

REVIEW

Allogeneic stem cell transplantation as treatment for myelofibrosis

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Idiopathic myelofibrosis (IMF) is a clonal disorder resulting from the proliferation of aberrant hematopoietic stem cells. Conventional treatment is unsatisfactory, and with the exception of supportive blood transfusions, none of the standard therapies have been shown to confer a survival advantage. Allogeneic stem cell transplantation represents the only treatment modality with proven curative potential. Myeloablative conditioning regimens are associated with high transplant-related mortality, particularly in the elderly, making most patients with IMF ineligible for this treatment. Strategies using reduced intensity conditioning regimens have allowed application of allogeneic transplantation to a broader range of patients and a number of recent reports have demonstrated potential efficacy.

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Introduction

Idiopathic myelofibrosis (IMF; also referred to as agnogenic myeloid metaplasia or myelosclerosis with myeloid metaplasia) is a chronic myeloproliferative disorder characterized by bone marrow fibrosis secondary to cytokine release from a clonal proliferation of hematopoietic stem cells and resulting in extramedullary hemopoiesis.¹ It is an uncommon disease, with an estimated incidence in the western world of 0.4–0.7 new cases per 100 000 person/year² and is predominantly a disease of the elderly with a median age at presentation of 65 years, although up to 20% of patients are younger than 55 years at the time of diagnosis.³ The most consistent clinical finding in IMF is splenomegaly, often massive, that is present in over 90% of patients at presentation. Peripheral blood examination typically demonstrates anemia, often with thrombocytosis,

together with a leukoerythroblastosis and tear drop poikilocytes on the blood film.⁴ Bone marrow aspiration is frequently difficult or impossible to achieve; a trephine biopsy characteristically shows patchy reticulin fibrosis, abnormal megakaryocyte clustering and intravascular hemopoiesis.⁵

The median survival of patients with newly diagnosed IMF ranges from 3.5–5 years⁶ with a number of factors including advanced age, constitutional symptoms, anemia, leucopenia or leukocytosis, thrombocytopenia, circulating blasts in the peripheral blood and karyotypic abnormalities associated with a worse survival (Table 1).^{3,7} Conventional treatment is unsatisfactory, and with the exception of supportive blood transfusions, none of the standard therapies (including hydroxyurea, α -interferon, androgens and corticosteroids) have been shown to confer a survival advantage.^{8–12} Splenectomy may be considered when the spleen is massively enlarged, resulting in pain or cytopenias, although the morbidity and mortality rates associated with this procedure are not insignificant.^{13,14} In addition, it has been suggested that splenectomy may be associated with an increased risk of blastic transformation in these patients.¹⁵

Myeloablative allogeneic stem cell transplantation (allo-SCT) is the only curative treatment for myelofibrosis, although it is associated with high transplant-related mortality (TRM), particularly in the elderly, making most patients with IMF ineligible for this treatment. The development of reduced intensity conditioning (RIC) has allowed application of allogeneic therapies to a broader range of patients and a number of recent reports have demonstrated that IMF may be successfully treated with allo-SCT following RIC regimens. Here, we review the published data surrounding allogeneic hematopoietic stem cell transplantation in patients with myelofibrosis.

Allogeneic hematopoietic stem cell transplantation with myeloablative regimens

Despite earlier concerns that the degree of marrow fibrosis observed in IMF may hinder hematopoietic recovery following allogeneic transplantation,^{16,17} a number of case reports and small series published in the early 1990s demonstrated that allo-SCT is feasible in IMF resulting in consistent engraftment with reversal of the marrow fibrosis.^{18–20} These results have subsequently been

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Table 1 Prognostic scores for patients with idiopathic myelofibrosis

Lille score		Cervantes score	
<i>Adverse prognostic factors</i>		<i>Constitutional symptoms</i>	
Hb < 10 g/dl		Hb < 10 g/dl	
WBC < 4 × 10 ⁹ /l or > 30 × 10 ⁹ /l		Blood blasts > 1%	
<i>Prognostic groups</i>		<i>Prognostic groups</i>	
Low risk: 0 factor	Median survival (months)	Low risk: 0–1 factor	Median survival (months)
Intermediate risk: 1 factor	93	High risk: 2–3 factors	176
High risk: 2 factors	26		33
	13		

Abbreviations: Hb = hemoglobin; WBC = white blood cell.

Table 2 Published studies of allo-SCT with myeloablative regimens in patients with myelofibrosis

Study	SCT type	No. of patients	Conditioning regimen	Median age in years (range)	% Survival	% Mortality at 1 year	% Grade II–IV acute GvHD	% With extensive chronic GvHD
Singhal <i>et al.</i> ²⁰	MRD (3)	3	MEL/TBI (3)	38 (45–75)	66 (1)	33	100	0
Anderson <i>et al.</i> ²¹	MRD (9), MUD (3), other (1)	13	BU/CY (10); CY/TBI (1); CY/ATG (1); BU/TBI (1)	38 (18–49)	77 (2)	23	46	46
Guardiola <i>et al.</i> ²²	MRD (11), other (1)	12	CY/TBI (8); CY/TBI/VP-16 (3); CY/THIO (1)	40 (14–49)	71 (4)	17	83	33
Przepiorka <i>et al.</i> ²⁷	MUD (5)	5	BU/CY/THIO (2); CY/TBI/VP-16 (2); TBI+ other (12)	43 (34–51)	60 (2)	20	20	20
Guardiola <i>et al.</i> ²³	MRD (49), other (6)	55	CY/TBI (19); CY/TBI/VP-16 (7); BU/CY (17); TBI+ other (12)	42 (4–53)	47 (5)	27	33	36
Deeg <i>et al.</i> ²⁴	MRD (36), MUD (20)	56	BU/CY (44); TBI (12)	43 (10–66)	58 (3)	20	21	51
Daly <i>et al.</i> ²⁵	MRD (13), MUD (10), other (2)	25	CY/TBI (23); BU/CY (2)	49 (46–50)	41 (2)	48	52	35
Mittal <i>et al.</i> ²⁸	MRD (3), MUD (2)	5	BU/CY (2); CY/TBI/VP-16 (1); BU/FLU (1); FLU/MEL/ATG (1)	54 (46–58)	60 (1)	40	60	80
Ditschkowski <i>et al.</i> ²⁶	MRD (16), MUD (4)	20	CY/TBI (16); TBI/FLU (1); CY/TBI/THIO (1); MEL/VP-16/Ara-C/ CY/TBI (1); CY/ATG/TREO (1)	45 (22–57)	39 (3)	45	15	30

Abbreviations: Allo-SCT = allogeneic stem cell transplantation; Ara-C = cytarabine; ATG = antithymocyte globulin; BU = busulfan; CY = cyclophosphamide; FLU = fludarabine; GvHD = graft-versus-host disease; MEL = melphalan; MRD = matched related donor; MUD = matched unrelated donor; TBI = total body irradiation; THIO = thiotepa; TREO = treosulfan; VP-16 = etoposide.

confirmed in a number of larger series,^{20–28} the results of which are summarized in Table 2.

Anderson *et al.*,²¹ from the Fred Hutchinson Cancer Research Center, treated 13 patients with myelofibrosis arising from either IMF, spent-phase polycythaemia vera (PV), or essential thrombocythaemia (ET) with allo-SCT. The median age at transplantation was 40 years (range: 18–49 years) and the median time from diagnosis to transplantation was 39 months (range: 5–192 months). Ten patients were conditioned with busulfan/cyclophosphamide and three with cyclophosphamide plus total body irradiation (TBI). Nine patients were transplanted using

human leukocyte antigen (HLA)-matched related donors and four patients received unrelated donor allografts. The median time to leukocyte and platelet engraftment was 21 days. TRM rate at 1 year was 23%, with the majority of deaths being due to graft-versus-host disease (GvHD). Two patients (15.4%) relapsed at 1-year post transplantation. The 2-year overall survival rate (OS) was 77%. Nine patients (60%) survived between 1 and 7 years with minimal marrow fibrosis and normal peripheral blood counts.

The French Society of Bone Marrow Transplantation followed 12 patients with IMF, of which 10 had undergone prior splenectomy. The median age at transplantation was

40 years (range: 14–49 years). Two-thirds of the patients received cyclophosphamide/TBI conditioning. The median time to leukocyte recovery over 5000/ μ l was 17 days, and to platelet recovery greater than 50 000/ml was 29 days. Graft failure occurred in 8.3% of cases and the 1-year TRM was 17%. The 4-year OS was 71% with a disease-free survival (DFS) of 59%.²²

Guardiola *et al.*²³ presented a retrospective multicenter study, looking at the results of conventional allo-SCT in 55 patients with myelofibrosis. The median age at transplantation was 42 years (range: 4–53 years) with a median time from diagnosis to transplantation of 21 months (range: 2–266 months). Thirty-five patients received a conditioning regimen including fractionated or single-dose TBI. HLA-matched related donors were used in 49 cases. Forty-two patients (76%) had intermediate- or high-risk disease (as defined by the Dupriez *et al.*⁷ or Lille score). The same number of patients had received prior therapies consisting of chemotherapy ($n=28$), splenectomy ($n=27$) or other forms of treatment ($n=20$). Graft failure occurred in 9% of cases and the overall 1-year TRM was 27%. Patients with HLA-identical donors had a TRM at 1 year of 22%. The median post transplant follow-up duration was 36 months (range: 6–223 months). Five-year OS and DFS were $47\pm 8\%$ and $39\pm 7\%$, respectively. Twenty-five patients died, either of infections ($n=5$), chronic GvHD ($n=5$), disease progression ($n=5$), acute GvHD ($n=4$), solid organ failure ($n=3$), lymphoproliferative disorder ($n=2$) and primary graft failure ($n=1$). Adverse factors on engraftment were the presence of osteosclerosis and lack of previous splenectomy. When stratified according to the Lille risk score, the best long-term outcome was seen in patients with low-risk disease, who enjoyed an 85% OS versus 30–45% in the high-risk and intermediate-risk groups, respectively. Hemoglobin values <10 g/dl, high-risk disease (according to the Lille score), osteosclerosis and presence of karyotypic abnormalities had an adverse effect on OS. Increased age, karyotypic abnormalities and absence of significant GvHD were all associated with post transplant relapse. In an update of the above series, extended to 66 patients, the most remarkable feature was the poor outcome of patients transplanted over the age of 45 years. Of patients in this group 14% survived at 5 years as compared to 62% 5-year survival in patients less than 45 years of age.²⁹ Outcome was also less favorable in those patients transplanted from unrelated donors.

In a retrospective study by Deeg *et al.*,²⁴ reporting data from a single institution, 56 patients received a myeloablative allo-SCT for myelofibrosis. In this study, patients received either related ($n=36$) or unrelated donor allografts ($n=20$). The median age at transplantation was 43 years (range: 10–66 years) and the median time from diagnosis to transplantation was 33 months (range: 3–312 months). Forty-four patients were conditioned with busulfan/cyclophosphamide and 12 with TBI plus chemotherapy. Thirty of 56 patients had intermediate-risk ($n=17$) or high-risk ($n=14$) features. Thirty-seven patients had received prior treatments either with chemotherapy ($n=16$), splenectomy ($n=20$) or other therapies. Engraftment was achieved in all but three patients. Among the 31 recipients of HLA-identical sibling transplants, no graft

failures occurred. Primary graft failure was observed in one out of five recipients from HLA non-identical related donors and in two out of 20 patients who were transplanted using unrelated donors. Two patients died from relapse/progressive disease, and 18 died from other causes including infections ($n=13$), GvHD ($n=3$), hemorrhage ($n=1$) and lymphoma ($n=1$). The estimated Kaplan–Meier survival at 3 years was 58%. Bone marrow biopsies were evaluable in 49 patients. In 30 patients, marrow fibrosis was noted to be trace or absent by 6 months post transplant. Disappearance of splenomegaly was documented in 27 patients who had not undergone prior splenectomy. The Lille score, presence or absence of cytogenetic abnormalities and degree of marrow fibrosis were the most important prognostic factors influencing TRM. In the 20 patients transplanted from unrelated donors, the results were comparable to those obtained using related donors, except for the higher frequency of graft failure in the former.

Experiences from two Canadian centers (Toronto and Vancouver) were reported by Daly *et al.*²⁵ In this study, 25 patients with myelofibrosis were treated using conventional myeloablative allo-SCT. The median age at transplantation was 48.7 years (range: 45.9–50.4 years) and the median time from diagnosis to transplantation was 10.7 months (range: 5.67–26.5 months). Twenty-three patients were prepared with cyclophosphamide/TBI and two with busulfan/cyclophosphamide. Thirteen patients were transplanted using related donors. Primary graft failure occurred in two patients (9.1%). Both went on to engraft following a second transplant from their original donors. Five patients (20%) died of transplant-related causes in the first 100 days and the cumulative TRM at 1 year was 48%. The estimated survival at 2 years was 41% and progression-free survival was 37%. High TRM rates were attributed to patient age group, the number of patients with long-standing or advanced disease and the significant number of patients who underwent unrelated donor transplantation (52%).

Finally, Ditschkowski *et al.*²⁶ recently published their results from 20 patients with IMF transplanted in Essen, Germany over a 14-year period. The median age at transplantation was 45 years (range: 23–59 years) and the median time from diagnosis to transplantation was 13 months (range: 3–180 months). Eighteen patients were prepared with conditioning regimens containing TBI (16 patients with TBI/cyclophosphamide, one with TBI/cyclophosphamide/thiotepa and one with TBI/fludarabine) and two patients received conditioning with chemotherapy alone. HLA-matched related donors were used in 13 cases. The 3-year OS was 38%. For those in the low-risk group, 3-year OS rates of 67% were achieved but this fell to 16% for high-risk patients. Deaths were due to treatment-related causes ($n=7$), relapse ($n=3$) and unrelated to the transplant in one patient.

The above results, clearly confirm the efficacy and curative potential of allo-SCT in patients with myelofibrosis. However, they also highlight some of the limitations in utilizing such a treatment strategy. Overall, patients transplanted early in the course of their disease had an excellent outcome but in those with an elevated Lille score or with advanced marrow fibrosis the outcomes were less favorable. Other unfavorable prognostic factors included

increasing patient age and abnormal karyotype. Conditioning-associated toxicity, infection and GvHD were the most common causes of death. Overall, the TRM was around 30% (range: 17–48%) in the published series.

The ideal conditioning regime for patients with advanced disease remains to be identified. Deeg *et al.*²⁴ suggested that the use of busulfan with doses adjusted to achieve targeted busulfan plasma levels had a positive effect on the outcome of allografted IMF patients, resulting in a reduced non-relapse mortality as compared to patients conditioned with regimes including TBI. However, cumulative TRM rates with this conditioning regime are still in the order of 23%. Further studies are required, focusing on strategies for reducing TRM, identifying subgroups of patients for whom myeloablative allo-SCT is most beneficial, and identifying the optimum timing of transplantation.^{30,31}

Allogeneic hematopoietic stem cell transplantation with reduced intensity/non-myeloablative conditioning regimens

The use of RIC is based on the concept that induction of a graft-versus-tumor (GvT) effect may be sufficient to obtain disease eradication without the need for fully myeloablative treatment. In addition, RIC may reduce TRM and expand the applications of allo-SCT in those patients with myelofibrosis. The increased relapse rate observed in recipients of myeloablative transplants without significant GvHD provides indirect evidence for the existence of a GvT effect in IMF.²⁹ More direct evidence of a graft-versus-myelofibrosis effect may be derived from two reports of responses to donor lymphocyte infusion (DLI) in patients with relapsed disease following allo-SCT.^{32,33}

The applicability of RIC transplantation to the treatment of IMF was first reported in a number of small series and case reports.^{34–37} Devine *et al.*³⁴ reported the results in four older patients between 48 and 58 years, all with intermediate- or high-risk IMF according to the Lille score and grade IV fibrosis. These patients underwent RIC allo-SCT using HLA-identical siblings. Conditioning consisted of fludarabine (30 mg/m²/day for 5 days) plus melphalan (70 mg/m²/day for 2 days). All four patients showed neutrophil engraftment by day 14 and platelet engraftment by day 28. With a minimum follow-up of 4 years, all four patients remain alive without evidence of disease.³⁸ Pre- and post transplant histological analyses revealed a marked regression of marrow fibrosis.

In a second small series, three patients with myelofibrosis received allo-SCT after conditioning regime consisting of fludarabine (80 mg/m²), busulfan (8 mg/kg) and antithymocyte globulin (ATG). All three patients achieved engraftment, full-donor hemopoietic chimerism, and complete histopathological remission with no TRM.³⁵

More recently, two larger series have been published confirming the efficacy of RIC transplantation in IMF including elderly and poor-risk patients. Rondelli *et al.*³⁹ reported the results of a retrospective multicentre study of RIC allo-SCT in 21 patients with IMF. The median age at transplantation was 54 years (range: 27–68 years). RIC regimens included fludarabine plus TBI (200 or 450 cGy), fludarabine plus melphalan, cyclophosphamide plus

thiotepa and thiotepa plus fludarabine. At the time of transplantation all of the patients were at intermediate or at high risk according to the Lille score. All but one patient achieved full engraftment. Post transplantation chimerism analysis revealed more than 95% donor cells in 18 patients. Two patients achieved complete donor chimerism after DLI. Acute GvHD grade II–IV was observed in seven patients, grade III–IV in two, and extensive chronic GvHD in eight of 18 evaluable patients. Use of the RIC regimes resulted in prolonged survival and lower TRM. Three patients died from acute GvHD, infections and relapse, respectively. Eighteen patients were alive at 12–122 months (median 31 months) after transplantation, 17 of these being in remission (one after a second transplant).

Secondly, Kroger *et al.*⁴⁰ reported the results of RIC allo-SCT in patients with IMF. Twenty-one patients with median age 53 years (range: 32–63 years), conditioned with busulfan (10 mg/kg), fludarabine (180 mg/m²) and ATG (rabbit, 10 mg/kg for related and 20 mg/kg for unrelated donors) followed by allo-SCT from related (*n* = 8) and unrelated donors (*n* = 13). All patients achieved full hematopoietic engraftment and the median time until leukocyte ($>1.0 \times 10^9/l$) and platelet ($>20 \times 10^9/l$) recovery was 16 days (range: 11–26 days) and 23 days (range: 9–139 days), respectively. Complete donor chimerism on day 100 was seen in 20 patients (95%). Acute GvHD grades II–IV and III/IV occurred in 48 and 19% of cases, respectively, and 55% of the patients developed chronic GvHD. TRM was 0% at day 100, and 16% at 1 year. Hematological response was observed in 100%, and complete histopathological remission was achieved in 75% of patients. After a median follow-up of 22 months (range 4–59 months), the 3-year estimated OS and DFS was 84%.

The above studies (Table 3) demonstrate that allogeneic transplantation following RIC is effective in achieving long-term disease control in a significant proportion of patients with IMF, with an acceptable toxicity even in older patients or those with poor-risk disease.

Discussion

The results of published studies strongly support allo-SCT as an effective treatment strategy in patients with IMF, indicating that it has moved from the experimental setting into that of a practical therapeutic option. Despite the potential for cure, the use of myeloablative protocols is hampered by the advanced age of most patients at diagnosis, and the high TRM associated with this procedure. For the treatment of myelodysplastic syndromes (MDS), a risk stratified approach to myeloablative allo-SCT has been proposed, recommending early allogeneic transplantation for patients with high-risk disease, and observation until disease progression for low-risk patients.⁴¹ However, whether a similar approach is justified for treating patients with IMF is unclear. Based on the available evidence, myeloablative transplantation should only be considered for younger patients (less than 45 years). However, even among younger individuals adverse risk factors, such as extensive marrow fibrosis or karyotypic

Table 3 Published studies of allo-SCT with reduced intensity regimens in patients with myelofibrosis

Study	No. of patients	Conditioning regimens	Median age in years (range)	% Survival	% Mortality at 1 year	% Grade II–IV acute GvHD	% With extensive chronic GvHD
Devine <i>et al.</i> ³⁴	4	FLU/MEL (4)	56 (48–58)	100 (1)	0	0	25
Hessling <i>et al.</i> ³⁵	3	BU/FLU/ATG (3)	51 (44–58)	100 (1)	0	0	33
Tanner <i>et al.</i> ³⁶	1	FLU/BU	38	100 (1)	0	0	100
Greyz <i>et al.</i> ³⁷	1	CDA/MEL/ATG	71	100 (2)	0	0	0
Rondelli <i>et al.</i> ³⁹	21	FLU/TBI (6), FLU/MEL (7), TT/CY (7), TT/FLU (1)	54 (27–68)	86 (3)	10	43	44
Kroger <i>et al.</i> ⁴⁰	21	BU/FLU/ATG	53 (32–63)	84 (3)	16	67	55

Abbreviations: Allo-SCT = allogeneic stem cell transplantation; ATG = antithymocyte globulin; BU = busulphan; CDA = cladribine; CY = cyclophosphamide; FLU = fludarabine; GvHD = graft-versus-host disease; MEL = melphalan; TBI = total body irradiation; TT = thiotepa.

abnormalities have been associated with increased TRM and inferior outcome.^{23–25,29}

The emerging data concerning the efficacy and reduced TRM following RIC has expanded the applicability of allogeneic transplantation to more patients with IMF. The results of the two largest series describing the use of reduced intensity transplantation (RIT) in patients with IMF are encouraging. Both series included patients up to their seventh decade, the majority with high-risk disease, and resulted in restoration of normal hematopoiesis, reversal of marrow fibrosis, 3-year survival rates of 80–85% and acceptable procedure-related mortality.^{39,40} These results compare very favorably with those obtained from series describing the use of RIT in the treatment of MDS/acute myeloid leukemia, that have typically reported 3-year survival rates of 35–40%.^{42,43} As a caveat, however, the current body of published data for RIT in IMF is limited and although it is emerging as an effective treatment for myelofibrosis, it is not yet possible to assess the long-term efficacy of this approach.

Based on the available evidence, it is difficult to accurately identify those patients who should be offered allo-SCT. Preliminary recommendations have been proposed suggesting that allogeneic transplantation should be considered for all patients under 50 years of age with intermediate- or high-risk features and an estimated survival of less than 10 years, although give no guidance on the choice of myeloablative or RIC.⁴⁴ More recently the same group has proposed a new prognostic scoring system based on the blood count at diagnosis in order to better identify patients who might benefit from a transplant procedure.⁴⁵ This system stratifies patients into good, intermediate-risk groups and high-risk groups with median survival of 155, 69 and 23.5 months, respectively, with better discrimination between high- and intermediate-risk groups than can be obtained using older classifications.^{6,7} However, despite the intention to stratify transplant eligible patients, this system fails to make any recommendations as to who should be transplanted especially in the intermediate group. It is possible that the use of other prognostic markers such as cytogenetic abnormalities may further refine these prognostic groups and help determine the patients that will benefit most from early intensive therapy,⁴⁶ however, as yet this approach is unproven.

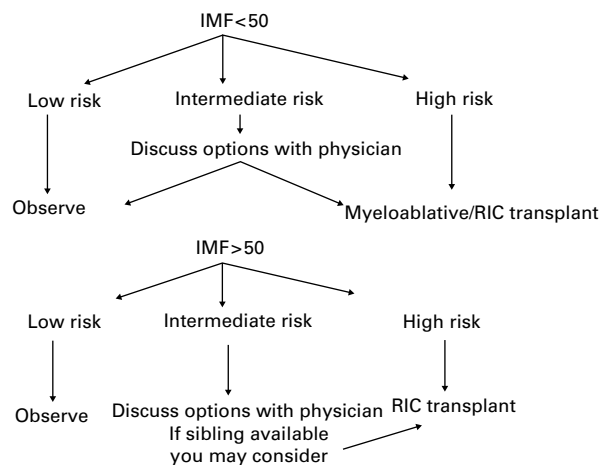


Figure 1 Transplant algorithm adapted to risk group as reported by Dingli *et al.*⁴⁵

Figure 1 illustrates our current approach to the use of allogeneic transplantation in patients with IMF based on the available evidence and adapted from the model suggested by Dingli *et al.*⁴⁵ Newly diagnosed patients with high-risk disease (prognosis 1–3 years), who are fit for transplant and have a suitable donor should be offered allo-SCT up to the age of 70 years. Based on the proven long-term efficacy, myeloablative conditioning could be considered in those less than 45 years, although RIC is likely to be indicated for the majority of patients. For younger patients with intermediate-risk disease, the risk–benefit ratio of allo-SCT is difficult to determine. Based on the prognosis of around 5 years in this group, we would recommend that allo-SCT is discussed with all patients. However, better prognostic systems (perhaps incorporating evaluation of cytogenetic abnormalities) are needed to more accurately stratify these patients according to risk, and identify those that may benefit most from early transplantation. For older patients with intermediate-risk disease, allo-SCT should be considered on an individual basis and perhaps reserved for those without significant comorbidity, good performance status and a sibling donor. For the majority of patients of all ages with low-risk disease (prognosis more than 10 years), a watchful waiting strategy is recommended.

In addition to the questions concerning the timing of transplantation in IMF, the optimal conditioning regimen and role of pre-transplant splenectomy have not been determined. For myeloablative procedures, it appears that cyclophosphamide and targeted level busulfan may be as effective as TBI-based protocols with a reduced procedure-related toxicity.²⁴ The majority of the published reports of RIT in IMF have been with dose-reduced conditioning rather than using non-myeloablative protocols (Table 3), and report excellent short- to medium-term disease control and acceptable toxicity. Whether it would be justified to attempt to further reduce the toxicity by using truly non-ablative regimens is unknown. However, it is possible that any benefit derived from reduced TRM may be offset by an increased relapse rate, as has been shown in treating patients with high-risk MDS/acute myeloid leukemia.⁴⁷

Incorporation of *in vivo* T-cell depletion into RIC protocols, using either Alemtuzumab (Campath-1H/mab-Campath) or antithymocyte globulin, lessens the GvHD-associated morbidity and mortality,^{48,49} although is associated with an increased incidence of infections post transplant (especially viral)^{50,51} and may result in an increased relapse rate consequent on reduced GvT effect. Of the two largest series describing RIT in IMF, one used T-cell depletion with ATG and the other used a T-cell replete strategy and both reported similar survival rates at 3 years post transplant. The incidence of grade II–IV and chronic GvHD were surprisingly similar (T-deplete: 48 and 55%, respectively, versus T-replete: 33 and 72%, respectively) although as expected T-cell depletion was associated with a higher incidence of CMV reactivation.^{39,40} Whether T-cell depletion will also translate into an increased late relapse rate is unknown and can only be investigated by larger studies with longer follow-up.

With regard to the role of splenectomy before transplantation, despite the reported association between splenomegaly and delayed hemopoietic recovery following myeloablative conditioning,²³ more recent evidence, particularly with reduced intensity protocols, suggests that splenectomy is not necessary before transplant.^{39,40} Therefore, given the hazards of the surgery, routine removal of the spleen before allo-SCT does not appear to be justified.^{13,14}

In conclusion, as the perception of IMF is changing, physicians are increasingly exploring allogeneic transplantation as a treatment option for the disease. However, many questions remain unanswered and future large studies are warranted in order to elicit clearer indications and draft recommendations for optimum management.

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