



HHS Public Access

Author manuscript

Biol Blood Marrow Transplant. Author manuscript; available in PMC 2016 November 01.

Published in final edited form as:

Biol Blood Marrow Transplant. 2015 November ; 21(11): 1883–1887. doi:10.1016/j.bbmt.2015.09.005.

Hematopoietic cell transplantation as curative therapy for patients with myelofibrosis: Long-term success in all age groups

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Abstract

Myeloproliferative neoplasms (MPN) are chronic marrow disorders with variable prognosis. Most patients with Polycythemia Vera, Essential Thrombocythemia or even Primary Myelofibrosis (PMF) are successfully managed by conservative strategies for years or even decades, and recent data suggest that even in patients with high-risk disease, in particular those with PMF, life expectancy can be extended by treatment with JAK2 inhibitors. However, none of those modalities are curative, and once marrow failure develops, the disease “accelerates” or transforms to acute leukemia, the only treatment option able to effectively treat and, in fact, cure MPN is allogeneic hematopoietic cell transplantation (HCT). Outcome is superior if HCT is performed

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before leukemic transformation occurs. Several reports document survival in unmaintained remission beyond 10 years. The most recent analyses show reduced regimen-related mortality (less than 10% or even 5% at day 100), and progressively improved survival with both HLA-identical sibling and unrelated donors. The development of low/reduced intensity conditioning regimens has contributed to the improved success rate and has allowed to successfully carry out HCT in patients in the 7th and even 8th decade of life. We propose, therefore, that HCT should be offered to fit patients in these age groups and should be covered by their respective insurance carriers.

Introduction

Primary myelofibrosis (PMF) is a rare myeloproliferative neoplasm (MPN), that occurs primarily in older individuals, with a median age at diagnosis of 67 years [1]. Median life expectancy is 4–5 years. However, the prognosis varies considerably. Some patients show progression to marrow failure or transformation to acute myeloid leukemia (AML) within a year or two, while others have a course that may extend over a decade or more.

Patients who present originally with other MPNs such as Polycythemia Vera (PV) or Essential Thrombocythemia (ET), tend to be younger at diagnosis and typically show a more protracted course, with median life expectancies approaching two decades. However, a proportion of those patients will also experience an acceleration of their disease with marrow fibrosis and marrow failure or transformation to acute myeloid leukemia (AML).

Some patients are managed effectively with conservative strategies (e.g. hydroxyurea or interferon) for years, but management of more advanced disease is challenging. The prognosis is especially poor with transformation to AML, which is associated with a median survival (after transformation) of a few months. One-year overall survival, regardless of treatment intervention, is less than 15 % [2,3].

The use of recently introduced compounds that interfere with Janus kinase (JAK) function, so called JAK inhibitors, has resulted in profound symptomatic improvement and reduction in spleen size in patients with myelofibrosis and may modify the natural course of the disease. Jakafi® (ruxolitinib), an oral JAK1/JAK2 inhibitor, has been approved by the FDA for the treatment of patients with intermediate or high-risk myelofibrosis, including PMF, post-PV and post-ET MF, and has been shown to improve patients' quality of life [4,5], although it may be associated with the development of anemia. In two phase III studies of patients with Dynamic International Prognostic Scoring System (DIPSS; see Table 1) intermediate-2 or high-risk myelofibrosis, ruxolitinib was associated with improvement in survival compared to placebo treated patients (COMFORT-I study) or patients who received "best available therapy" (COMFORT-II study) [4,6]. The COMFORT-II study showed a modest survival advantage for patients who had been treated for more than 3 years [6]. However, while recent data suggest that molecular remissions can be achieved with ruxolitinib [7], this compound is not curative and may not affect the risk for transformation to AML. At 3 years 60% of patients are off treatment because of toxicity or a lack of or loss of response. Therefore, while it is appropriate to offer symptomatic patients and those with morbid splenomegaly a trial of ruxolitinib, physicians and patients must remain alert to the

possibility of disease progression (e.g., cytogenetic/clonal evolution, transformation to AML) while on such therapy. Particularly patients who are considered candidates for HCT must be monitored carefully in order not to miss the opportunity of receiving a transplant before prominent disease progression.

Transplantation

At present, allogeneic hematopoietic cell transplantation (HCT) is the only modality with proven curative potential, i.e HCT currently represents the only definitive therapy for MPN. Because of this, the number of patients undergoing HCT for MPN has increased progressively (Figure 1).

Transplantation for hematopoietic failure

Numerous clinical trials have shown the efficacy of allogeneic HCT (Table 2). In a prospective multicenter phase II trial involving 66 patients, with a median follow-up of 2 years, Rondelli et al observed a survival of 75% after transplantation from HLA-identical siblings; results were inferior, with survival of 32%, in patients transplanted from unrelated donors [8]. In another prospective phase II multicenter trial that enrolled 103 patients, 5-year overall survival was 67% [9].

In a retrospective registry analysis of results in 289 patients ranging in age from 18–73 years, long-term survival was observed in about one third of patients; however, the probability of survival varied dependent upon the transplant conditioning regimen and, similar to the observations of Rondelli et al., the source of stem cells used for the transplant [10]. Another retrospective registry analysis of data on 233 patients showed similar results, with 5-year survival ranging from 56% to 34%, dependent on donor type and stem cell source [11]. In that cohort, 27% of patients were older than 60 years, and after adjusting for other risk factors, multivariate analyses failed to show an association of age at HCT with overall survival or progression-free survival. The relative risk of overall survival for patients >60 years, compared to patients 41–60 years of age, was 0.77 (95% CI, 0.52–1.12; P=0.171), and the relative risk for progression-free survival was 1.02 (95% CI, 0.72–1.45; P=0.904). Additional similar results were reported by Lussana et al. [12] in a retrospective cohort of 250 patients, 22–75 (median 56) years of age, with post-PV or post-ET MF, showing a 3-year overall survival of 55%. Survival was affected negatively by older age, as also noted in other studies [13], by transformation of the disease to AML [14,15], and by the use of unrelated rather than sibling donors. However, these transplants were carried out as far back as 1994, and analysis of results in more recently transplanted patients does not show a significantly inferior outcome with HLA-matched unrelated donors [16,17].

Of course, HCT in older patients is subject to selection bias, by focusing on fit patients without comorbidities [18]. However, this limitation applies to all diagnoses (and *all age groups*) and needs to be considered in *any* discussion regarding suitability for HCT [19]. In a report of results in 30 patients, 60–78 years of age, Samuelson et al. [20] showed an overall survival of 45% and progression-free survival of 40% at 3 years. No significant differences in survival were noted between patients 60–65 years of age and those 66–78 years of age. Transplant-associated mortality was 13% at day 100 after HCT.

Scott et al. presented yet another retrospective analysis of HCT results in 170 patients, 12–78 years of age, with PMF, post-PV, or post-ET MF. These authors used the DIPSS [21] to prognosticate transplant outcome in dependence of the DIPSS score [16]. DIPSS considers patient age, the presence of symptoms (e.g. night sweats), anemia (Hgb<10g/L), leukocytosis (WBC 25×10^9 /L), and circulating myeloblasts (1%) (Table 1). Overall survival and progression-free survival after HCT were closely correlated with pre-HCT DIPSS classification (Table 3). The probability of survival was approximately 80% in patients in the lowest DIPSS risk group (score 0) and 40% in the highest risk group (score >4). The incidence of disease relapse was similar for all DIPSS categories; however, non-relapse mortality increased progressively with higher DIPSS risk, presumably related to disease manifestations, in particular fibrosis, in non-hematopoietic organs such as liver and lungs, providing another argument in favor of earlier HCT. In this particular cohort some patients have been followed now for two decades after HCT, and remain in remission.

Disease progression and timing of HCT

Based on data reported to date it is challenging to decide upon the ideal time for HCT. Therefore, a decision analysis was conducted, restricted to patients with PMF, based on data on 190 patients transplanted at European centers or the Fred Hutchinson Cancer Research Center in Seattle, and 248 patients, treated at European centers with conventional non-HCT modalities [22]. Results in patients followed for as long as 30 years showed a clear advantage of HCT for patients in DIPSS categories intermediate 2 (scores 3–4) and high (scores >4). The data also indicate that patients in DIPSS risk group “low” have superior life expectancy with conventional management. DIPSS group intermediate 1 comprises patients in whom recommendations should be made on an individual basis. Of course, as MPNs progress, extramedullary manifestations tend to become more prominent, and the patient may acquire new comorbidities, underscoring the need for close monitoring and sequential re-assessment of patient and disease risk parameters in order not to miss the optimum time for HCT. Patients who are “triple negative (non-mutated JAK2, MPL1 and CALR)” [23,24] and patients with ASXL1 mutations in the presence of wild type CALR [25] have a more aggressive disease course [26]. These observations are reflected in the modified DIPSS (MIPSS; Table 1) Those patients should probably be considered for early HCT.

As stated above, patients whose disease has accelerated (increase in blood or marrow myeloblast count to >10%, decline in platelet count to $<50 \times 10^9$ /L, abnormalities of chromosome 17) or progressed to frank AML have a median life expectancy of less than a year [27]. While HCT is the only promising treatment strategy, outcome tends to be inferior to that in patients with less advanced disease because of a higher risk of relapse as well as non-relapse mortality [16]. Nevertheless, Ciurea et al. have reported a long-term success rate of 40% in a small cohort of patients who received “debulking” treatment *followed* by HCT [28]. Similar results were reported by Kennedy et al. who showed a 2-year overall survival of 47% in patients responding to chemotherapy and undergoing HCT [3]. Alchalby et al. [29] reported a 1-year treatment-related mortality of 28% and a 3-year progression-free survival of 26% among 46 patients whose MPN had evolved to AML. The major cause of failure was disease relapse, which occurred in 47% of patients.

Based on a comprehensive evidence review, an international group of experts (European LeukemiaNet) recommends allogeneic HCT for patients with MPN with a projected median life expectancy of less than 5 years, which, therefore, includes patients in DIPSS categories intermediate-2 and high, as well as patients with accelerated disease and transformation to AML [30].

Patient age and transplantation

In patients with myelofibrosis up to 60 or 65 years of age, allogeneic HCT is considered standard therapy, both for those with PMF and those with post-PV and post-ET MF [30]. Published data on the use of allogeneic HCT for older patients with MPN, specifically for patients who are typically covered by Medicare, are limited. The analysis by Samuelson, presented above, shows a probability of long-term survival in the range of 30% [20]. Alchalby et al. suggested a model to predict survival after reduced-intensity conditioning (RIC) transplants in patients with myelofibrosis in which constitutional symptoms, non-mutated JAK2 and age >57 years predicted inferior outcome [31].

However, transplant outcomes have been improving. Data from the Center for International Blood and Marrow Transplant Research (CIBMTR) on 254 patients, age 60 years, who received allogeneic HCT for myelofibrosis from 2008 to 2013, show a day-100 survival of 83%, and a 1-year survival rate of 61%. A report from the FHCRC on 22 patients up to 65 years of age, transplanted for MPN, showed a day-100 survival of 100% [17]. The oldest long-term survivor in the report by Scott et al. was aged 78 years at the time of HCT [16].

Summary and Conclusions

While ideally one would like to see results from a prospective trial comparing HCT with non-transplant therapy for patients with MPN, considering the rarity of these disorders and limited resources, it is unrealistic to expect that such a trial will be conducted. Thus, the present data, while not exhaustive, represent the best available evidence in support of HCT for patients with MPNs, including patients in the 7th or even 8th decade of life. Survival probabilities, certainly for patients in DIPSS risk groups intermediate 2 and high, are significantly higher after HCT than observed with conservative therapy. Comorbidities, in addition to disease classification (by DIPSS), significantly impact post-HCT outcome. As the probability of comorbidities increases with age, the selection of older individuals for HCT is profoundly affected by the presence of comorbidities. This is true for patients with MPN as it is for patients with other diagnoses. However, selection of the *appropriate* fit patients for HCT has led to rewarding results, and HCT for MPN should not be withheld solely on the basis of age.

Currently, “myelofibrosis” is not one of the indications listed in NCD 110.8.1 and, therefore, is not covered by Medicare insurance. This represents a major access barrier to effective treatment for patients with these diseases. It appears from available data, however, that it is time to reassess this scenario and, in view of progressively improving results with HCT, provide insurance coverage for appropriately selected older patients with MPN.

Acknowledgments

We thank Helen Crawford and Bonnie Larson for help with manuscript preparation.

Grant support: N/A

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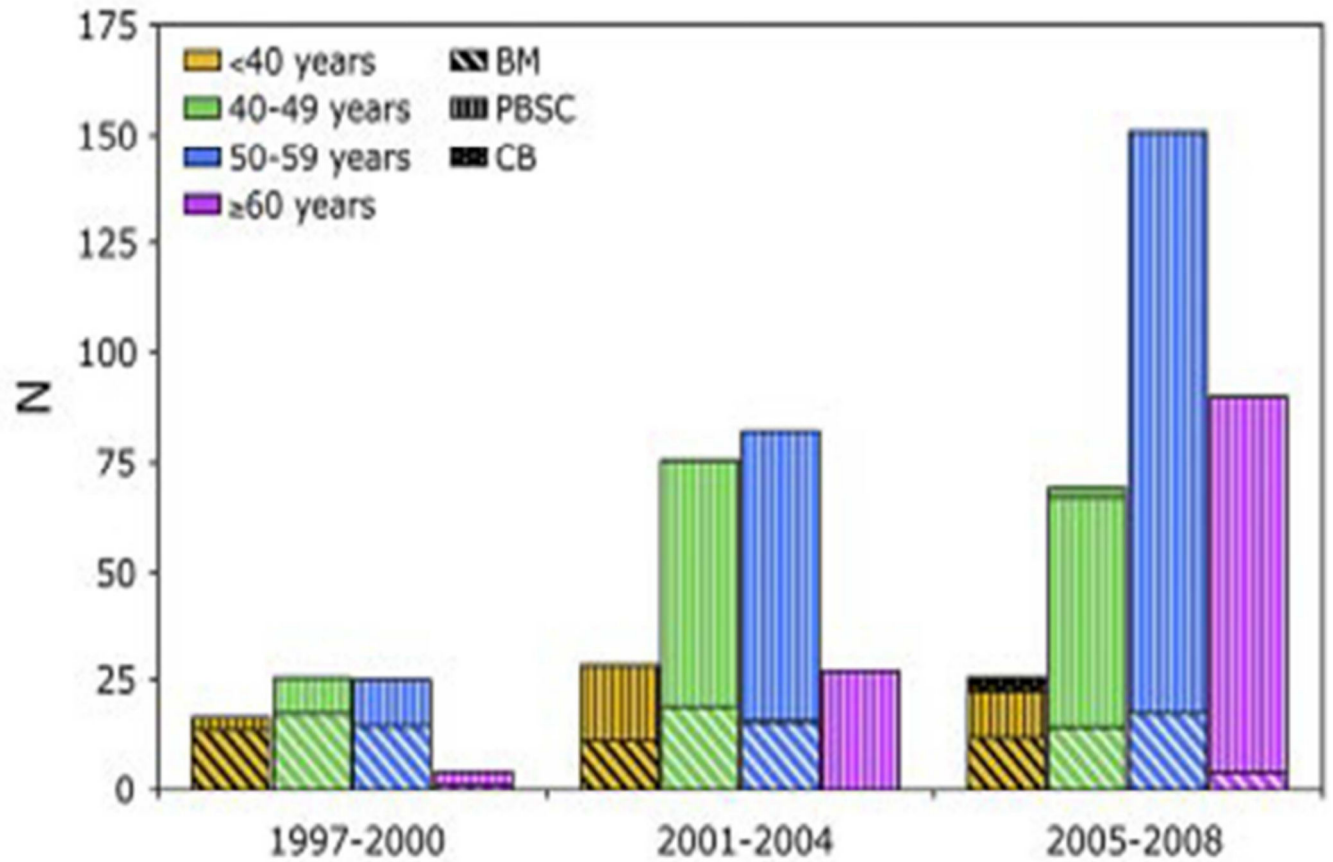


Figure 1. Increase in transplants for myelofibrosis since 1997 by patient age and source of stem cells.#

Data provided by CIBMTR (Center for International Bone Marrow Transplant Research)
 BM= bone marrow; PBSC= mobilized peripheral blood stem cells; CB= cord blood cells.

Table 1

Parameters in current prognostic scoring systems for primary myelofibrosis

	DIPSS[21]	MIPSS [32]
Age	65 (1 Point) vs. <65	> 60 (0.5 Points)
Leukocyte Count ($\times 10^9/L$)	> 25 (1 point) vs. 25	N/A
Hemoglobin (g/dL)	<10 (2 points) vs. 10	<10 (0.5 points)
Constitutional Symptoms	Present (1 point)	Present (0.5 points)
Circulating Blasts	1% (1 point) vs. absent	N/A
Platelets ($\times 10^9/L$)	N/A	<200 (1 point)
Triple Negative[#]	N/A	Present (1.5 points)
JAK2 V617F or MPL Mutation	N/A	Present (0.5 points)
ASXL1 Mutation	N/A	Present (0.5 points)
SRSF2 Mutation	N/A	Present (0.5 points)

[#] Triple Negative = Wild type for JAK2 (V617F), MPL, and CALR mutations
 N/A= not applicable.

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Table 2

Selected reports of HCT outcomes in patients with myelofibrosis [33]

Reference	Timeline of HCT	N	Median age (range), years	Conditioning regimen	% of patients with RIC	NRM	PFS	OS	Comment
Rondelli [34]	NR	21	54 (27–68)	Multiple	100	10% at 1 y	81% at 2.7 y	85% at 2.7 y	Extensive cGVHD in 44%; 2 patients needed DLI for 100% donor chimerism; resolution of fibrosis and splenomegaly in majority
Kerbaui [35]	NR	104	49 (18–70)	Multiple, Bu/Cy (62%)	9	35% at 5 y	NR	61% at 5 y	3 syngeneic donors, 54 of the patients overlapped with a prior report[0]; targeted Bu improved OS; comorbidity score had impact on survival
Patriarca [36]	1986–2006	100	49 (21–68)	Multiple, Bu/Cy 50% of full intensity; Thiotepa + Cy in 46% of RIC	52	43% at 3 y	35% at 3 y	42% at 3 y	AHCT before 1995; unrelated donor and longer interval from diagnosis predicted worse outcome but not conditioning intensity; relapse at 2 y 41%, progressive decline in NRM over 20 y studied
Kroger [9]	2002–2007	103	55 (32–68)	Flu-Bu (100%)	100	16% at 1 y	51% at 5 y	67% at 5 y	First prospective study in MF, cGVHD in 43%; 12% NRM for fully matched donor AHCT; age > 55 y and HLA mismatch adversely affected OS; JAK2-positive recipients had better EFS and OS; splenectomy increased risk of relapse
Ballen [10]	1989–2002	289	47 (18–73)	Multiple, Bu/Cy (43%)	21	35% siblings 50% for URD at 5 y	33% siblings 27% for URD at 5 y	37% siblings 30% for URD at 5 y	Relapse at 5 y, 32% in sibling and 23% in URD; performance status, peripheral blasts sibling donor status impacted OS; RIC was similar in outcomes, except early NRM
Alchalby [31]	1999–2009	162	56 (32–73)	Flu-Bu in 96%	100	22% at 1 y	46% at 5 y	62% at 5 y	82 patients reported previously[54]; age and HLA mismatch impacted NRM; 23% relapse at 3 y; clearance of mutated JAK2 at median of 96 days, and this reduced relapse risk
Bacigalupo [37]	1994–2007	46	51 (24–67)	Thiotepa-Cy + melphalan	100	24% at 5 y	NR	45% at 5 y	A risk score based on transfusion history, spleen > 22 cm and alternative donor use predicted lower OS; no benefit for splenectomy
Robin [38]	1997–2008	147	53 (20–68)	Multiple	69	39% at 4 y	32% at 4 y	39% at 4 y	19% patients had LT; poor outcome with mismatched donor
Samuelson [20]	1999–2007	30	65 (60–78)	Multiple	63	13% at day 100	40% at 3 y	45% at 3 y	Studied outcomes in patients 60 y, 7 patients had preceding LT
Ditschkowski [13]	1994–2010	76	50.5 (22–67)	Multiple	NR	36% at 5 y	50% at 5 y	53% at 5 y	Significant high risk of relapse in patients without cGVHD; DIPSS was predictive of survival

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Reference	Timeline of HCT	N	Median age (range), years	Conditioning regimen	% of patients with RIC	NRM	PFS	OS	Comment
Scott [16]	1990–2009	170	51.5 (12–78)	Multiple	NR	34% at 5 y	57% at 5 y	57% at 5 y	Post-HCT success was dependent on pre-HCT DIPSS scores

MRD=HLA matched related donor; PFS = progression-free survival; OS = overall survival; TBI=, total body irradiation; Hb = hemoglobin; Bu= busulfan; Cy = cyclophosphamide; cGvHD= chronic GVHD; NR= not reported; DLJ= donor lymphocyte infusion; AHCT= allogeneic HCT; PFS= event-free survival; NRM= non-relapse mortality; OS= overall survival; KFS= Kamofsky performance status; ATG= antithymocyte globulin.

Table 3Median survival by DIPSS, without and with transplantation [§]

DIPSS Risk *	Median Survival (years)	
	No Transplant (at reporting)	Transplant (median follow-up 5.9)
Low	Not reached	Not reached
Intermediate 1	14.2	Not reached
Intermediate 2	4	7
High	1.5	2.5

* [15,21]

[§] No data on HCT outcome by MIPSS scores (see Table 1) have been reported to date

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