

Allogeneic Hemopoietic Stem Cell Transplantation in Patients with Myelodysplastic Syndrome or Myelofibrosis

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Abstract

Myelodysplastic syndrome (MDS) and myeloproliferative disorders associated with myelofibrosis (MF) are stem cell disorders, and hemopoietic stem cell transplantation (HSCT) is currently the only therapy with curative potential. Among patients with less advanced MDS, 3 year survivals of 65% to 70% are achievable with HLA-identical related and HLA-matched unrelated donors. The probability of relapse is <5%. Among patients with advanced disease ($\geq 5\%$ marrow blasts), about 35~45% and 25~30%, respectively, are surviving in remission after transplantation from related or unrelated donors. The incidence of post-transplant relapse is 1035%. Criteria of the International Prognostic Scoring System (IPSS), originally developed for nontransplanted patients, also predict survival following transplantation. Patients with MF, either idiopathic or on the basis of pre-existing disorders, are also transplanted successfully with stem cells from related or unrelated donors. Transplants early in the disease, before leukemic transformation, are successful in 60~80% of patients. Success rates are lower in patients who have developed MDS or leukemia. New conditioning regimens have permitted successful HSCT even in patients in the seventh decade of life. Results with a regimen using a combination of busulfan (targeted to predetermined plasma levels) and cyclophosphamide are particularly encouraging. Improved survival with transplants from unrelated volunteer donors may, in part, reflect selection of donors on the basis of high resolution (allele-level) HLA typing. Nevertheless, transplant-related morbidity and mortality, including graft- vs. -host disease, remain challenges that need to be addressed with innovative approaches.

Key Words: MDS; Hemopoietic stem cell transplantation; Cytogenetic risk group; Relapse; Organ toxicity

1. Introduction

Myelodysplastic syndrome (MDS) is a term applied to several hemopoietic disorders that are characterized by ineffective hemopoiesis and a propensity to develop acute leukemia [1,2]. Dysplastic features may be more or less pronounced, and approximately half of the patients have clonal cytogenetic abnormalities [3]. The French-American-British (FAB) classification categorizes MDS on the basis of the proportion of marrow (and peripheral blood) myeloblasts into refractory anemia (RA), RA with ringed sideroblasts (RARS), RA with excess blasts (RAEB) and RAEB in transformation (RAEB-T) [3]. A recent proposal by WHO suggests that

RAEB-T be lumped with acute myeloid leukemia (AML). An additional category, chronic myelomonocytic leukemia (CMML), has now been reclassified as a myeloproliferative disorder. While the FAB categories have proven very useful for diagnostic, prognostic and therapeutic purposes, the incorporation of cytogenetic findings and the number of cytopenias, in addition to the blast count, into a new scoring system termed International Prognostic Scoring System (IPSS) may provide further prognostic precision [4].

Myelofibrosis is considered a myeloproliferative disorder (MPD) and may arise de novo (agnogenic myeloid metaplasia [AMM]), or may develop in the spent phase of polycythemia vera (P. vera) or essential

thrombocytopenia (ET). However, substantial degrees of myelofibrosis can also be observed in patients with MDS. Both MDS and these MPD have in common that they are hemopoietic stem cell (HSC) disorders. As such, they should be amenable to HSC transplantation as a curative therapeutic approach.

2. MDS

2.1. Less Advanced Disease

The best results with allogeneic HSC transplants are achieved in patients with less advanced (or low grade) MDS defined here as patients with RA or RARS. We reported originally relapse-free survival of approximately 60% and a probability of relapse of <5% among patients with RA conditioned with cyclophosphamide (CY) and total body irradiation (TBI), and transplanted from HLA-identical related donors [5]. Very similar results were obtained with a regimen of busulfan (BU), 16 mg/kg plus CY, 120 mg/kg [5]. Relapse rates were low [6,7], however, non-relapse mortality due to infections, GVHD, and single and multi-organ toxicity was in the range of 30~35%. A subsequent Fred Hutchinson Cancer Research Center (FHCRC) study combined CY (60 mg/kg/day \times 2) with TBI at doses of 800 to 1,200 cGy using lung and liver shielding, in an attempt to reduce toxicity. However this trial was closed early because of a relapse probability of 36%, compared to <5% in previous MDS trials ($P=0.001$) [8].

A combination of BU, 16 mg/kg given orally, plus CY, 60 mg/kg/day for two days, with adjustments of the BU dose to achieve steady-state plasma concentrations of 800~900 ng/ml (targeted BU), had yielded encouraging results in patients with chronic myeloid leukemia (CML), and BU/CY regimens have been used by other transplant teams in patients with MDS [6,7,9,10]. Therefore, we tested this regimen in patients with RA (or RARS) transplanted from unrelated volunteers or from family donors. The 3-year probability of relapse-free survival was 68% among patients transplanted from HLA-identical siblings, and 70% with unrelated donors. The incidence of regimen-related mortality was 20~25%, and relapse occurred in about 7% of patients. Similarly encouraging results were observed in a cohort of 510 patients with MDS transplanted from unrelated donors under the auspices of the NMDP [11]. Among patients with RA, 1~62 years of age, the probability of survival at 2 years was 60% after BU/CY conditioning, better than with TBI-containing regimens.

Overall, these studies show excellent results and suggest that the lack of a suitably matched related donor should not be cause to abandon plans for a transplant.

2.2. Advanced MDS

Post-transplant relapse has been reported in the range of 15% to 50% in patients with RAEB, RAEB-T and tAML [10,12-14]. These patients may also have a higher incidence of non-relapse mortality, possibly because

of a more prolonged disease course and duration of supportive care before transplantation.

A study in 131 patients (who had not received pre-transplant induction therapy) reported to the European Bone Marrow Transplant (EBMT) group showed a 5-year disease-free survival of 34% for patients with RAEB, and 19% for patients with RAEB-T [15]. The overall probability of relapse was 39%, 13% for RA/RARS, 44% for RAEB, and 52% for RAEB-T. Transplant-related mortality ranged from 40% in patients with RA to 60% in patients with RAEB-T. Younger age and a shorter interval from diagnosis to transplant were associated with better outcome. A report from the International Bone Marrow Transplant Registry (IBMTR) on results in 581 patients with RAEB, RAEB-T or CMML, shows 3-year probabilities of relapse and disease-free survival of 35% and 40%, respectively [16].

Initial trials at the FHCRC, generally using CY and TBI containing regimens, have been reported elsewhere [17,18]. CY is not stem cell toxic but may contribute to non-relapse toxicity. Thus, a cohort of patients was conditioned with BU (7 mg/kg) plus TBI (6 x 200 cGy) and no CY. Sixty patients, median age 47 years, with RAEB, RAEB-T or CMML were transplanted from related (n=20) or unrelated donors (n=40) [19]. By FAB criteria, 21 patients had RAEB, 16 had RAEB-T, 15 had tAML (AML, transformed from MDS), and 8 had CMML. By IPSS criteria, 1 patient had low, 10 had intermediate-1, 13 intermediate-2, and 31 high-risk MDS (5 patients had proliferative CMML and were not scored). The cumulative incidence of acute GVHD grades II to IV was 83% with unrelated donors and 85% with related donors. The incidence of relapse was 25% at 3 years. The incidence of nonrelapse mortality at 100 days was 38%. The Kaplan-Meier estimate of survival was 26% at 3 years. Major causes of death were relapse, organ failure, GVHD, and infection. In multivariate analysis, improved relapse-free survival was associated with good cytogenetic risk ($P=.004$) and shorter disease duration ($P=.002$). Non-relapse mortality was increased with longer disease duration ($P=.0002$), positive cytomegalovirus serology ($P=.02$), and male sex ($P=.02$). Relapse was associated with poor cytogenetic risk ($P=.0004$). Thus, BU/TBI conditioning was associated with relapse rates comparable to those observed with a more intensive regimen combining BU/TBI with CY. However, despite the omission of CY, transplant-related mortality was considerable, particularly with transplants from unrelated donors. These data indicate that CY is not required for a successful transplant in either related or unrelated transplant recipients [20]. These data also suggested that TBI may not be the best modality to prepare patients with MDS for transplantation. An analysis of results in 510 transplants for MDS from unrelated donors already mentioned above showed that patients in all FAB categories prepared with nonTBI regimens had a higher probability of overall ($P=0.02$) and disease-free survival ($P=0.01$) than patients conditioned with TBI [11]. Results from ongoing FHCRC trials support those findings.

Recent data from the EBMT group indicate that the use of peripheral blood stem cells may be superior to that of marrow stem cells in patients with high-risk MDS [21].

We analyzed separately results in 21 patients with CMML, a disease entity with different kinetics [22]. Patients were 1~62 (median 47) years old and had carried their diagnoses for 2~60 (median 9) months. Twelve patients had more than 5% blasts in the marrow; 12 had normal, and nine, abnormal karyotypes. Patients were prepared either with BU/CY/TBI, BU/TBI or CY/TBI or received a combination of BU (14 mg/kg) plus CY (60 mg/kg \times 2), and were transplanted from a related (n=15) or unrelated (n=6) donors. Nine patients (39%) are surviving in remission with a median follow-up of 7 years. Five patients relapsed, five died with organ failure, and two with GVHD/infections. While only one patient with normal blast counts relapsed, there were four relapses among 12 patients with excess blasts. Shorter disease duration was associated with improved outcome. As with other disease categories, it appears preferable to carry out transplants earlier in the course of CMML.

2.3. Secondary MDS

Treatment-related (secondary) MDS occurs after therapy for various disorders. Incidence figures of 1.1% to 19.8% at 10 years have been reported in patients after autologous HSC transplantation [23-26]. Abnormal, usually high-risk karyotypes (monosomy 7; complex abnormalities), are present in 4 out of 5 patients with secondary MDS. Exposure to irradiation and chemotherapy, as given for the patient's original disease, is thought to be causative. In addition, prior therapy may have resulted in tissue damage, the sequelae of which would predispose the patient to substantial morbidity and mortality while undergoing a transplant for secondary MDS.

Friedberg and colleagues observed 41 patients (7.4%) who developed MDS at a median of 47 months among 552 patients after autologous HSC transplantation for NHL [24]. The actuarial incidence at 10 years was 19.8%. Karyotypes were available in 33 patients, and 29 of these showed monosomy 7 or complex abnormalities. Thirteen patients underwent allogeneic HSC transplantation, and all died. These results are in agreement with an earlier report by the EBMT group which showed a 5-year survival of 0% in patients with secondary MDS [27].

We recently analyzed results in 111 patients with secondary MDS transplanted at the FHCRC from either related or unrelated donors using the same conditioning regimens as employed for patients with de novo MDS [28]. The primary diagnoses included Hodgkin disease, non-Hodgkin lymphoma, carcinoma of the breast, aplastic anemia, multiple myeloma, polycythemia vera, and other solid tumors or hematologic or immunologic disorders. The 5-year relapse-free survival was 8% for patients prepared with TBI, 19% for those given BUCY, and 30% for those prepared with targeted BUCY (p=0.000). The 5-year incidence of relapse was 40% for

tAML, 40% for RAEB-T, 26% for RAEB, and 0% for RA and RARS (P=0.0009). Relapse-free survival at 5 years was 9% for AML, 18% for RAEB-T, 17% for RAEB, and 42% for RA/RARS (P=0.08). Thus, as with de novo MDS, disease stage was the most important risk factor for outcome, and the conditioning regimen had a major impact. The most frequent causes of death were relapse, infections, and single or multiorgan failure. Similar results have been reported for pediatric patients by Leahy et al. [29], and by Ballen et al. [30].

Clearly, these results are not satisfactory. Efforts must be directed at the prevention of secondary MDS, and secondly at improved tolerability of transplant conditioning.

2.4. Relevance of IPSS Score for Transplant Outcome

The IPSS attempts to improve our ability to assess the prognosis of patients with de novo MDS [4]. The IPSS considers the percentage of blasts in the marrow, the number of peripheral blood cytopenias, and the patient's cytogenetic risk (low, intermediate, high), and assigns the patient a numeric score. While originally based on the survival of non-transplanted patients, recent reports suggest that IPSS scores also impact on survival after HSCT [31,32].

Among 251 patients transplanted at the FHCRC in Seattle, the 5-year relapse-free survival was 60% with low and intermediate1 risk, 36% for intermediate2 risk, and 28% for high-risk disease. The major cause of failure among higher risk patients was disease recurrence [31]. Similar results have been reported by Neville et al. [32] who showed that 7-year relapse-free survivals for patients in the good, intermediate and poor risk cytogenetic subgroups (as determined by IPSS) were 51%, 40% and 6%, respectively. The corresponding figures for actuarial relapse were 19%, 12% and 82%, respectively. There was no difference for nonrelapse mortality between the three groups.

Results in a recent cohort of patients transplanted at the FHCRC support these findings: The probabilities of relapse among patients with IPSS low-, intermediate-1, intermediate-2 and high-risk disease were 0%, 6%, 29% and 29%, respectively (P=0.009). Corresponding figures for relapse-free survival were 80%, 64%, 40% and 29%, respectively (P=0.14). It appears, therefore, that IPSS scores should be incorporated into the design of new HSC transplant protocols.

3. Myelofibrosis

Chronic myeloproliferative disorders, including AMM, P.vera, and ET, are characterized by expansion of a hemopoietic stem cell clone resulting in excessive production of cells in one or more myeloid lineages and, with varying frequency, in blast crisis similar to acute leukemia. The hallmark features of AMM are marrow fibrosis, leukoerythroblastic peripheral blood smear, splenomegaly, and extramedullary hemopoiesis. The marrow fibrosis is a reactive process of non-clonal fibroblasts. The

majority of patients with AMM are anemic, while white blood cell and platelet counts can be either elevated or reduced. The median survival is 4-5 years (range of <1 year to >15 years) compared to approximately 14 years for age-matched controls [33]. Patients with either Hgb 10, WBC 4,000, or WBC 30,000 have a median survival of 26 months; abnormal karyotype and possibly osteomyelofibrosis are also poor prognostic features [34].

Several small series of transplants in patients with myelofibrosis have documented the feasibility and potential therapeutic success of HSC transplantation. Guardiola et al. carried out an analysis of results obtained at multiple institutions with HSC transplantation, most from HLA-identical siblings, for AMM or myelofibrosis after ET [35]. Outcome suggested that low hemoglobin values and advanced fibrosis/osteosclerosis of the marrow identified high-risk patients.

We recently summarized results in 53 patients treated at the FHCRC and transplanted from HLA-identical siblings or alternative (related or unrelated) donors [36]. Forty-three patients 1066 years of age, underwent transplantation for cytopenias, progressive myelofibrosis, leukemic transformation or symptomatic splenomegaly after disease durations of 3312 (median 33) months. The underlying diagnosis was AMM in 33, spent phase of ET or P.vera in 13, myelofibrosis with excess blasts in five, and other manifestations in two patients. Conditioning consisted of BUCY in 39 patients (with BU targeting in 34), high-dose BUTBI or CYTBI in 13, and non-myeloablative fludarabine plus TBI in two patients. Thirty-six patients received transplants from related (27 HLA-identical siblings; 9 HLA non-identical family members), and 17 from unrelated donors. All but two patients transplanted from unrelated donors achieved sustained engraftment. Thirty-five patients are surviving at 0.510 years. Overall survival was 67% for patients transplanted from HLA-identical siblings, 78% with HLA non-identical related donors, and 56% with unrelated donors. One patient died with progressive disease, and 17 patients from other causes, predominantly pneumonia and infections. Multifactorial analysis identified conditioning regimens other than targeted BUCY, and increasing disease severity by the Lille classification as significant risk factors for relapse-free survival. Pre-transplant splenectomy, type of donor, and source of stem cells had no significant impact on outcome.

In a separate study, we analyzed results in patients with pre-existing ET (n=13) or P. vera (n=12) who were transplanted either for myelofibrosis (n=14, included in the analysis above) or because of leukemic transformation (n=11) [37]. The median disease duration was 168 months. Various conditioning regimens were used. In 16 patients, the donor was related, and in nine, unrelated. Nineteen patients were given marrow, and six, peripheral blood stem cells. All patients engrafted. Seven patients with leukemic transformation, and two with myelofibrosis died. Sixteen are surviving 5-116 (median 41) months after transplantation for a probability of 64% at 3 years. If disease duration was modeled as a continuous variable, then an increase by 60 months was

associated with an increase in hazard of death by 87% ($P=0.01$). Organ failure, infection, and GVHD were the major causes of death.

These data provide strong evidence that HSC transplantation offers curative therapy for patients with myelofibrosis and advanced ET or P. vera.

4. The "Older" Patient

While the age of patients at the time of diagnosis of an MPD may range from the '20s to '80s, the median age of patients with MDS is in the seventh decade. Physicians have generally been reluctant to consider HSC transplantation in patients with rather slowly progressing disorders, and in particular in patients more than 55 or even 50 years of age.

We recently analyzed results in fifty patients with MDS 55~66 years of age [38]. Conditioning regimens consisted of CY or BU combined with fractionated TBI, or BU plus CY. Donors were HLA-identical siblings in 34, HLA-nonidentical family members in four, identical twins in four, and unrelated volunteers in six patients. At the time of reporting, 22 patients (44%) were surviving at 10~81 months post-transplant, for Kaplan-Meier estimates of disease-free survival at 3 years of 53%, 46%, and 33% among patients with RA, RAEB, and RAEBT/AML/CMML, respectively. Survival in all FAB categories was highest among patients conditioned with targeted BUCY (68% for patients with RA).

As stated above, results are similarly encouraging among patients with AMM and other MPD in the sixth or seventh decade of life at the time of transplantation, in particular when targeted BUCY regimens were used for conditioning.

These data suggest that allogeneic HSC transplantation should not be withheld as a potentially curative treatment modality simply on the basis of age.

5. Post-Transplant Relapse

Post-transplant relapse remains a problem in patients with advanced MDS and high risk cytogenetics. Reports on the efficacy of donor lymphocyte infusions in patients with MDS are limited [39,40]. We have given DLI to seven patients with MDS (five with RAEB and two with RA), and three (all with RAEB) achieved complete remissions. Two are alive, disease free, at more than 2 years (M. Flowers et al, unpublished observations). These observations are of interest, but firm conclusions cannot be drawn at this point. Second transplants are possible in some patients (see below).

In patients transplanted for AMM or myelofibrosis developing after P. vera or ET, relapse has been rather infrequent. Disease recurrence may be a problem, however, in patients with transformation into MDS or leukemia. These observations suggest that patients should be transplanted before leukemic transformation occurs.

6. Non-Myeloablative Conditioning Regimens

The recent development and application of non-myeloablative transplant conditioning regimens ("mini-transplants") has stirred considerable interest [41]. The rationale to this approach is that reduction in the intensity of the conditioning regimen will reduce transplant-related toxicity. Post-transplant administration of immunosuppressive drugs (e.g., cyclosporine plus mycophenolate mofetil) will facilitate donor cell engraftment. If needed, infusions of graded doses of donor lymphocytes may facilitate conversion to full donor chimerism [42]. Such an approach is certainly of interest for the treatment of older patients with MDS and MPD, and may be attractive in patients with relapse after a conventional transplant (or with secondary MDS), particularly if debulking with chemotherapy before transplantation is successful. The field is developing rapidly [43,44].

7. Conclusions

Patients diagnosed with high-risk MDS or MPD who have suitably HLA-matched related or unrelated donors should be transplanted early in their disease course. Patients with less advanced MDS by FAB criteria (<5% marrow blasts) but with high-risk cytogenetic findings (-7; complex abnormalities) or severe multilineage cytopenias according to IPSS, and transfusion dependence, and patients with high-risk myelofibrosis by Lille criteria also should be considered for early transplantation. Patients with MDS with low-risk cytogenetic features (normal karyotype; -Y; 5q-; 20q-) and without severe cytopenias may do well for extended periods of time with more conservative management. Patients with myelofibrosis, either AMM or after ET or P. vera, in general fare better with early transplantation before myelofibrosis has developed or evidence of leukemic transformation is present. For both MDS and myelofibrosis, transplantation can be carried out successfully, even in the seventh decade of life. Overall, non-TBI regimens are better tolerated than TBI containing regimens. The use of peripheral blood stem cells may offer an advantage over marrow cells. The place of non-myeloablative transplants, other than for patients of advanced age (older than 60 or 65 years), remains to be determined.

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