# Allogeneic Stem Cell Transplantation for Myelofibrosis in 2012

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## Summary

Myelofibrosis (MF) is a heterogeneous disease for which long-term, effective medical therapeutic options are currently limited. The role of allogeneic haematopoietic stem cell transplant (AHSCT) in this population, many of whom are elderly, often provides a challenge with regard to the identification of suitable candidates, timing of transplantation in the disease course and choice of conditioning regimen. This review summarizes key findings from published data concerning AHSCT in MF and attempts to provide a state of the art approach to MF-AHSCT in 2012. In addition, we postulate on how the era of JAK inhibition might impact on transplantation for MF.

Keywords: myelofibrosis, stem cell transplant, splenectomy, JAK inhibitors.

Primary myelofibrosis (PMF) is a myeloproliferative neoplasm (MPN) which is characterized by clonal expansion of abnormal haematopoietic cells, accompanied by increased secretion of cytokines resulting in secondary bone marrow fibrosis, osteosclerosis and angiogenesis. Patients develop variable degrees of anaemia, cytopenias, peripheral blood (PB) leucoerythroblastosis and extramedullary haemopoiesis often associated with marked hepatosplenomegaly. PMF is an uncommon disease, with an estimated incidence of 0·5–1·5 per 100 000, and a median age at presentation of 67 years. The clinical course is heterogeneous, ranging from an indolent disease in some patients, who may survive for decades, to an aggressive disease in other cases, often associated with disabling constitutional symptoms, poor quality of life and a survival measured in months. Myelofibrosis (MF) can also arise following a prior diagnosis of Polycythaemia Vera (post-PV MF) or Essential Thrombocythaemia (post-ET MF). Whilst such cases of secondary myelofibrosis (sMF) are often

phenotypically similar to PMF, it is important to recognize these conditions as distinct entities, as classified by International Working Group consensus criteria (Barosi et al, 2008).

No available conventional drug therapies for MF have been shown to prolong survival. Palliative agents include erythropoietin, androgens, immunomodulatory agents, interferon, cytoreductive therapies and non-pharmacological approaches, such as blood transfusion, splenic irradiation and splenectomy. The only potentially curative therapy for MF is allogeneic haematopoietic stem cell transplantation (AHSCT). As MF is primarily a disease of the elderly, this has historically been a rare indication of AHSCT. However, with the advent of reduced intensity conditioning (RIC) regimens, the applicability of this approach has been broadened to include a larger proportion of MF patients (Samuelson et al, 2011). Nonetheless, as MF occurs in a heterogeneous patient group and is often associated with frequent comorbidities and disease-related complications, a number of challenges relating to patient selection, timing and choice of conditioning regimen are inevitably created. Furthermore, following the description of aberrant Janus Kinase (JAK) activation in the majority of MF patients, often due to presence of the *JAK2* V617F mutation, JAK2-inhibitor therapies have been developed for patients with MF. Clinical trials have shown that these agents have considerable therapeutic potential in MF patients, thus offering an additional treatment option as a potential alternative or adjunct to AHSCT. The purpose of this article is to review the role of AHSCT in the management of patients with MF, and how this might be influenced by the introduction of JAK2-inhibitor therapies for this group.

## Patient selection for AHSCT

Given the marked heterogeneity in the clinical course of MF, a risk-adapted approach is essential to guide therapeutic decision-making. Suggested approaches to current management have recently been published (Barbui et al, 2011; Tefferi et al, 2011). Historically, the 'Lille score' has been paramount in guiding risk-adjusted therapy for MF- patients, with consideration of AHSCT for those individuals with intermediate or higher risk disease (Dupriez et al, 1996; Hoffman & Rondelli, 2007). At present, the International Prognostic Scoring System (IPSS) is the most widely used approach for risk stratification

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(Cervantes et al, 2009) and has largely superseded older prognostic scoring schemes (Cervantes & Pereira, 2012). The IPSS estimates survival from the time of diagnosis, based on five risk factors: age > 65 years, haemoglobin < 100 g/l, leucocyte count > 25 × $10^9$/l, circulating blasts ≥ 1% and the presence of constitutional symptoms. Patients are then classified as low risk (score = 0), intermediate risk-1 (score = 1), intermediate risk-2 (score = 2) and high risk (score ≥ 2) with median survivals of 135, 95, 48 and 27 months, respectively. A dynamic IPSS score (DIPSS) has subsequently been developed using the same five variables, but allowing prediction of prognosis at any time during the course of PMF (Passamonti et al, 2010a). Using this model, unlike the original IPSS, a haemoglobin concentration <100 g/l accrues two points. Patients are then classified as low risk (score = 0), intermediate risk-1 (score = 1 or 2), intermediate risk-2 (score = 3 or 4) high risk (score = 5 or 6). The DIPSS has been subsequently refined to the 'DIPSS plus', which includes three additional independent risk factors; transfusion dependence, unfavourable karyotype (including +8, −7/7q-, i(17q), inv(3), −5/5q-, 12p-. 11q23 rearrangements and complex karyotypes) (Hussein et al, 2010) and platelet count < 100 × $10^9$/l (Gangat et al, 2011). Patients are scored as 0, 1, 2 or 3 on the basis of the DIPSS risk groups. Thus, patients can then be classified as low risk (score = 0), intermediate risk-1 (score = 1), intermediate risk-2 (score = 2 or 3) or high risk (score = 4–6), with corresponding median survival estimates of 185, 78, 35 and 16 months. Importantly, all of these prognostic-scoring systems are based on analyses of patients with PMF and not sMF. These prognostic-scoring systems are summarized in Table I.

A key utility of these systems is to inform AHSCT management decisions. The current European LeukaemiaNet recommendations suggest that it is 'reasonable to justify the risk of alloSCT-related complications in otherwise transplantation eligible patients whose median survival is expected to be <5 years' (Barbui et al, 2011). Thus, using the above scoring systems, intermediate-2 and high-risk patients would be considered eligible for AHSCT. The recommendations also suggest that patients with transfusion dependence or unfavourable cytogenetics should be considered for AHSCT, reflecting the inclusion of these factors in the DIPSS plus scoring system. As discussed below, a number of important non-disease related factors, such as age, donor type and co-morbidities, also have a major influence on the outcome following AHSCT (Sorror et al, 2005), and these have to be carefully integrated into the decision to proceed to AHSCT. Furthermore, much of the literature estimating non-relapse mortality (NRM) in this patient group is outdated and improvements in supportive care and conditioning regimens are likely to have already translated into lower levels of NRM for these patients than might be apparent from the earlier published cohorts (Deeg & Appelbaum, 2011). Consequently, it remains controversial whether patients with low-risk or intermediate-1 risk disease should proceed to AHSCT (Tefferi, 2010, 2011; Deeg & Appelbaum, 2011). For example, a

young patient aged < 30 years with IPSS intermediate-1 PMF would have an estimated median survival of 95 months. However, if this patient has a matched sibling donor (MSD) available, there could be a strong argument in favour of proceeding with AHSCT at an early stage rather than delaying until the patient was older with higher-risk advanced disease and associated co-morbidities. This is supported by the Gruppo Italiano Trapianto di Midollo Osseo (GITMO) study that identified a long interval between diagnosis and transplantation as an adverse prognostic factor (Patriarca et al, 2008). A number of other studies have attempted to examine this issue by assessing the predictive value of conventional prognostic factors for survival in MF patients who underwent AHSCT. A retrospective analysis of transplants carried out for MF at the Fred Hutchinson Cancer Center demonstrated prognostic significance of the IPSS score for predicting post-transplant survival. The 6-year survival for low, intermediate-1, intermediate-2 and high-risk groups was 80%, 67%, 54% and 38%, respectively (Scott et al, 2010). Furthermore, the same group have recently demonstrated the utility of the DIPSS score in predicting outcome post- AHSCT (Scott et al, 2012). Earlier studies from this centre also suggested that cytogenetic abnormalities, degree of marrow fibrosis, low platelet count, older age and adverse comorbidity score (Sorror et al, 2005) may act as prognostic factors predicting outcome following myeloablative conditioned (MAC)-AHSCT for MF (Deeg et al, 2003; Kerbauy et al, 2007). The French group indicated that a MSD, chronic phase disease and splenectomy in men had a favourable impact on overall survival (OS) in a multivariate analysis (Robin et al, 2011).

Increasingly, transplant physicians are receiving referrals of patients over the age of 65 years for consideration of AHSCT. An early study of MAC-AHSCT for MF identified abnormal karyotype as well as age as predictors of treatment failure (Guardiola et al, 1999). Furthermore, both the Nordic group (age > 60 years) and the Australian/New Zealand cooperative group (age > 50 years) identified 'older age' as an adverse prognostic factor for AHSCT in MF (Abelsson et al, 2011; Nivison-Smith et al, 2012). In contrast, Samuelson et al (2011) retrospectively investigated the outcomes of RIC-AHSCT in 30 patients aged 60–78 years (median age 65), many with high Haematopoietic Cell Transplant-Comorbidity Index (HCT-CI) scores. Engraftment, acute graft-versus-host disease (aGVHD) and chronic GVHD (cGVHD) rates were similar to those seen in studies with a higher proportion of younger individuals. Respectable 3-year OS and progression-free survival (PFS) rates of 45% and 40%, respectively, were achieved. Comparing patients less than and greater than 65 years old failed to reveal a significant survival difference, although this cohort may well represent a highly selected group.

There have been a number of attempts to develop prognostic risk scores using data from MF patients who have underwent AHSCT. A German group identified haemoglobin < 100 g/l, grade III marrow fibrosis and PB blast count > 1% as risk factors for adverse outcome following

Table I. A summary of the key prognostic scoring systems in myelofibrosis.

| Prognostic system | Age (years) | Haemoglobin | WCC | Circulating blasts | Constitutional symptoms* | Platelet count | Karyotype | RBC transfusion need | Risk score | | Median survival (months) |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Lille (Dupriez et al, 1996) | – | <100 g/l 1 point | <4 or >30 × 10⁹/l 1 point | – | – | – | – | – | Low | 0 | 93 |
| | | | | | | | | | Intermediate | 1 | 26 |
| | | | | | | | | | High | 2 | 13 |
| IPSS (Cervantes et al, 2009) | >65 1 point | <100 g/l 1 point | >25 × 10⁹/l 1 point | ≥1% Blasts on PB film 1 point | Constitutional Symptoms 1 point | – | – | – | Low | 0 | 135 |
| | | | | | | | | | Intermediate-1 | 1 | 95 |
| | | | | | | | | | Intermediate-2 | 2 | 48 |
| | | | | | | | | | High | >2 | 27 |
| DIPSS (Passamonti et al, 2010a) | >65 1 point | <100 g/l 2 points | >25 × 10⁹/l 1 point | ≥1% Blasts on PB film 1 point | Constitutional Symptoms 1 point | – | – | – | Low | 0 | NR |
| | | | | | | | | | Intermediate-1 | 1–2 | 170 |
| | | | | | | | | | Intermediate-2 | 3–4 | 48 |
| | | | | | | | | | High | 5–6 | 18 |
| DIPSS Plus (Gangat et al, 2011) | >65 | <100 g/l | >25 × 10⁹/l | ≥1% Blasts on PB film | Constitutional Symptoms | <100 × 10⁹/l | Unfavourable† | Dependent | Low | 0 | 185 |
| | | | | | | | | | Intermediate-1 | 1 | 78 |
| | | | | | | | | | Intermediate-2 | 2–3 | 35 |
| | | | | | | | | | High | 4–6 | 16 |

IPSS, International Prognostic Scoring System; DIPSS, Dynamic International Prognostic Scoring System; WCC, white cell count; RBC, red blood cell; NR, not reached; PB, peripheral blood.

*Constitutional symptoms defined as night sweats, loss of >10% body weight in the last 6 months, noninfectious fever.

†Unfavourable Karyotype defined as a complex karyotype or either a sole or two abnormalities including +8, 7/7q−, i(17q), 5/5q−, 12p−, inv(3) or 11q23 rearrangement.

MAC-AHSCT. Patients with 2 or 3 of these risk factors had a 3-year survival of 16% compared with 67% for patients with 0 or 1 risk factor (Ditschkowski et al, 2004). A recent study examined a cohort of 46 PMF patients who received a thio-tepa-based RIC-AHSCT and identified three factors predicting an adverse outcome: transfusion history > 20 units, spleen size > 22 cm, or those who had an alternative donor. Patients with low risk (0–1 risk factors) or high-risk (2–3 risk factors) features had a transplant-related mortality (TRM) of 8% and 41%, respectively, with a 5-year OS of 77% and 8% (Bacigalupo et al, 2010). Whilst these studies are limited by small cohort size and retrospective nature, taken together they demonstrate, perhaps unsurprisingly, that older patients, when compared to younger patients, with longstanding and/or advanced disease tend to have a worse prognosis following AHSCT. This supports that proceeding to early AHSCT should be carefully considered whenever possible.

In the event of blastic transformation of MF, where the median survival is only 2·7 months (Mascarenhas et al, 2010), if eligible, AHSCT may offer a chance of long term survival, with some encouraging results in a small series (Ciurea et al, 2010). Of note, a recent case report has described the successful use of Pegylated Interferon (IFN)-α-2a in achieving remission in a patient with transformed PMF who refused polychemotherapy (Berneman et al, 2010).

## Is there a role for splenectomy pre-AHSCT for myelofibrosis?

Experience suggests that the vast majority of MF patients referred for consideration of allografting have bulky spleno-megaly. Conflicting data exists in the literature regarding the role of splenectomy pre-AHSCT for MF. Its attraction as a tumour debulking strategy is often upheld in clinical practice and the question still remains if there is a sub-group of patients who will benefit from splenectomy pre-AHSCT. Historical data from the Mayo Clinic on 314 MF patients undergoing splenectomy has suggested significant peri-operative complications in up to almost 28% of individuals (Mesa et al, 2006). The associated morbidity and mortality risk necessitates great caution in routine recommendation. One group has described decreased transfusion requirements and enhanced neutrophil recovery in a small cohort ($n = 26$) of MF patients undergoing AHSCT favouring pre-transplant splenectomy (Li et al, 2001). The Société Française de Greffe de Moelle et de Thérapie Cellulaire (SFGM-TC) cohort of patients [RIC ($n = 101$) and MAC ($n = 46$)] included a higher than expected proportion of patients who had undergone splenectomy (39%) pre-AHSCT (Robin et al, 2011). Multivariate analysis demonstrated improved engraftment with the use of PB stem cells, a sibling donor, a lack of thrombocytopenia (when compared to those with normal platelet counts) and in patients lacking splenomegaly/those who had undergone splenectomy. Furthermore, a large, prospective study, ($n = 103$), coordinated by the Chronic Leu-

kaemia Working Party (CLWP) of the European group Blood and Marrow Transplant (EBMT) group reported a trend towards more rapid neutrophil engraftment in splenectomized ($n = 14$) versus non-splenectomized ($n = 89$) RIC-AHSCT recipients (Kröger et al, 2009a). However, univariate analysis suggested a higher rate of relapse at 3-years in those who underwent splenectomy [51% (20–82) versus no splenectomy 20% (10–20); $P = 0·005$]. This adverse effect on relapse risk was confirmed on multivariate analysis [Hazard Ratio (HR) = 3·58; 95% confidence interval (CI), 1·44–8·86; $P = 0·006$]. In contrast, retrospective Center for International Blood and Marrow Transplant Research (CIBMTR) data did not suggest an effect of prior splenectomy on either graft failure rates or disease-free survival (DFS) (Ballen et al, 2010). Neither have other retrospective analyses demonstrated an association of splenectomy with either NRM (Stewart et al, 2010) or OS post-AHSCT (Kerbauy et al, 2007). It is important to note that successful engraftment can still occur despite the presence of even massive spleno-megaly. Ciurea et al (2008) recently described a cohort of patients ($n = 10$) with splenomegaly, five of whom were defined as extensive with a longitudinal spleen diameter > 30 cm, undergoing RIC-AHSCT. All patients engrafted and had a progressive reduction in spleen size, occurring as marrow fibrosis resolved (Ciurea et al, 2008).

The exact role of the spleen in immune reconstitution/immunomodulation post-AHSCT and the potential association with GVHD risk is unclear. Early work suggested a correlation between splenectomy and subsequent development of GVHD. In a study of 157 patients undergoing AHSCT for various diagnoses, an increased severity, but not incidence, of aGVHD was demonstrated in splenectomized versus non-splenectomized patients (Michallet et al, 1999). Furthermore, others have described a potential link between splenectomy and development of cGVHD in a large cohort of leukaemic patients undergoing AHSCT (Boström et al, 1990). In contrast, subsequent work in a chronic myeloid leukaemia (CML) AHSCT cohort did not find a significant effect on either GVHD incidence or severity attributable to splenectomy, but did describe a significantly increased risk of leukaemic relapse, potentially due to a reduced 'graft-versus-leukaemia' effect (Kalhs et al, 1995). In addition, the SFGM-TC group found no association between splenectomy (39% of patients) and subsequent development of GVHD (Robin et al, 2011). In conclusion, it is our view that pre-emptive splenectomy cannot be recommended as routine practice in candidates in an attempt to improve AHSCT outcome.

## Myeloablative transplantation

It is well established that MAC-AHSCT carries a significant risk of morbidity and mortality. The results of selected MAC- and RIC-AHSCT studies are summarized in Table II. Conclusions from initial reports of outcomes and complications of MAC-AHSCT for MF were limited by small cohort sizes.

**Table II.** Selected studies of allogeneic haematopoietic stem cell transplant in myelofibrosis.

| Author | Number of patients | Regimen (n) | Age, years (median) | GVHD | | TRM | Overall survival |
|---|---|---|---|---|---|---|---|
| **Predominantly MAC** | | | | | | | |
| Guardiola et al (1999) | 55 | MAC (55) | 42 (4–53) | Acute II–IV | 60% | 27% 1 year | 14% at 5 years (age > 45 years) 67% at 5 years (age < 45 years) |
| Deeg et al (2003) | 56 | MAC (56) | 43 (10–66) | Acute II–IV | 68% | 32% 1 year | 58% at 3 years |
| Kerbauy et al (2007) | 104 | MAC (95) RIC (9) | 49 (18–70) | Acute II–IV Chronic | 64% 84% | 34% 5 years | 61% at 7 years |
| Ballen et al (2010) | 289 | MAC (229) RIC (60) | MSD 45 (18–73) URD 49 (18–70) RO 46 (20–65) | Acute II–IV | MSD 43% URD 40% RO 24% | MSD 22% URD 42% RO 27% Day + 100 | MSD 37% at 5 years URD 30% at 5 years RO 40% at 5 years |
| **RIC** | | | | | | | |
| Rondelli et al (2005) | 21 | RIC (21) | 54 (27–68) | Acute II–IV | 33% | 10% 1 year | 85% at 2·5 years |
| Kröger et al (2005) | 21 | RIC (21) | 53 (32–63) | Acute II–IV | 48% | 16% 1 year | 84% at 3 years |
| Kroger et al (2009b) | 103 | RIC (103) | 55 (32–68) | Acute II–IV Chronic | 27% 49% | 16% 1 year | 67% at 5 years |
| Bacigalupo et al (2010) | 46 | RIC (46) | 51 (24–67) | ND | – | 24% 1 year | 45% at 5 years |
| **Both RIC and MAC** | | | | | | | |
| Patriarca et al (2008) | 100 | MAC (48) RIC (52) | 49 (21–68) | Acute II–IV Chronic | 41% 43% | 35% 1 year | 59% at 1 year 42% at 3 years 31% at 5 years |
| Lissandre et al (2011) | 39 | MAC (15) RIC (24) | 49 (15–65) | Acute II–IV Chronic | 69% 49% | – | 60% at 3 years |
| Abelsson et al (2011) | 92 | MAC (40) RIC (52) | 46 (5–63) 55 (22–66) | Acute II–IV | 23% | MAC 17·5 RIC 5·8 day + 100 | MAC 49% at 5 years RIC 59% at 5 years |
| Robin et al (2011) | 147 | MAC (46) RIC (101) | 53 (20–68) | Acute II–IV Chronic | 43% 39% | – | 39% at 4 years |

RIC, reduced intensity conditioning; MAC, myeloablative conditioning; MSD, matched sibling donor; URD, unrelated donor; RO, related other; GVHD, graft-versus-host disease, TRM, transplant-related mortality; ND, not documented.

Guardiola et al (1999) subsequently reported on a collaborative study involving 55 patients (median age 42 years) undergoing MAC-AHSCT, describing a 1-year TRM of 27%, aGVHD grade II–IV rates of 60% and an encouraging 47% survival at 5 years for the entire cohort. It should be noted, however, that for those >45 years of age, the 5-year OS was a sobering 14%. The CIBMTR reported the largest retrospective series of patients undergoing AHSCT (n = 289), the majority of who underwent MAC-AHSCT (n = 229) (Ballen et al, 2010). Analyses demonstrated a day-100 TRM of 22–42% [higher in Unrelated Donor (URD) versus MSD] and an OS of 30–40% at 5 years. Graft failure rates were higher in patients receiving stem cells from an URD but were not influenced by the presence of splenomegaly. Among the 56 (19%) patients who had favourable risk factors (performance status > 90%, no circulating blasts and a MSD), the 1- and 3-year OS probabilities were encouraging, at 69% and 60%, respectively. For

MAC-AHSCT, primary graft failure rates from <5% (Kerbauy et al, 2007) up to 30% (Gupta et al, 2009) have been reported, most likely reflecting the heterogeneity of stem cell source, patient characteristics and the conditioning regimen employed. Published TRM rates for MAC-AHSCT range from 20% at 1 year to 34% at 5 years and OS rates ranged from 39% at 3 years, nearly 50% at 5 years, and in one cohort, an impressive 61% at 7 years (Guardiola et al, 1999; Deeg et al, 2003; Ditschkowski et al, 2004; Kerbauy et al, 2007). This latter group demonstrated that patients conditioned with targeted busulphan (steady state levels between 800 and 900 ng/ml) plus cyclophosphamide (tBuCY) achieved a higher probability of survival than those not undergoing this regimen. It should also be remembered that the median age of the MF population often excludes the majority from a MAC approach despite recent elevation of the conventional upper age limit for this procedure.

## Reduced intensity transplantation

RIC-AHSCT extends the possibility of transplantation to a disease such as MF where the median age of presentation is higher and significant co-morbidities are often present. The first small case series demonstrating the feasibility of either busulphan/fludarabine or melphalan/fludarabine-conditioned AHSCT for MF were published in 2002 (Devine *et al*, 2002; Hessling *et al*, 2002). In the RIC-AHSCT study coordinated by the EBMT group, patients were enrolled over a 5-year period into a multicentre Phase-II trial investigating the efficacy of a fludarabine (30 mg/m$^2$ for 6 d), busulphan (1 mg/kg in 10 doses over 3 d) and anti-thymocyte globulin (ATG) [(Fresenius, Bad Homburg, Germany) 3 × 10 mg/kg (MSD) or 3 × 20 mg/kg (URD) based regimen (Kröger *et al*, 2009a]. The median age of the cohort was 55 years (range 32 –68). Regarding donor source, 33 had a MSD and of the remaining URD cohort, 30% were mismatched. Graft failure rates were low, with only two patients failing to gain neutrophil engraftment. With a median follow up of 33 months (range 12–76), low incidences of relapse at both 3 (22%) and 5 years (29%) were encouraging and confirmed the feasibility of this approach. Multivariate analyses revealed higher incidences of relapse correlated with increased Lille score at the time of transplantation and pre-transplant splenectomy, as mentioned above. NRM in the cohort was 16%, and only 8% of the study population died due to relapse or progression during the follow-up period. NRM rates were significantly higher in the human leucocyte antigen (HLA)-mismatched setting when compared to the fully HLA-matched cohort. Encouraging estimated 5-year DFS (51%) and OS (67%) figures were achieved. Impaired DFS survival was significantly associated with HLA-mismatched transplantation and advanced Lille Score and impaired OS was associated with age > 55 years and HLA-mismatched transplantation. Within the aforementioned CIBMTR series (Ballen *et al*, 2010), 60 patients (21%) underwent RIC conditioning (28 MSD; 29 URD and three other-related). Graft failure occurred in seven patients, none of who survived. The TRM rate at 1 year for sibling allografts was 15%, but much higher (49%) in the 28 patients who underwent URD allografts. Corresponding DFS was 39% for MSD but a dismal 17% for the URD group at 3 years. An interim analysis of 58 MF patients who underwent RIC-AHSCT enrolled in the prospective Myeloproliferative Disorder Research Consortium (MPD-RC) 101 protocol of Fludarabine and Melphalan, in addition to rabbit-ATG, for URD has recently been described (Rondelli *et al*, 2010). Graft rejection occurred in five patients (9%) and primary graft failure in six individuals (10%). Of the 44 who engrafted, grade II-III aGVHD occurred in 22 (50%) of patients and grade III–IV in 11 (25%). At 6 months, overall clinical response was 79% in the MSD setting (complete/partial response rates of 49%) but high TRM rates of 49% occurred in the URD setting. Follow-up data is awaited. The above studies highlight the importance of donor source in determining outcome in RIC-AHSCT, with URD uniformly being associated with worse outcome.

## Can we compare RIC *versus* MAC-AHSCT in MF?

Differences in outcome can be secondary not only to regimen intensity and heterogeneity but also potential publishing/patient selection bias and hence direct comparison of the available data is difficult. Gupta *et al* (2009) performed a retrospective analysis of 46 patients who underwent either MAC- or RIC-AHSCT over a 7-year period. The majority had intermediate- to high-risk disease (*n* = 39), as defined by the Lille scoring system, whereas low risk patients (*n* = 7) underwent transplant for constitutional symptoms or recurrent thrombus. Of note, 70% of those in the RIC group received ATG or alemtuzumab, in contrast to the majority in the MAC group. RIC-AHSCT was significantly associated with more rapid neutrophil engraftment, a reduced risk of GVHD and reduced hospitalization within the first 100 d. There was no statistical difference detected in the time for regression of marrow fibrosis nor, importantly, in the cumulative relapse rate between RIC *versus* MAC cohorts. A non-significant trend was noted for improved OS and PFS in the RIC group at a median follow-up of 50 months (range 20–89). In another retrospective study, a total of 39 patients were reported from four major French transplant centres, 15 of who underwent MAC- and 24 RIC-AHSCT (Lissandre *et al*, 2011). The median age of the cohort (45 years) was somewhat lower than other published studies. Primary engraftment occurred in all but one patient and those in the RIC cohort did not display either lower NRM rates or improved OS compared to those undergoing MAC-AHSCT. Furthermore, the GITMO consortium did not find a significant difference in outcome in patients undergoing MAC-*versus* RIC-AHSCT (Patriarca *et al*, 2008). These cumulative results are in contrast to data from the Nordic group (Abelsson *et al*, 2011) who reported on 92 patients (MAC (*n* = 40) and RIC (*n* = 52)). The probability of 5-year OS, when adjusted for age, was 49% in the MAC cohort but higher in the RIC cohort at 59% (HR 3·58 (95% CI 1·54–8·28, *P* = 0·003). In general, MAC-AHSCT may remain a suitable approach for younger individuals with higher risk disease/blast crises but the question still remains if other disease- or patient-specific parameters exist that justify this approach over a RIC regimen in others. In practice, we would tend to favour the t(BuCy) approach over total body irradiation (TBI)-based regimens, but it is important to note that there has been no direct comparison of efficacy.

## Complications of AHSCT for MF

### *Sinusoidal Obstructive Syndrome: are MF patents at higher risk?*

Early transplant-related complications are relatively common for MF patients (Abelsson *et al*, 2011). Sinusoidal Obstruc-

tive Syndrome (SOS) results from direct hepatic sinusoidal endothelial cell damage, occurring in up to 10% of AHSCT recipients (Ho et al, 2008). Indeed, MF may be associated with pre-AHSCT impaired hepatic function secondary to a variety of reasons, such as hepatic infiltration by extramedullary cells and treatment-related toxicity. Patients with MF may therefore be at a higher SOS risk (Wong et al, 2011). Reporting of SOS rates in the retrospective studies is not standardized and interpretations are limited due to correct recognition and reporting. An incidence of over 30%, predominantly non-severe, was reported in a small cohort of chronic MPN patients (n = 25) undergoing MAC-AHSCT (Daly et al, 2003). Furthermore, retrospective analysis of a cohort of 53 MF AHSCT patients (MAC = 66% and RIC = 34%) revealed a relatively high incidence of early hepatotoxicity and a SOS incidence of 35% (Gupta et al, 2009). In contrast, in the prospective EBMT RIC-AHSCT study, the vast majority (80%) did not demonstrate evidence of SOS (Kröger et al, 2009a). The remaining 20% who did develop SOS were predominantly categorized as mild/moderate (18%). Review of the available studies reveals SOS rates of 0–35% and hence it is paramount that conventional SOS risk stratification occurs for MF patients undergoing transplant (Gupta et al, 2009; Snyder et al, 2010).

### Graft-versus-host disease

Heterogeneous conditioning and T-cell depletion regimens, variable donor type and stem cell source hinders valid interpretation of GVHD rates post-AHSCT for MF. In the predominantly MAC CIBMTR cohort, grade II-IV aGVHD occurred in 43% of MSD, 40% of URD and 24% of other related donors (Ballen et al, 2010). The SFGM-TC data showed a cumulative incidence of grade II-IV aGVHD of 43% by day 100 and, in survivors, the 4-year cumulative incidence of cGVHD was 39% (Robin et al, 2011). Data from the EBMT RIC-AHSCT, with a standard conditioning regimen inclusive of ATG for both MSD and URD, showed a low incidence of aGVHD, with grade II–IV rates of 27% and III–IV of only 11% (Kröger et al, 2009a). Overall the incidence of cGVHD was 49%. Subsequent analysis of patients surviving at least 1 year post-transplant revealed improved survival in those with cGVHD compared to those without, supporting a graft-versus-MF effect. In the comparative retrospective analysis discussed above, Gupta et al (2009) described significantly higher rates of GVHD in the MAC-AHSCT group, where there was a cumulative incidence of grade II–IV aGVHD at day-100 of 78% (62–99) in comparison to the RIC-AHSCT group [18% (7–46)]. This most likely reflects not only conditioning intensity but also that 70% of those in the RIC group received ATG or alemtuzumab. Furthermore, the Nordic data demonstrated an absence of GVHD at 3-months in 72% of individuals in the RIC-AHSCT group in contrast to 24% in the MAC-AHSCT

group (Abelsson et al, 2011). In contrast, the British Society for Blood and Marrow Transplantation data failed to show a reduced incidence of GVHD in the RIC versus MAC groups, despite the vast majority of RIC transplant candidates receiving T-cell depletion – this may well reflect differences in age, donor source and use of donor lymphocyte infusions (DLI) (Stewart et al, 2010). In the GITMO group, the intensity of the conditioning did not appear to have a significant effect on the incidence or severity of either acute (Grade II-IV 41% at day 100) or chronic (43% at 2-years) GVHD (Patriarca et al, 2008).

Significant improvements in day-100 NRM, incidence of grade III–IV aGVHD and OS have been reported in 14 patients who received GVHD prophylaxis with combination tacrolimus/sirolimus +/− methotrexate when compared to patients who had received ciclosporin A/mycophenolate mofetil +/− methotrexate (Snyder et al, 2010). There was no increased incidence of SOS. In conclusion, the optimal RIC, T-cell depletion strategy and GVHD protocol needs to be addressed in large, prospective clinical trials.

Tefferi et al (2011) have recently investigated cytokine-phenotype associations in PMF. Multivariate analysis revealed that augmented levels of interleukin (IL)-8, IL-2 receptor (R), IL-12 and IL-15 were associated with adverse prognosis. In general, it is accepted that elevated systemic pro-inflammatory cytokines can enhance dendritic and T-cell interaction and promote GVHD. Intriguingly, a group studying potential biomarkers for GVHD development has described a 4-protein signature composed of circulating levels of IL-8, IL-2R, Hepatocyte Growth Factor (HGF) and Tumour Necrosis Factor Receptor (TNFR) 1 that strongly predicted onset/grade of GVHD in a selected cohort of admixed patients (Ferrara et al, 2009). An unanswered, yet extremely important, question concerns the role of pro-inflammatory cytokines on GVHD development in MF and the effect of JAK inhibitor therapy on the modulation, if any, of GVHD incidence and severity. CP-690550, a novel JAK inhibitor, has been shown in mice models of aGVHD to suppress donor CD4$^+$ T cell IFN-γ production and abrogate GVHD-related mortality (Park et al, 2010). Ruxolitinib, predominantly a JAK1 and JAK2 inhibitor, has been shown to profoundly reduce pro-inflammatory cytokines. It will be essential to investigate the effect of Ruxolitinib, and other JAK inhibitors, on GVHD-specific cytokine pathways as we integrate novel medical and transplant treatment options for MF.

### Alternative donor stem cell sources for transplantation in MF: is there a role?

Utilization of umbilical cord blood (UCB) units or a haplo-identical source must still be considered as experimental for MF. The incidence of delayed engraftment/graft failure associated with an UCB transplant (UCBT) approach would theoretically be of great concern in this population due to the presence of marrow fibrosis-induced hostile microenvi-

ronment. The Japanese UCBT programme recently reported on 14 patients, predominantly high-risk candidates with SMF and co-existing acute myeloid leukaemia (AML), who underwent RIC-UCBT (Takagi et al, 2010). Encouragingly, neutrophil engraftment occurred in more than 92% of patients (median 23 d) and platelet engraftment in 43% of patients (median 56 d). Complete donor chimerism was achieved rapidly in evaluable patients. Approximately 36% developed aGVHD grade II-IV and the estimated 4-year OS was only 28·6%. This small experimental study, however, demonstrates the feasibility of this approach, even in the setting of severe marrow fibrosis and poor risk secondary AML, and warrants further investigation in multinational prospective trials where no other donor source is available. At present, there is little evidence defining the role of haploidentical transplantation in the treatment of MF. Interestingly, in the non-MF setting, 45 patients underwent a combined RIC haploidentical-unrelated UCBT and demonstrated rapid engraftment kinetics, low rates of GVHD and encouraging outcomes (Liu et al, 2011). In the future, this approach could well be an experimental option for MF-AHSCT transplant candidates lacking a suitable MSD or URD.

## Role of the JAK2 V617F mutation as a prognostic marker in MF-AHSCT

The JAK2 V617F mutation is the most common molecular abnormality in PMF, occurring in approximately 45–68% of cases (Tefferi et al, 2005, 2008; Campbell et al, 2006; Barosi et al, 2007; Guglielmelli et al, 2009). A number of studies have observed an association between JAK2 V617F allelic level and development of post-PV MF. For example, JAK2 V617F mutant allele burden is higher in post-PV MF than in PV (Passamonti et al, 2006), reflecting higher rates of transformation to MF from PV in patients with high mutant allele burden (Tefferi et al, 2006; Vannucchi et al, 2007; Passamonti et al, 2010b). Whether the association of high allelic level JAK2 V617F with transformation to MF is a direct consequence of JAK2 signalling, or simply a marker of patients with clonal evolution, however, remains unclear. There are divergent results with regards to the impact of JAK2 V617F mutation status on prognosis in PMF, with some studies demonstrating an adverse prognostic impact of JAK2 V617F mutations on survival (Campbell et al, 2006) whereas other have shown no effect (Tefferi et al, 2005; Barosi et al, 2007; Guglielmelli et al, 2009). These conflicting results may partly be resolved by study of mutant allele burden as it has been suggested that MF patients with a low level JAK2 V617F mutation have an adverse prognosis, with deaths in this group primarily due to bone marrow failure rather than leukaemic transformation (Tefferi et al, 2008; Guglielmelli et al, 2009). In addition to JAK2 mutational status, nullizygosity for the JAK2 46/1 haplotype has been shown to be associated with inferior survival in MF (Tefferi et al, 2010a,b).

A number of studies have also addressed the prognostic impact of JAK2 V617F in MF patients who received an AHSCT, again with divergent findings. A small study initially concluded that JAK2 V617F was not a useful prognostic marker in this setting (Ditschkowski et al, 2006). Subsequently, however, it was suggested that the presence of JAK2 V617F mutation predicts a favourable outcome post-AHSCT for MF on univariate analysis (Kröger et al, 2009a). Mutation status was not included in multivariate analysis due to incomplete data. Analysis of a larger cohort of 139 patients, however, confirmed a significant adverse prognostic impact of JAK2 V617F negativity on OS for patients with MF undergoing AHSCT (Alchalby et al, 2010a). No significant impact of JAK2 V617F allele burden was noted. The impact of JAK2 46/1 haplotype is unknown in the setting. In conclusion, there are multiple factors involved in determining outcome in MF-AHSCT and hence it is difficult to accurately reach a definitive conclusion regarding JAK2 V617F mutation or allele burden status and AHSCT outcome.

## Disease monitoring post-AHSCT and treatment of relapse

Several studies have assessed whether the presence of JAK2 V617F can be used as a marker of minimal residual disease (MRD) post-AHSCT in order to institute pre-emptive immunotherapy prior to overt relapse. One study used a sensitive real-time polymerase chain reaction (PCR) detection method to monitor and quantify JAK2 V617F levels following 22 RIC-AHSCT procedures for 21 JAK2 V617F positive MF patients (Kroger et al, 2007). Patients became JAK2 V617F negative in 17 of 22 (78%) cases after a median of 89 d following transplant. Of the five patients who remained PCR-positive, four fulfilled the criteria for complete remission, demonstrating the utility of this technique as a marker for MRD and hence depth of remission achieved. In one of these cases, residual JAK2 positivity was eliminated following DLI. A subsequent study demonstrated that achievement of JAK2 V617F negativity after AHSCT for MF was significantly associated with decreased incidence of relapse (Alchalby et al, 2010a). Patients who achieved PCR negativity 6 months following AHSCT had a relapse risk of 5% compared with 35% in those who remained PCR positive. These findings are supported by an earlier study, which demonstrated that JAK2 V617F monitoring post-transplant can predict relapse in patients who become mutation-positive after transplant (Steckel et al, 2007). Information on other molecular markers in the AHSCT setting for MF is limited, although, use of MPL (Thrombopoietin Receptor) mutation status as a MRD marker has been reported (Alchalby et al, 2010b; Rumi et al, 2010).

The timing of DLI, whether as a pre-emptive or salvage approach, post-AHSCT is less clear-cut in PMF than other diseases, such as CML. The concept of a graft-versus-MF

effect stemmed from small case series documenting significant associations between grade II-IV GVHD and reduced treatment failure, in addition to successful salvage of relapsed disease with DLI (Guardiola *et al*, 1999; Byrne *et al*, 2000; Cervantes *et al*, 2000). Kröger *et al* (2009b) initially reported on the use of both salvage and pre-emptive DLI (triggered by *JAK2* V617F persistence on sequential monitoring) in 17 patients, with a median time from transplant to relapse of 269 d (127–1570). DLI was used pre-emptively in eight patients and as salvage in 9. Grade II-IV aGVHD occurred in three patients (18%) in the salvage cohort. Encouragingly, the overall complete molecular response rate was 68% (100% in pre-emptive group *versus* 44% in salvage group ($P = 0.04$), confirming the efficacy of this approach. Pre-emptive DLI, it appears, therefore takes precedence over a salvage approach.

Little evidence is available to help delineate the role of chemotherapy or second allograft in relapsed-MF post-AHSCT. Recently, a co-operative reported on the use of DLI +/− second AHSCT for relapsed patients [morphological relapse ($n = 24$) and molecular relapse ($n = 6$) (Kröger *et al*, 2010)]. A total of 17 patients underwent a second RIC-AHSCT at a median time of 17 months (11–77) post-initial AHSCT. This cohort consisted of 13 non-DLI responders, one blastic transformation and three patients who remained fully donor chimeric. Outcome data was encouraging; a total of 16 engrafted and responses identified in 12 evaluable patients, demonstrating the feasibility of second AHSCT in this group. However, the toxicity of a second AHSCT should not be underestimated, particularly given the median age of this patient population.

## Integrating JAK2 inhibitor therapy and AHSCT in MF patients: conclusions and future directions

In 2012, transplant–eligible MF patients with intermediate-2 and high-risk disease should be considered for AHSCT, in addition to those with transfusion dependency or an unfavourable karyotype. In general, we suggest a MAC approach in those <45 years old, with acknowledgment that some patients between 45 and 50 years with low HCT-CI scores may well also be suitable for a MAC-AHSCT, and a RIC approach for those over the age of 45 years. Patients older than the age of 65 years should not be definitively excluded from potential AHSCT on age criteria alone, but a frank discussion with the patient regarding the association of older age and, in general, an adverse post-AHSCT outcome should occur in addition to a detailed risk assessment. As explored by Deeg and Appelbaum (2011), the benefits and risks of AHSCT in less advanced MF should always be considered on a case-by-case basis. MF patients that may have a higher risk of progression, such as those with intermediate-1 risk disease based on $\geq 1\%$ circulating blasts only, could well benefit from AHSCT early in the disease course (Deeg & Appelbaum, 2011) This is indirectly supported by recent data demonstrating that the IPSS score can predict AHSCT-outcome (Scott *et al*, 2010).

Considerable work has focused on the development of targeted JAK2 therapies. Clinical trials assessing the safety and efficacy of various JAK2 inhibitors in MF have reached advanced phases. Preliminary results suggest that many patients will have a favourable response to JAK inhibition,
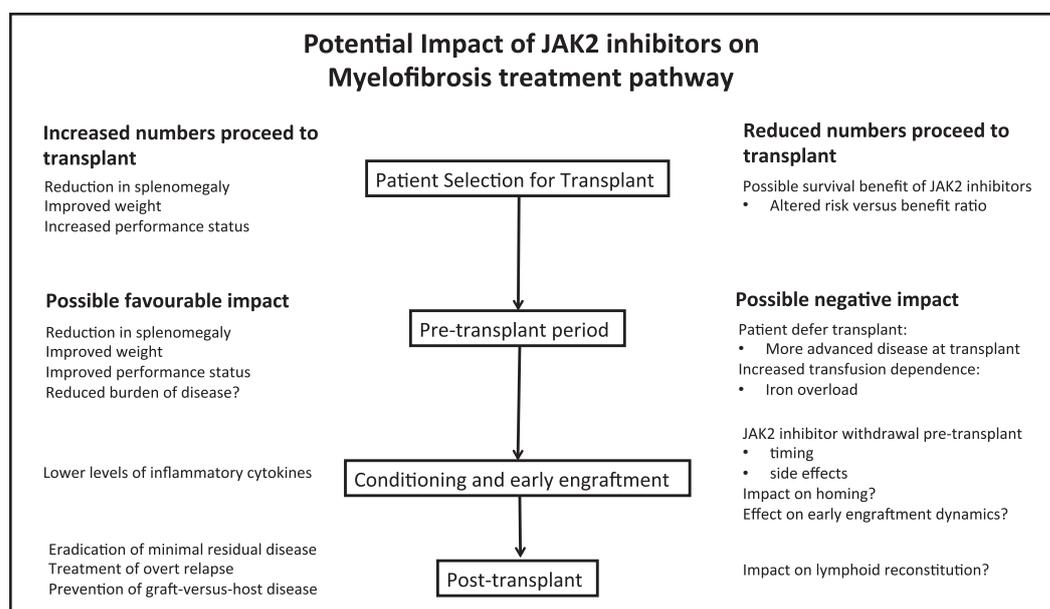


**Fig 1.** Diagrammatic representation of the postulated impact of JAK2 inhibitors on the myelofibrosis AHSCT pathway.

with over 50% reduction in palpable spleen size, which occurs regardless of *JAK2* V617F mutation status (Verstovsek *et al*, 2010). However, current results also suggest that few are likely to achieve a complete response with these therapies with, as yet, little evidence of a substantial reduction in clonal disease burden. Nevertheless, in addition to a role in symptom palliation, a number of lines of evidence also suggest that JAK2 inhibition could have an important role in the context of a patient being considered for RIC-HSCT, as highlighted in Figure 1. Firstly, as discussed above, splenectomy is associated with earlier neutrophil and platelet recovery in multiple studies of RIC-AHSCT. However, splenectomy is associated with considerable morbidity and mortality and may influence immune reconstitution post-transplant. Considerable reductions in spleen size achieved with JAK2 inhibitors might improve engraftment dynamics without the need for splenectomy. Furthermore, JAK2 inhibitors lead to a marked reduction in levels of inflammatory cytokines in patients with MF (Verstovsek *et al*, 2010) and might play a role in reducing the rates of GVHD post-AHS-CT, as discussed above. Finally, constitutional symptoms and leucocytosis are important prognostic factors in MF patients as part of the IPSS score which, along with the poor performance status frequently associated with MF, predicts adverse outcome following AHSCT (Scott *et al*, 2010). JAK2 inhibitors have been shown to have a beneficial effect on all of these prognostic factors (Verstovsek *et al*, 2010) and may well have the potential to improve outcome post-AHSCT.

The timing of JAK2 inhibitor therapy as part of AHSCT protocols requires careful consideration, as the impact on early engraftment dynamics and lymphoid reconstitution is currently unknown. It should also be noted that JAK2 inhibitors may cause both anaemia and thrombocytopenia, which could potentially have a negative impact on AHSCT-outcome. Thus, there is also a potential for these agents to have a negative, as well as a favourable impact on post-AHSCT outcome. Furthermore, we are currently finding that some transplant-eligible patients are opting for a trial of JAK2 inhibitors instead of AHSCT and it may well be that JAK2 inhibitor therapy simply prolongs the time to transplant. Consideration should also be given to the potential impact on quality of life measures, both for those under treatment with JAK2 inhibitors or electing to undergo AHSCT. It is important, therefore, to assess the safety and efficacy of administration of JAK2 inhibitors as part of an AHSCT regimen in prospective clinical trials. These trials should also aim to define the optimal transplant conditioning regimen for MF-AHSCT. Until these future trials become reality, the impact of JAK2 inhibitor therapy on patient selection and timing of AHSCT for MF is currently rather difficult to predict.

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