REVIEW

Allogeneic stem cell transplant for myelofibrosis patients over age 60: likely impact of the JAK2 inhibitors

V Fauble, J Leis and RA Mesa

The myeloproliferative neoplasm, myelofibrosis (MF), has only one therapeutic intervention that is potentially curative in these individuals, specifically that of allogeneic stem cell transplantation (ASCT). ASCT has been utilized up to this juncture, primarily in younger individuals with higher risk disease. There is more limited data on outcomes in individuals over the age of 60 years. The choice of an individualized therapeutic intervention for a patient with MF is a very complex issue and is dependent on several factors. The first factor being their overall prognosis with their illness (which can vary from a median of 2 years in high-risk patients to over 10 years in low-risk patients) and the potential impact of a therapeutic intervention not only on survival but also on quality of life. Current available therapies have been strictly palliative for disease-associated anemia and/or splenomegaly. At present, we have a new generation of inhibitors of JAK2 (Ruxolitinib, CYT387, SB1518, TG101348, with others in development), which have been shown to improve splenomegaly, improve symptomatic burden of illness and improve quality of life. In addition, these inhibitors of JAK2 may have an impact on the natural history of MF, but confirmation of the presence and degree of this impact is still pending. Clinical availability of JAK2 inhibitors may alter the timing of transplant in marginal transplant candidates (that is, those over the age of 60), may have a role preceding ASCT to improve spleen size and performance status before transplant and might be frontline therapy in intermediate and high-risk patients who are not candidates for ASCT.

Leukemia Supplements (2012) 1, S2–S7; doi:10.1038/leusup.2012.2

Keywords: myelofibrosis; JAK2 inhibitor; Ruxolitinib; allogeneic stem cell transplant; myeloproliferative neoplasm; splenomegaly

MYELOFIBROSIS NATURAL HISTORY AND HETEROGENEOUS PROGNOSIS

Myeloproliferative neoplasia (MPN)-associated myelofibrosis (MF)¹ is recognized to comprise clinically the entities of both individuals with primary myelofibrosis (PMF) and those who have progressed from an antecedent polycythemia vera or essential thrombocythemia (post PV MF/post ET MF). MF is a progressive, chronic myeloid neoplasm that clinically involves progressive cytopenias, splenomegaly and intramedullary fibrosis, resulting in significant symptomatic accumulation. It can potentially transform to either acute myeloid leukemia or the blast phase of MPN. We recognize that in 2011 the prognosis for this group of individuals is heterogeneous (Table 1). Prognostic markers that have been of great value in understanding the disease have been identified through both the International Prognostic Scoring System² and the subsequent Dynamic International Prognostic Scoring System (DIPSS).³ These prognostic criteria have identified that age over 65 years, hemoglobin of less than 10 g/dl, white count of greater than 25×10^9 per liter, the presence of circulating blood blasts and significant constitutional symptoms (weight loss greater than 10%, fevers, night sweats) have been each multivariately associated with worsening survival. A further iteration on the prognosis was identified to involve three additional factors in the DIPSS Plus criteria,⁴ including transfusion-dependent red cell anemia, a platelet count of less than 100×10^9 per liter and complex karyotype or specific chromosomal abnormalities. By utilizing these dynamic criteria, we can stratify the prognosis for individuals from high-risk disease with a median survival of 16 months to a low-risk disease with a mean survival of 185 months. By utilizing these approaches, we can best estimate the natural history of MF

for the patient under our care and try to delineate the role of allotransplantation, that of experimental therapies or a combination of both.

ALLOGENEIC STEM CELL TRANSPLANT FOR MF: BRIEF HISTORY AND CURRENT OUTCOMES

Allogeneic stem cell transplant (ASCT) remains the only potentially curative option that exists for MF. However, given the heterogeneous nature of this life-threatening disorder, it is imperative to tailor a treatment modality to the patient and the disease specifications. Historically, ASCT has been reserved for a highly select group of patients based on age and prognostic features of a disease given its significant morbidity and mortality due to graft failure, graft versus host disease and regimen-related toxicity. The use of conventional intensity conditioning in all patients with MF is associated with significant mortality (35–45%; Table 2). The breakdown of age-specific mortality has not been well delineated as yet, especially in elderly patients. The stepwise alteration of the high-dose regimens and the subsequent development of the reduced intensity conditioning (RIC) have enabled ASCT to be offered to elderly patients with comorbid conditions by including them in the potential candidacy for ASCT.⁵

There are currently no randomized prospective studies to know exactly who is the optimal candidate for transplant and when should transplant be implemented. However, the application of specific prognostic scoring systems designed to help guide decisions related to hematopoietic stem cell transplantation (HCT) has been quite helpful with identifying appropriate candidates. More aggressive treatment modalities are favored in

intermediate 2 and high-risk patients where the patients have a median survival of 2–4 years, whereas conventional therapy is applied in the low-risk to intermediate 1 risk group where the patients have a median survival of 8–11 years (Table 1). Many prognostic scoring systems have been developed as mentioned above.

A transplant-specific prognostic score based on transfusion requirement, spleen size and donor type was recently proposed. Forty-six patients were classified into either high- or low-risk groups based on the criteria listed above. The actuarial survival of low-risk and high-risk patients was 77 and 8%, respectively. This was because of a higher transplant related mortality (TRM) for the high-risk group (relative ratio 6.0) and a higher relapse-related death (relative ratio 7.69).⁶ Another prognostic factor that has been identified is the presence of the JAK2 v617f mutation. Earlier studies suggested that positivity for the JAK2 mutation did not represent a prognostic factor.^{7,8} However, more recent studies

suggest that the presence of the JAK2 v617f mutation may improve disease-free and overall survival (OS) in patients receiving an ASCT.⁹ In the European Bone Marrow Transplant study, it was found that JAK2 v617f mutation-positive patients had a better disease-free and OS rate than JAK2 v617f-negative patients (56 vs 34% and 76 vs 42%); however, the data set was incomplete and was therefore not included in the multivariate analysis.¹⁰ In a recent abstract by Alchaby *et al.*,¹¹ yet another transplant-specific prognostic scoring system was proposed with the intention of defining a prognostic model for predicting outcome of RIC-ASCT for MF. The result was a simple prognostic scoring system that took into account age (> 57 years), constitutional symptoms and JAK2 v617f status. These factors in conjunction with other scoring systems (Lille) helped define distinct groups to predict OS after RIC-ASCT (abstract by Alchaby *et al.*¹¹). Further studies are needed to clearly define the prognostic significance of the JAK2 v617f mutational status on ASCT outcome.

A very interesting observation was made in the analysis by Scott *et al.*¹² The prognostic utility of the DIPSS in 170 patients with MF who were considered candidates for ASCT was studied. The study showed that the DIPSS classification directly correlated with transplant outcomes such as overall mortality, failure due to relapse or death, as well as non-relapse mortality. Patients with high-risk disease were 4.11 times more likely to die after ASCT than patients with low-risk disease. Additional factors such as donor type, ASCT comorbidity index, stem cell source, JAK2 V617f mutational status and pre-ASCT splenectomy were analyzed to delineate any association, if present, with post-ASCT outcomes. Pre-ASCT splenectomy was the only variable that was significantly associated with mortality (Scott *et al.*;¹² Zihai *et al.*¹³).

Patients with MF who are early in their disease typically have an indolent slowly progressive course. Challenges in therapy become increasingly more arduous as the disease advances. The only treatment modality with curative and sustainable benefit remains transplant. However, this has historically been reserved for patients with advanced disease stages. The most appropriate timing of transplant in MF has been debated in many studies and remains unclear. Because the median survival of patients with PMF is 4–5 years, the decision about timing of transplant needs to be a balance of risk to benefit. An argument could be made for transplantation upfront for all younger patients with suitable donors, and more conservative approaches could be utilized for patients who are older with comorbid conditions. This has clearly been the approach in the past with the use of RIC regimens. This is of particular significance given that the median age at diagnosis is in the seventh decade of life.¹⁰ Many patients with PMF, post-PV

Table 1. Prognostic scoring models for myelofibrosis

Risk model	Risk factors	Points earned	Risk score and stratification
Lille ³⁶	Hgb < 10 g/dl	1	Low: 0 Intermediate: 1 High: 2
	WBC < 4.0 or > 30 × 10 ⁹	1	
Cervantes ³⁷	Hgb < 10 g/dl	1	Low: 0–1 High: 2–3
	Circulating blasts > 1%	1	
	Presence of constitutional symptoms	1	
Dynamic IPSS ³	Age > 65 years	1	Low: 0 Intermediate 1: 1 Intermediate 2: 2–3 High: > 4
	Hgb < 10	2	
	WBC > 25 × 10 ⁹	1	
	Circulating blasts > 1%	1	
	Presence of constitutional symptoms	1	
DIPSS plus ⁴	The above plus:		
	Red cell transfusion needs	1	
	Platelet count < 100K	1	
	Unfavorable karyotype	1	

Table 2. Summary of recent allogeneic HCT trials in myelofibrosis

	Ballen ²	Kerbaui ³⁸	Patriarca ³⁹	Stewart ⁴⁰	Merup ⁴¹	Rondelli ⁴²	Samuelson ⁵	Snyder ⁴³	Kroger ¹⁰	Bacigalupo ⁶
N	289	104	100	51	27	21	30	23	103	46
Median age	47 (18–73)	49 (18–70)	49 (21–68)	49 (19–64)	40 (5–63)	54 (27–68)	65 (60–78)	54 (46–68)	55 (32–68)	51 (24–67)
Conditioning	229 MA NMA 21/RIC 39	95 MA 9 RIC	49 MA 51 RIC	27 MA 24 RIC	17 MA 10 RIC	RIC	RIC	RIC	RIC	RIC
OS	30–40% at 5 years	61% at 7 years	42% at 3 years	31–44% at 3 years	71%	84% at 3 years	45% at 3 years	56% at 2 years CsA/MMF 93% at 2 years tacro/siro	67% 5 years	45% at 5 years
NRM	32–48% at 1 year	34% at 5 years	43% at 3 years	32–41% at 3 years	10–30%	10%	30% at 3 years	33% CsA/MMF 0% Tacro/siro	16%	24%
Graft failure	9–27%	10%	12%	17%	3/27	5%	3/30	1/23	2%	NR
GVHD risk	24–43% acute 23–40% chronic	64% acute 85% chronic	41% acute 43% chronic	29–38% acute 30–35% chronic		33% acute 45% chronic	15–40% acute 45% chronic	10–60% acute 61% chronic	27% acute 43% chronic	37% acute 31% chronic

Abbreviations: CsA, cyclosporine A; GVHD risk, Graft versus host disease risk; HCT, hematopoietic stem cell transplantation; MA, myeloablative; MMF, mycophenolate mofetil; NRM, non-relapse mortality; OS, overall survival; RIC, reduced intensity conditioning.

and post-ET-related MF are 60 years and older. They have been previously excluded from HCT given the concern of regimen-related toxicity.⁵ Age represents one of the most significant factors that adversely impacts ASCT outcomes. This inverse relation between age and transplant outcome is related to many factors such as comorbidities and age-specific metabolic disorders that render those patients susceptible to regimen-related toxicity.

The use of conventional dose conditioning regimens has resulted in 5-year survival rates ranging from 40 to 60%, but associated with significant non-relapse mortality at 1 year ranging from 20 to 48%. The use of conventional myeloablative conditioning regimens is associated with a high TRM, which is more likely in patients older than 45 years (Stewart *et al.*¹⁴). Supporting this, advanced age was considered the most significant prognostic factor in several studies.^{15,16} With the advent of RIC regimens, the paradigm for allogeneic transplant has shifted in ASCT for older patients with PMF; the clear advantage being reduction in treatment-related morbidity and mortality, as well as the ability to offer transplant as a therapeutic option to more patients with an advanced age. Successful engraftment, durable remissions and lower transplant-related mortality have been demonstrated with the use of RIC in a number of studies that included older individuals (Table 2). A recent study by Samuelson *et al.*,⁵ in which 30 patients aged 60 years or older were transplanted for MPN-associated MF, showed that patients in their 60s and even into their 70s could be successfully transplanted achieving complete hematological recovery. In this group of patients, OS and progression-free survival were 45 and 40% at 3 years, respectively, with a non-relapse mortality of 30%. Several other previous reports have also highlighted SCT as a therapeutic option in older patients with MF (Table 2). Given that the median age MF and post ET/PV MF is 67 years, many patients are excluded from the option of HCT because of concerns about regimen-related toxicity. Over time, stepwise modification of the high-dose conditioning regimens and the tolerability of RIC regimens in patients well into the seventh decade of life have opened new avenues of potential cure for these individuals. With regard to the appropriate timing for ASCT, the data suggest that patients would benefit most with ASCT if seen while in the intermediate-risk category and before the age of 60 years.

RELEVANCE OF THE SPLENOMEGALY AND SPLENECTOMY IN ASCT FOR MF

Splenomegaly in PMF or post-PV/ET MF is the result of extra-medullary hematopoiesis occurring in the spleen. This can severely affect quality of life and be quite burdensome. If spleen enlargement is massive, patients may suffer from abdominal pain, early satiety and other severe manifestations. Goals of therapy have been directed primarily toward reduction in spleen size, which favorably affects quality of life. This can be accomplished in various ways with varying risk. The risks related to splenomegaly before ASCT revolve around graft failure and increase the risk of alloimmunization from multiple blood transfusions. Splenectomy has been found to be effective in relieving these. The largest contiguous series of splenectomy in MF was conducted at the Mayo Clinic. A total of 314 patients were retrospectively studied between 1976 and 2004. Indications for splenectomy were mechanical symptoms, anemia, portal hypertension and thrombocytopenia. Palliative benefit was seen in a majority of the patients (76%) but not without risk. Perioperative complications occurred in 27.7% of patients with mortality in the range of 5–10%. In addition, post-splenectomy leukemic transformation occurred in 14.3% of patients after a median follow-up of 28.3 months, which, interestingly, did not translate to shortened survival.¹⁷ Extensive splenomegaly has been anecdotally associated with delayed hematological recovery in patients with MF

receiving an ASCT. This may be related to excessive sequestration of transplanted stem cells within the spleen, leading to struggles with transfusion support post ASCT. Support for this was provided in a study that demonstrated a trend toward more rapid neutrophil and platelet engraftment in splenectomized patients before ASCT.¹⁸

The role of splenectomy before transplant has been extensively debated in the literature. Earlier studies did not show that splenectomy before ASCT enhanced survival. Several recent studies suggested that splenectomy may enhance survival in select HCT patients. In the French study, men who had not undergone splenectomy had a higher mortality (hazard ratio 3.45) even when adjusted for the Lille score that was still highly statistically significant.¹⁶ In the Center for International Blood and Marrow Transplant Research study, there was a trend toward increased disease-free survival in splenectomized patients (relative risk 0.77).² A recent large series of patients who underwent splenectomy before ASCT was reported by the Seattle group. They found in their study that patients who underwent splenectomy before ASCT had a lower mortality than those patients with their spleen intact.¹²

What seems clear is that splenectomy remains a viable palliative procedure that may reduce transplant-related mortality. The decision to pursue splenectomy is one that needs to be carefully considered by the clinician weighing both risks and benefits before ASCT.

JAK2 INHIBITORS: CLINICAL IMPACT COMPARED WITH CURRENT MEDICAL THERAPIES

As we evaluate medical therapies that are available for MF, in the past our therapies have been limited and palliative in scope with therapeutic goals that have been reached to include improvements in anemia, improvements in splenomegaly or perhaps both.¹⁹ No treatments in the past have been clearly shown to either prolong survival, decrease the likelihood of transformation to blast phase or cure individuals. Currently available medical therapies can be divided into two main groups. The first group comprises agents that are able to improve cytopenias associated with a disease, most specifically agents that can help improve anemia such as erythropoietin in individuals who have an inadequate endogenous erythropoietin response²⁰ and medications that have been sometimes helpful for improving anemia and thrombocytopenia, including androgens,²¹ steroids and thalidomide with steroids.²² In individuals who have massive splenomegaly, the options are limited and can be divided into modalities that are helpful for only improving splenomegaly such as hydroxyurea, splenectomy²³ or splenic radiotherapy,²⁴ or agents that potentially can help both splenomegaly and cytopenias such as thalidomide or lenalidomide.²⁵ Other more advanced chemotherapy drugs can be helpful for very advanced splenomegaly, but are quite myelosuppressive, including 2-CdA.²⁶ The lack of available medical therapies has greatly increased the desire to find better therapies.

At present, there are three main lines of investigation of agents for patients with MF. The first line of agents is along the immunomodulatory group of agents. Thalidomide and lenalidomide have both been demonstrated to offer improvements in MF-related anemia, and at times splenomegaly. Pomalidomide²⁷ is an immunomodulatory drug currently undergoing Phase III testing for its ability to improve anemia in MF, but without the neuropathy that is sometimes inherent with thalidomide therapy or the myelosuppression that sometimes occurs with lenalidomide therapy. Given that anemia is a very strong negative prognostic factor in MF, it remains possible that improvement of anemia through pomalidomide may alter the natural history of the illness. The current Phase III studies that are being conducted with this agent may provide some information in this regard as to whether

Table 3. JAK2 inhibitors in clinical trials for myelofibrosis

Drug	Target	Phase	Disease	Efficacy	Toxicity	Ref
Ruxolitinib	JAK2	III	MF	Splenomegaly	Anemia	28–30
TG101348	JAK1		PV/ET	Symptoms	Thrombocytopenia	
(SAR302503)	JAK2	II	MF	Splenomegaly	Anemia	31
	FLT3			Symptoms	Thrombocytopenia	
SB1518	JAK2	II	MF	Splenomegaly	Gastrointestinal	33
	FLT3			Symptoms	Gastrointestinal	
CEP701	JAK2	II	MF	Splenomegaly	Gastrointestinal	44 and 45
	FLT3		PV/ET	Symptoms	Anemia	
CYT-387	JAK1	I	MF	Splenomegaly	Thrombocytopenia	32
	JAK2			Symptoms	First dose effect	
				Anemia	Cytopenias	
LY2784544	JAK2	I	MF	NPR	NPR	46 and 47
			ET/PV			
NS-018	JAK2	I	MF	NPR	NPR	48 and 49

Abbreviations: ET, essential thrombocythemia; MF, myelofibrosis; PV, polycythemia vera. NPR: no results in public domain on these ongoing trials.

individuals who are successfully treated with such agents may have an alteration in their natural history and whether this alteration would be sufficient enough to impact the timing or decision making for transplantation.

The next group of targeted therapies is the JAK2 inhibitor group (Table 3). These agents are inhibitors of the native JAK2 and were developed after the discovery of the JAK2 v617f mutation in 2005. The first of these agents is Ruxolitinib, which has now undergone testing in two Phase III studies of ruxolitinib versus placebo in North America and Australia (COMFORT I Trial)²⁸ and a comparison of ruxolitinib versus the best available therapy in the European Union.²⁹ These two trials had their initial reports reported at the American Society of Clinical Oncology in June 2011, where both studies found significant impact of ruxolitinib against disease-associated splenomegaly and significant constitutional symptoms against the illness. These two Phase III studies were built upon the results of the Phase I–II study conducted at MD Anderson and Mayo Clinic, reported in September 2010.³⁰ In this study, it was found that ruxolitinib significantly improved symptomatic splenomegaly and disease-associated symptoms. Outcomes of all of these studies are being closely scrutinized to evaluate whether these agents have an impact on both the natural history of the illness and whether they may prolong survival. Given the significant negative contribution against disease-associated symptoms in splenomegaly, it remains very possible that they impact the natural history of the illness. Other JAK2 inhibitors in development, which are also displaying important activity, include TG101348,³¹ which has recently been reported to offer strong benefit against splenomegaly and disease-associated symptoms, CYT387,³² which may have an impact on disease-associated splenomegaly and symptoms and, to perhaps some degree, anemia, and SB1518,³³ which has an impact on splenomegaly and symptoms, but with less potential for the development of anemia or thrombocytopenia, which has been somewhat common across the other JAK2 inhibitors. Several other JAK2 inhibitors are undergoing development and are still early in their testing and include agents such as LY2784544 and NS-018.

WILL TREATMENT PARADIGM FOR TRANSPLANT IN MF CHANGE WITH JAK2 INHIBITION?

At this point, we perceive two different scenarios on how targeted therapies, particularly JAK2 inhibitors, may impact the timing of allogeneic transplant for MF. The first, which requires investigation, is whether JAK2 inhibitors may indeed lead to an improved performance status and reduce splenomegaly, which may

improve the outcomes with allogeneic stem cell transplant. This is an area of great interest and will be the subject of clinical trials, which are planned, looking at these to some degree pre-allogeneic stem cell transplantation. The role of the JAK-2 inhibitors as a class at this point seems to be palliative, with an impeccable ability to reduce spleen size and improve quality of life. Although these novel agents have addressed a very important aspect in this disease process (quality of life through palliation of symptoms), they unfortunately lack the ability to affect disease outcome as far as we know. At present, the JAK2 inhibitors do not seem to lead to a complete or partial remission and do not appear to have curative potential. ASCT remains the only potential curative treatment; however, risks of TRM, graft failure and relapse remain. The high TRM due to toxicity of conditioning, graft failure and graft versus host disease are major obstacles to the absolute success of ASCT in MF. The JAK2 inhibitors have demonstrated a potential for improving symptoms, performance status and spleen size, which are all factors that have demonstrated a significant impact on the outcome of HCT by altering the timing at which to implement ASCT for MF. Their use early in the disease process may precondition patients by improving performance status and reducing spleen size, allowing them to tolerate this vigorous treatment better. A combination of allogeneic HCT with a targeted agent, such as the JAK2 inhibitor, may be a fruitful marriage to enhance transplant-related outcomes. Improved outcomes with this combination may potentially be seen because of the reduction of spleen pre-ASCT, improvement of performance status and decrease in proinflammatory cytokines that may contribute toward TRM in patients with MF.³⁴ The reduction in spleen size offered by these newer agents before transplant may allow for more rapid neutrophil and platelet engraftment, serving as a medical substitute to splenectomy. This may then provide the same benefit, without the surgical risk, and in the post-HCT setting may see a reduction in the risk of relapse.

The other area, which is more provocative, is whether these agents will have an impact on the natural history that may otherwise delay the timing for allotransplant in patients with MF. At this point in time, we would say that there are little data to guide us. We would say that in individuals with intermediate-2 and high-risk MF disease there may be the ability of the agents, if active, to prolong survival. I think that it requires further validation, and if we were to use analogous situations such as azacitidine for myelodysplastic syndrome³⁵ one would expect that improvements in survival, given that these therapies are not completely remitting, would probably be in the range of months to a likely duration that would be at most in the 2- to 3-year range, but

unlikely to be in the marked changes in survival that we have enjoyed with the complete remissions obtained in chronic myeloid leukemia chronic phase with tyrosine kinase inhibitor (TKI) therapy. Therefore, we think that the impact might be greatest for individuals of such an age, performance status and so on, where the impact of JAK2 inhibitors might be philosophically beneficial and sufficient for this group of patients than those in which we are more on the fence regarding allogeneic transplantation. We think they would not likely impact very young, high-risk individuals in which we are looking for a dramatic change in the disease natural history, i.e. the 48 individual who is at high risk of transformation to acute leukemia, we think such an individual we have not seen therapies yet that would alter this decision, but do think it might potentially impact the individual in their late 60s or early 70s in which transplant is being considered but has not seen JAK2 inhibitor therapy and if these therapies were strongly efficacious might delay or forestall the decision for undergoing allogeneic stem cell transplantation. We foresee in the future that rather than utilizing any of these agents alone, a series of combinations can be used, either combined or in a serial manner, as well as involving immunomodulatory drugs to try to improve anemia and JAK2 inhibitors, either as a pretransplantation approach or when transplantation is considered at the time of clear progression. The past 4 years, in particular, represent the greatest advance in activity of clinical trials and the development of targeted therapeutic agents for MF. At a time where outcomes with stem cell transplantation continue to improve, including better selection for unrelated donor matches, better antimicrobial prophylaxis and better control of graft versus host disease, we foresee that our options for MF continue to improve in a very thoughtful and structured manner.

CONCLUSIONS

The potential impact of JAK2 inhibitors on ASCT for MF is alluring, but a number of questions emerge: Has the development of these targeted agents for MF altered the timing of allogeneic HCT? Is it possible to improve outcomes with transplant by combining modalities either before or after HSCT? How can we improve transplant outcomes and decrease morbidity and mortality? Will the treatment paradigm for transplant in MF shift in the era of targeted therapy? The rapid development of clinical trials in JAK2 inhibitors before ASCT will likely help address these questions and will be an area of great interest in the upcoming years. Searching for their place in the algorithm of treatment of patients with MPN-associated MF will be paramount to give patients and clinicians more options. What we know thus far is that their role will be to enhance the effects of transplant rather than replace the need for HCT. What remains to be answered is how this will occur. Hopefully, these important questions will be resolved in future clinical trials.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

REFERENCES

- Mesa RA, Green A, Barosi G, Verstovsek S, Vardiman J, Gale RP. MPN-associated myelofibrosis (MPN-MF). *Leukemia Res* 2011; **35**: 12–13.
- Ballen KK, Shrestha S, Sobocinski KA, Zhang MJ, Bashey A, Bolwell BJ et al. Outcome of transplantation for myelofibrosis. *Biol Blood Marrow Transplant* 2010; **16**: 358–367.
- Passamonti F, Cervantes F, Vannucchi AM, Morra E, Rumi E, Pereira A 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**: 1703–1708.
- Gangat N, Caramazza D, Vaidya R, George G, Begna K, Schwager S 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**: 392–397.
- Samuelson S, Sandmaier BM, Heslop HE, Popat U, Carrum G, Champlin RE et al. Allogeneic haematopoietic cell transplantation for myelofibrosis in 30 patients 60–78 years of age. *Br J Haematol* 2011; **153**: 76–82.
- Bacigalupo A, Soraru M, Dominietto A, Pozzi S, Geroldi S, Van Lint MT et al. Allogeneic hemopoietic SCT for patients with primary myelofibrosis: a predictive transplant score based on transfusion requirement, spleen size and donor type. *Bone Marrow Transplant* 2010; **45**: 458–463.
- Ditschkowski M, Elmaagacli AH, Trensche R, Steckel NK, Koldehoff M, Beelen DW. No influence of V617F mutation in JAK2 on outcome after allogeneic hematopoietic stem cell transplantation (HSCT) for myelofibrosis. *Biol Blood Marrow Transplant* 2006; **12**: 1350–1351.
- Kroger N, Badbaran A, Holler E, Hahn J, Kobbe G, Bornhäuser M et al. Monitoring of the JAK2-V617F mutation by highly sensitive quantitative real-time PCR after allogeneic stem cell transplantation in patients with myelofibrosis. *Blood* 2007; **109**: 1316–1321.
- Alchalby H, Lioznov M, Fritzsche-Friedland U, Badbaran A, Zabelina T, Bacher U et al. Circulating CD34(+) cells as prognostic and follow-up marker in patients with myelofibrosis undergoing allo-SCT. *Bone Marrow Transplantation* 2012; **47**: 143–145.
- Kroger N, Holler E, Kobbe G, Bornhäuser M, Schwerdtfeger R, Baumann H et al. Allogeneic stem cell transplantation after reduced-intensity conditioning in patients with myelofibrosis: a prospective, multicenter study of the Chronic Leukemia Working Party of the European Group for Blood and Marrow Transplantation. *Blood* 2009; **114**: 5264–5270.
- Alchalby H, Yunus D, Kobbe G, Holler E, Schwerdtfeger R. Risk Models Predicting Survival after Reduced Intensity Transplantation for Myelofibrosis. *Br J Haematol* 2011 (in press).
- Scott BL, Gooley Ted A, Sorror ML, Rezvani AR, Linenberger L et al. The dynamic international prognostic scoring system for myelofibrosis predicts outcomes after hematopoietic cell transplantation. *Blood* 2011 (in press).
- Zihai Li, Gooley Ted A, Appelbaum Frederick R, Deeg Joachim. Splenectomy and hemopoietic stem cell transplantation for myelofibrosis. *Blood* 2001; **97**: 2180–2181.
- Stewart WA, Pearce R, Kirkland KE, Bloor A, Thomson K, Apperley J. The role of allogeneic SCT in primary myelofibrosis: A British society for blood and marrow transplantation study. *Bone Marrow Transplant* 2010; **45**: 1587–1593.
- Guardiola P, Anderson JE, Bandini G, Cervantes F, Runde V, Arcese W et al. Allogeneic stem cell transplantation for agnogenic myeloid metaplasia: a European Group for Blood and Marrow Transplantation, Societe Francaise de Greffe de Moelle, Gruppo Italiano per il Trapianto del Midollo Osseo, and Fred Hutchinson Cancer Research Center Collaborative Study. *Blood* 1999; **93**: 2831–2838.
- Robin M, Espérour H, de Latour RP, Petropoulou AD, Xhaard A, Ribaud P et al. Splenectomy after allogeneic haematopoietic stem cell transplantation in patients with primary myelofibrosis. *Br J Haematol* 2010; **150**: 721–724.
- Mesa RA, Nagorney DS, Schwager S, Allred J, Tefferi A. Palliative goals, patient selection, and perioperative platelet management: outcomes and lessons from 3 decades of splenectomy for myelofibrosis with myeloid metaplasia at the Mayo Clinic. *Cancer* 2006; **107**: 361–370.
- Li Z, Gooley T, Applebaum FR, Deeg HJ. Splenectomy and hemopoietic stem cell transplantation for myelofibrosis. *Blood* 2001; **97**: 2180–2181.
- Mesa RA. How I treat symptomatic splenomegaly in patients with myelofibrosis. *Blood* 2009; **113**: 5394–5400.
- Huang J, Tefferi A. Erythropoiesis stimulating agents have limited therapeutic activity in transfusion-dependent patients with primary myelofibrosis regardless of serum erythropoietin level. *Eur J Haematol* 2009; **83**: 154–155.
- Cervantes F, Hernandez-Boluda JC, Alvarez A, Nadal E, Montserrat E. Danazol treatment of idiopathic myelofibrosis with severe anemia. *Haematologica* 2000; **85**: 595–599.
- Mesa RA, Steensma DP, Pardanani A, Li CY, Elliott M, Kaufmann SH et al. A phase 2 trial of combination low-dose thalidomide and prednisone for the treatment of myelofibrosis with myeloid metaplasia. *Blood* 2003; **101**: 2534–2541.
- Tefferi A, Mesa RA, Nagorney DM, Schroeder G, Silverstein MN. Splenectomy in myelofibrosis with myeloid metaplasia: a single-institution experience with 223 patients. *Blood* 2000; **95**: 2226–2233.
- Elliott MA, Chen MG, Silverstein MN, Tefferi A. Splenic irradiation for symptomatic splenomegaly associated with myelofibrosis with myeloid metaplasia. *Br J Haematol* 1998; **103**: 505–511.
- Tefferi A, Cortes J, Verstovsek S, Mesa RA, Thomas D, Lasho TL et al. Lenalidomide therapy in myelofibrosis with myeloid metaplasia. *Blood* 2006; **108**: 1158–1164.
- Faoro LN, Tefferi A, Mesa RA. Long-term analysis of the palliative benefit of 2-chlorodeoxyadenosine for myelofibrosis with myeloid metaplasia. *Eur J Haematol* 2005; **74**: 117–120.
- Begna KH, Mesa RA, Pardanani A, Hogan WJ, Litzow MR, McClure RF et al. A phase-2 trial of low-dose pomalidomide in myelofibrosis. *Leukemia* 2011; **25**: 301–304.

- 28 Verstovsek S, Mesa RA, Gotlib JR, Levy RS, Gupts V, DiPersio J *et al*. Results of COMFORT-I, a randomized double-blind phase III trial of JAK 1/2 inhibitor INCB18424 (424) versus placebo (PB) for patients with myelofibrosis (MF). *ASCO Meeting Abstracts* 2011; **29**: 6500.
- 29 Harrison CN, Kiladjian J, Al-Ali HK, Gisslinger H, Waltzman RJ, Stalbovskaya V *et al*. Results of a randomized study of the JAK inhibitor INC424 compared with best available therapy (BAT) in primary myelofibrosis (PMF), post-polycythemia vera-myelofibrosis (PPV-MF) or post-essential thrombocythemia myelofibrosis (PET-MF). *ASCO Meeting Abstracts* 2011; **29**: LBA6501.
- 30 Verstovsek S, Kantarjian H, Mesa RA, Pardanani AD, Cortes-Franco J, Thomas DA *et al*. Safety and efficacy of INCB018424, a JAK1 and JAK2 inhibitor, in myelofibrosis. *N Engl J Med* 2010; **363**: 1117–1127.
- 31 Pardanani A, Gotlib JR, Jamieson C, Cortes JE, Talpaz M, Stone RM *et al*. Safety and efficacy of TG101348, a selective JAK2 inhibitor, in myelofibrosis. *J Clin Oncol* 2011; **29**: 789–796.
- 32 Pardanani AD, Caramazza G, George G, Lasho TL, Hogan WJ, Litwov MR *et al*. Safety and efficacy of CYT387, a JAK-1/2 inhibitor, for the treatment of myelofibrosis. *ASCO Meeting Abstracts* 2011; **29**: 6514.
- 33 Deeg JH, Odenkio O, Scott BL, Estrov Z, Cortes JE, Thomas DA *et al*. Phase II study of SB1518, an orally available novel JAK2 inhibitor, in patients with myelofibrosis. *ASCO Meeting Abstracts* 2011; **29**: 6515.
- 34 Tefferi A, Vaidya R, Caramazza D, Finke C, Lasho T, Pardanani A. Circulating interleukin (IL)-8, IL-2R, IL-12, and IL-15 levels are independently prognostic in primary myelofibrosis: a comprehensive cytokine profiling study. *J Clin Oncol* 2011; **29**: 1356–1363.
- 35 Fenaux P, Mufti GJ, Hellstrom-Lindberg E, Santini V, Finelli C, Giagounidis A *et al*. Efficacy of azacitidine compared with that of conventional care regimens in the treatment of higher-risk myelodysplastic syndromes: a randomised, open-label, phase III study. *Lancet Oncol* 2009; **10**: 223–232.
- 36 Dupriez B, Morel P, Demory JL, Lai JL, Simon M, Plantier I *et al*. Prognostic factors in agnogenic myeloid metaplasia: a report on 195 cases with a new scoring system [see comments]. *Blood* 1996; **88**: 1013–1018.
- 37 Cervantes F, Dupriez B, Pereira A, Passamonti F, Reilly JT, Morra E *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**: 2895–2901.
- 38 Kerbaui DM, Gooley TA, Sale GE, Flowers ME, Doney KC, Georges GE *et al*. Hematopoietic cell transplantation as curative therapy for idiopathic myelofibrosis, advanced polycythemia vera, and essential thrombocythemia. *Biol Blood Marrow Transplant* 2007; **13**: 355–365.
- 39 Patriarca F, Bacigalupo A, Sperotto A, Isola M, Bruno B, van Lint MT *et al*. Outcome of allogeneic stem cell transplantation following reduced-intensity conditioning regimen in patients with idiopathic myelofibrosis: the g.I.T.m.o. Experience. *Mediterr J Hematol Infect Dis* 2010; **2**: e2010010.
- 40 Stewart WA, Pearce R, Kirkland KE, Bloor A, Thomson K, Apperley J *et al*. The role of allogeneic SCT in primary myelofibrosis: a British Society for Blood and Marrow Transplantation study. *Bone Marrow Transplant* 2010; **45**: 1587–1593.
- 41 Merup M, Lazarevic V, Nahi H, Andreasson B, Malm C, Nilsson L *et al*. Different outcome of allogeneic transplantation in myelofibrosis using conventional or reduced-intensity conditioning regimens. *Br J Haematol* 2006; **135**: 367–373.
- 42 Rondelli D, Barosi G, Bacigalupo A, Prchal JT, Popat U, Alessandrino EP *et al*. Allogeneic hematopoietic stem-cell transplantation with reduced-intensity conditioning in intermediate- or high-risk patients with myelofibrosis with myeloid metaplasia. *Blood* 2005; **105**: 4115–4119.
- 43 Snyder DS, Palmer J, Gaal K, Stein AS, Pullarkat V, Sahebi F *et al*. Improved outcomes using tacrolimus/sirolimus for graft-versus-host disease prophylaxis with a reduced-intensity conditioning regimen for allogeneic hematopoietic cell transplant as treatment of myelofibrosis. *Biol Blood Marrow Transplant* 2006; **16**: 281–286.
- 44 Hexner E, Goldberg JD, Prchal JT, Demakos EP, Swierczek S, Weinberg RS *et al*. A Multicenter, Open Label Phase I/II Study of CEP701 (Lestaurtinib) in adults with myelofibrosis; a Report On Phase I: A Study of the Myeloproliferative Disorders Research Consortium (MPD-RC). *Blood* 2009; **114**: A754.
- 45 Moliterno AR, Hexner E, Roboz GJ, Carroll M, Luger S, Mascarenhas J *et al*. An Open-Label Study of CEP-701 in patients with JAK2 V617F-positive PV and ET: update of 39 enrolled patients. *Blood* 2009; **114**: A753.
- 46 Ma L, Zhao B, Walgren R, Clayton JA, Blosser WD, Burkholder TP *et al*. Efficacy of LY2784544, a small molecule inhibitor selective for mutant JAK2 kinase, in JAK2 V617F-induced hematologic malignancy models. *Blood* 2010; **116**: 4087.
- 47 Florensa L, Bellosillo B, Arenillas L, Ma L, Walgren R, Alvarez A *et al*. LY2784544, a novel JAK2 inhibitor, decreases *in vitro* growth of hematopoietic human progenitors from JAK2 V617F positive polycythemia vera patients. *Blood* 2010; **116**: 5054.
- 48 Shide K, Nakaya Y, Kameda T, Shimoda H, Hidaka T, Kubuki Y *et al*. NS-018, a potent novel JAK2 inhibitor, effectively treats murine mpn induced by the Janus Kinase 2 (JAK2) V617F mutant. *Blood* 2010; **116**: 4106.
- 49 Nakaya Y, Naito H, Homan J, Sugahara S, Horio T, Niwa T *et al*. Preferential inhibition of an activated form of Janus Kinase 2 (JAK2) by a Novel JAK2 inhibitor, NS-018. *Blood* 2010; **116**: 4107.