the Ruxolitinib group with a median reduction of 32% compared with 0% in the BAT group. Ruxolitinib was especially noted to result in improvements in pruritus, depression, concentration and resulted in a greater ability to perform normal activities compared with BAT.

While the results from MAJIC-ET do not suggest that Ruxolitinib should be preferred to currently available therapies in the management of most patients with ET, it has shown similar efficacy and therefore could be considered as an alternative option if available. Furthermore, for a subset of patients with particularly troublesome symptoms, it has shown to be efficacious and should be considered at an earlier time point where possible. The relatively high costs of Ruxolitinib treatment and potential for toxicities, particularly infective complications, relating to the long-term exposure required in patients with ET, are probably the main barriers to routine implementation. Further studies are also warranted to evaluate, in more depth, the role of Ruxolitinib in preventing both thrombosis and transformation.

Conclusion

Though the use of Ruxolitinib as a first-line therapy has been well established in MF, usage in ET, and perhaps PV, needs further evaluation. This is in part due to the fact that these patients with ET have near-normal life expectancy, unlike in MF, and hence potential exposure to this agent could be long. Survival benefits may therefore be harder to detect in ET. Similarly, the long-term use of Ruxolitinib in patients with ET has to be balanced with the potential risks, albeit small, of infection and secondary malignancy, particularly cutaneous squamous cell cancers, and by the lack of long-term follow-up data. Nonetheless, Ruxolitinib may play a crucial role in patients with high-risk ET patients refractory/intolerant of HC since there are limited options of therapy currently available. For example, more than half of the BAT in RESPONSE study was HC. ET is a chronic long-term condition and while other second-line therapies exist many patients become intolerant of them and/or are too young to be considered for agents such as busulfan. Future studies will also need to directly address the question of Ruxolitinib's impact on symptom improvement and reduction of thrombotic events. In fact, a recent study demonstrated possible biological reasons behind reduction of thrombosis by Ruxolitinib.[76]

As the first therapy that specifically targets the deregulated JAK-STAT signaling in MPN, Ruxolitinib has the potential to transform therapeutic options for these disorders. In MF, Ruxolitinib has been shown to have a profound effect on symptoms, spleen size, and improved survival. In HC resistant/intolerant PV, control of the blood count, symptoms, and splenomegaly were demonstrated for patients where treatment options may be limited. Importantly there was a suggestion of reduced thrombotic events, but no evidence of effects upon transformation of disease to MF or AML in PV patients.

To date there is much less data concerning efficacy of Ruxolitinib in ET yet there is a well-defined need for new therapeutic approaches. This condition, the commonest of the classical MPNs, often requires treatment over the course of many decades, patients often cycle through many of the conventional therapies which do usually control the blood count and reduce the risk of thrombosis but do not affect the natural history of the disease or symptom burden which can be profound. These data to date suggest that Ruxolitinib can control myeloproliferation in ET though its efficacy in controlling thrombocytosis per se is relatively low, control of the leukocyte count, which may be of

augmented importance, is more impressive. The relevance of improvement in quality of life also cannot be overemphasized where some patients have a high symptom burden from a disease that will be present for several decades. Recently available preliminary data suggesting some ET patients may enter a molecular remission with Ruxolitinib are tantalizing. However, the economic justification for using this expensive therapy will also be more challenging in ET. Furthermore, while considered relatively safe, Ruxolitinib is an immunosuppressant: increasing propensity for infection and developing skin cancers, especially in those predisposed. Hence, a thorough risk-benefit assessment is mandated before considering Ruxolitinib as an agent with therapeutic benefit in ET.

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