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Review

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Hemopoietic cell transplantation for the myelodysplastic syndromes

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Summary

Myelodysplastic syndromes (MDS) are hemopoietic stem cell disorders, and hemopoietic stem cell transplantation is currently the only therapeutic modality with curative potential. Among patients with less advanced/low-risk MDS (<5% marrow blasts), 3-year survivals of 65–70% are achievable with HLA-identical related and unrelated donors. The overall probability of disease recurrence in these patients is <5%. Among patients with more advanced disease (≥5% marrow blasts), the relapse probability is higher, ranging from 10–40%, and relapse-free survival is correspondingly lower. The criteria proposed by the International Prognostic Scoring System, derived from non-transplanted patients, also predict survival following transplantation. The development of reduced-intensity conditioning regimens and modification of conventional regimens, all aimed at optimizing the transplant approach, have permitted successful hemopoietic stem cell transplants even in patients 60–70 years of age. Improved survival with transplants from unrelated volunteer donors reflects to a large extent selection of donors on the basis of high resolution (allele-level) HLA typing. Graft-versus-host disease and associated problems remain major challenges after allogeneic transplantation. Autologous stem cell transplantation may be beneficial for selected patients who have obtained complete remissions with conventional chemotherapy.

Key words: **MDS • prognostic scoring systems • hemopoietic cell transplantation • conditioning regimens**

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INTRODUCTION

Hemopoietic cell transplantation (HCT) has been shown to have curative potential for patients with myelodysplastic syndrome (MDS). However, the indications and, in particular, the timing of HCT are a matter of dispute. Firstly, MDS occurs predominantly in older patients, and transplant-related morbidity and mortality have often been high in that age group. Secondly, MDS may progress slowly over many years, and a high-risk procedure such as transplantation may be ill advised[12]. Thirdly, as our understanding of the pathophysiology of MDS has improved, several interesting non-transplant strategies have been developed which have shown efficacy, at least transiently[14, 29, 33, 39, 47].

Thus the indications for HCT depend upon disease stage/risk, patient interest, patient age, donor availability, the promise of alternative modalities and, in the end, the probability of success with a transplant. According to the French-American-British (FAB) classification, MDS includes refractory anemia (RA; <5% marrow myeloblasts), RA with ringed sideroblasts (RARS; >15% marrow ringed sideroblasts), RA with excess blasts (RAEB; 5–20% marrow blasts), RAEB in transformation (RAEB-T; 21–30% marrow blasts), and chronic myelomonocytic leukemia (CMML)[6]. The WHO recently defined MDS subgroups more narrowly in a revised classification including RA, RARS, refractory cytopenia with multilineage dysplasia (RCMD), 5q-syndrome, RAEB-1 (5–9% marrow blasts) and RAEB-2 (10–19% marrow blasts), and unclassifiable MDS (MDS-U). Furthermore, the threshold for the diagnosis of acute myeloid leukemia (AML) was reduced to 20% myeloblasts, effectively eliminating RAEB-T as a diagnostic category[51]. In addition, CMML was reclassified as a myeloproliferative/myelodysplastic disorder.

The incorporation of cytogenetic findings and the number of cytopenias, in addition to the myeloblast count, into the International Prognostic Scoring System (IPSS) provides improved prognostic precision[23] (Table 1), not only for the natural history of the disease, but also for results with HCT[16, 34].

GENERAL CONSIDERATIONS

Until recently few patients above the age of 55 years were offered HCT from allogeneic donors (autologous "transplants", using the patient's own cells, have been performed in a higher-age population). This policy was based on the increased severity and frequency of transplant-related morbidity and mortality (TRM) with increasing age. TRM, such as organ toxicity and infections, were related not only to the intensity of the transplant conditioning regimens, but also to graft-versus-host disease (GVHD), which remains the most frequent complication after allogeneic HCT. Even in the most favorable groups of patients overall mortality rates have been in the range of 25–30%, and careful assessment of the indications for and timing of transplantation is therefore essential.

Table 1. International Prognostic Scoring System for MDS

Risk group	Score*	Median survival (years)		Time to 25% risk of AML evolution (years)	
		all patients	≤60 years	all patients	≤60 years
Low	0	5.7	11.8	9.4	>9.4
Intermediate-1	0.5–1.0	3.5	5.2	3.3	6.9
Intermediate-2	1.5–2.0	1.2	1.8	1.1	0.7
High	≥2.5	0.4	0.3	0.2	0.2

* Total score is based on the sum of individual scores for marrow blast percentage, karyotype, and peripheral cytopenias. For marrow blast percentage, a score of 0 is given for blasts <5%; 0.5 for 5–10%; 1.5 for 11–20%; and 2.0 for 21–30%. For karyotype, a score of 0 is given for normal, -Y, del(5q), or del(20q); 1.0 for ≥3 abnormalities or chromosome 7 anomalies; and 0.5 for other abnormalities. For peripheral cytopenias, a score of 0 is given for none or a single cytopenia and 0.5 for 2 or 3 cytopenias. Cytopenias were defined as a hemoglobin <10 g/dl, platelet count <100,000/mcl, and an absolute neutrophil count <1,500/mcl.

In addition to single- or multi-organ failure, the major causes of TRM after allogeneic HCT are GVHD and associated complications, in particular infections. Figure 1 illustrates the impact of acute GVHD on relapse-free survival (RFS) among patients with MDS transplanted from unrelated donors[11].

Patients in IPSS risk groups low or intermediate-1 may have life expectancies in the range of 5–10 years with

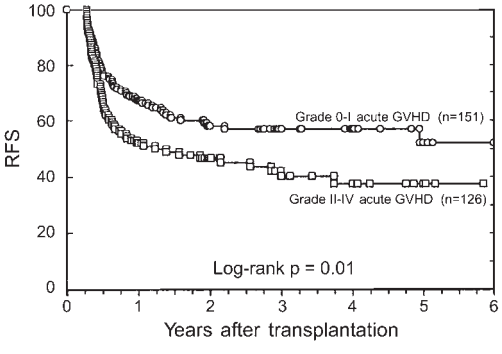

Figure 1. Probability of relapse-free survival (RFS) according to grade of acute GVHD (from Castro-Malaspina et al.[11]; copyright American Society of Hematology, used with permission).

supportive care only or with low-intensity therapy[23]. However, patients must be monitored for evidence of disease progression to allow for a timely decision on transplantation when the probability of success is still good. With intermediate-2 or high-risk MDS by IPSS, HCT is considered the treatment of choice if patients are younger than 65 years and have good performance status. For patients more than 65 years of age with adequate performance status, low-intensity (non-transplant) therapy might be an alternative, unless they qualify for transplantation using non-myeloablative (NMA)/reduced-intensity conditioning (RIC).

While the IPSS was originally derived from data on survival and leukemic transformation in non-transplanted patients, IPSS scores also impact on survival after HCT. Among 251 patients transplanted at the Fred Hutchinson Cancer Research Center (FHCRC), the 5-year RFS was 60% with low and intermediate-1 risk, 36% for intermediate-2 risk, and 28% for patients with high-risk disease[2]. Similar results have been reported by Nevill et al.[34], who showed 7-year RFS for patients in the good, intermediate, and poor risk cytogenetic subgroups (as determined by IPSS) to be 51, 40, and 6%, respectively. The corresponding figures for actuarial relapse were 19, 12, and 82%. There was no difference for non-relapse mortality (NRM) between the three groups. These observations have been confirmed in several studies since then[16, 24].

A Markov model was used to determine the relevance of IPSS scores and expected transplant outcome for the optimum timing of HCT[12]. Results suggest that patients in IPSS risk groups intermediate-2 and high will have the best overall life expectancy if they proceed to transplantation without delay. Patients with low to intermediate-1 risk disease may have the longest life expectancy if HCT is delayed, maybe by several years while being monitored for disease progression[12], unless they present, for example, with severe cytopenias (intermediate-1) (Fig. 2).

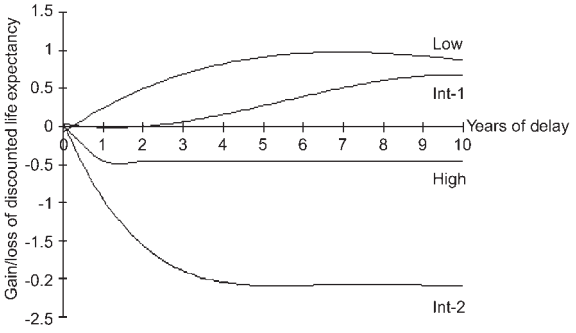

Figure 2. Impact of IPSS risk category on likely benefit from HCT (from Cutler et al.[12]; copyright American Society of Hematology, used with permission).

While based on several assumptions, the data suggest that patients in risk groups intermediate-2 and high, if candidates for HCT, should be transplanted without delay. Patients in the lower risk groups may benefit from delaying transplantation until there is evidence for disease acceleration.

Since a major problem in patients with more advanced MDS is the risk of post-transplant relapse, one strategy might be to give pre-transplant "debulking" chemotherapy. However, the role of intensive remission-induction (and consolidation) chemotherapy before HCT has remained controversial**.** De Witte et al.[20] reported on 184 patients who received 1 or 2 remission-induction courses followed by consolidation (in patients with complete remission [CR] after induction; patients who did not achieve a CR with induction were advised to undergo HCT as salvage therapy or receive therapy with high-dose Ara-C). Following consolidation, patients then proceeded to either allogeneic or autologous HCT depending on donor availability. Four-year overall survival in the entire cohort was 26%, and RFS was 29%[20]. Yakoub-Agha et al.[56] showed that patients who achieved remissions with pre-transplant chemotherapy had a substantially better outcome after HCT than patients who did not achieve a remission. However, patients who were given induction chemotherapy and failed to respond had a lower probability of a successful post-transplant course than patients who were not treated pre-transplant. This indicates that susceptibility to pre-transplant chemotherapy may select for a population of patients with an improved post-transplant outcome regardless of prior therapy. A retrospective analysis of our own data suggests that pre-transplant chemotherapy reduces the risk of post-transplant relapse, but fails to show an advantage for post-transplant RFS[44]. Controlled studies comparing HCT with and without prior chemotherapy are necessary to definitively answer the question regarding the role of pre-transplant induction chemotherapy.

TRANSPLANT STRATEGIES

Source of stem cells

A large retrospective survey of the European Group for Blood and Marrow Transplantation (EBMT) group compared results with marrow and granulocyte colony-stimulating factor (G-CSF)-mobilized peripheral blood progenitor cells (PBPC) for allogeneic HCT from HLA-identical siblings (total body irradiation [TBI]- or chemotherapy-based conditioning regimens). The incidence of treatment failure in all MDS subgroups was lower with PBPC than with mar-

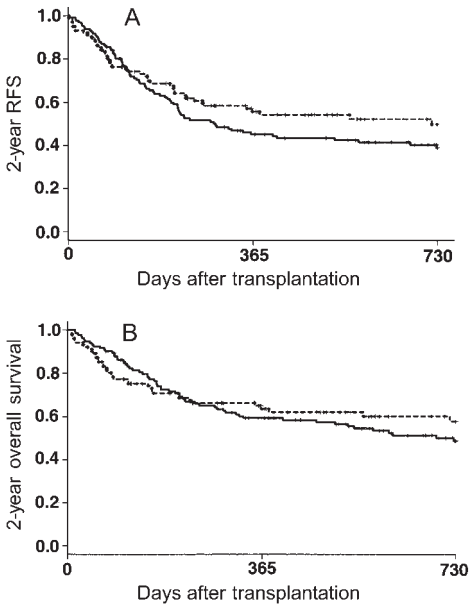

Figure 3. Relapse-free (**A**) and overall survival (**B**) after HCT for MDS. All patients received transplantats from HLA-identical siblings, using either bone marrow (—) or peripheral blood (····) as a source of stem cells (from Guardiola et al.[24]; copyright American Society of Hematology, used with permission).

row[24] (Fig. 3), similar to our observation at FHCRC. The only subgroup of patients not deriving a benefit from PBPC were patients with RA and poor-risk cytogenetics. The incidences of acute GVHD with marrow and PBPC were comparable, while chronic GVHD was more frequent with PBPC. Overall, these studies showed excellent results, with allogeneic HCT in less advanced MDS resulting in RFS in the range of 70%. Importantly, available data also suggest that the lack of a suitably matched related donor should not be cause to abandon plans for transplantation, and a search for an unrelated donor should be pursued. Results with transplants from unrelated donors who are matched with recipients on the basis of high--resolution (DNA level) HLA typing are approaching those with HLA-identical sibling transplants[53].

"Conventional" HCT

Low-risk/"less advanced" MDS. The best results with allogeneic HCT are achieved in patients with low myeloblast counts in the marrow, i.e. RA/RARS, RCMD, or RCMD-RS, at the time of transplantation and patients without poor-risk clonal cytogenetic abnormalities (less advanced MDS; Table 1). Despite improved results with HCT in "less advanced" MDS, the data from Cutler et al.[12] still suggest that delaying HCT until disease progression is superior to HCT at the time of diagnosis. Therefore it is vital that "less advanced" patients who are eligible for HCT be followed closely for any signs of disease progression. This would include new peripheral cytopenias, new karyotype abnormalities, or an increase in bone marrow blast percentage. This close follow-up is necessary so that the potentially curative procedure of HCT can be offered as soon as indicated.

Runde et al.[40] on behalf of the EBMT group reported on 131 patients, most conditioned with TBI-based regimens (70%) and transplanted from HLA genotypically identical siblings. Five-year RFS was 52%, and the cumulative incidence of relapse 13% for patients with RA/RARS[40]. Among 510 patients with MDS transplanted from unrelated donors (National Marrow Donor Program), those conditioned with busulfan (BU) plus cyclophosphamide (CY) [BUCY] fared better than patients prepared with other, generally TBI-containing regimens[11]. RFS and relapse rate in patients with RA were 40 and 5%, respectively[11]. BUCY regimens have been used by several transplant teams[34, 35]; some have added cytosine arabinoside[38]. Despite encouraging results, however, NRM due to infections, GVHD, and single- or multi--organ toxicity was in the range of 25–54%[11, 34, 40].

The team at the FHCRC has reported results achieved with a BUCY regimen in which sequential BU doses were adjusted to maintain steady-state plasma levels of 800–900 ng/ml (targeted BUCY)[16] (Fig. 4). The probability of 3-year RFS was 68%

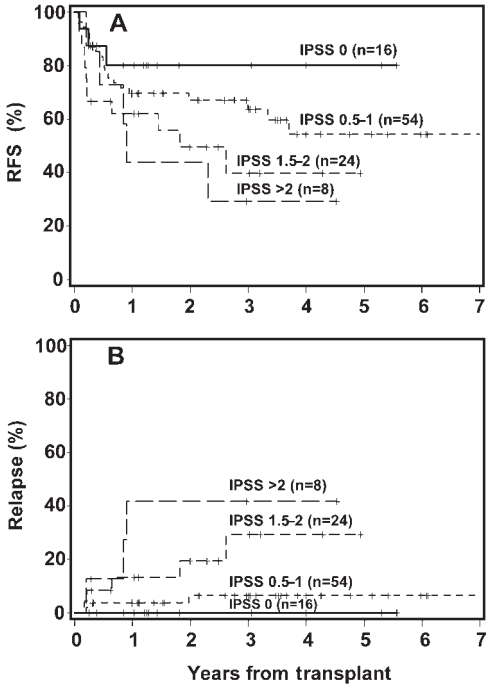

Figure 4. Impact of pre-transplant IPSS risk on RFS (**A**) and relapse (**B**) after allogeneic HCT by IPSS score (from Deeg et al.[16]; copyright American Society of Hematology, used with permission).

among 69 patients with RA/RARS transplanted from HLA-identical sibling donors, and 70% with unrelated donors. NRM among all patients combined was 12% at 100 days and 31% at 3 years; relapse occurred in 5% of patients. Outcomes tended to be superior in patients transplanted with G-CSF-mobilized PBPC rather than marrow.

High-risk/"advanced" MDS. The probability of post--transplant relapse increases with the proportion of marrow blasts present at the time of transplantation (advanced MDS [RAEB/RAEB-T by FAB]) and with increasing IPSS scores, reflecting primarily the impact of poor-risk karyotypes in addition to the proportion of myeloblasts[11, 16, 34, 46]. Relapse rates of 15% to 80% have been reported[3, 11, 16, 40]. Studies in the 80's using CY and TBI-containing regimens reported 30–40% RFS[3]. To determine if more intensive conditioning would improve results by lowering the relapse rate, 31 patients with RAEB, RAEB-T, or CMML, to be transplanted from related or unrelated donors at the FHCRC were prepared with a regimen that combined BU (7 mg/kg), CY (120 mg/kg), and TBI (6×200 cGY)[1]. Compared with historical controls conditioned with CY (120 mg/kg) and TBI (6×200 cGY), the cumulative incidence of relapse was indeed lower (28% vs. 54%), but NRM was markedly increased (68% vs. 36%) and RFS at 3 years was not improved (23% vs. 30%).

In the previously cited report by Runde et al.[40], 63 patients were also included with RAEB/RAEB-T, and in 18 patients the disease had transformed to AML (tAML). About 70% of patients were prepared with TBI-containing conditioning regimens. Relapse occurred in 28 patients (at 1–33 months). RFS at 5 years was 34, 19, and 26% for patients with RAEB, RAEB-T, and tAML, respectively[40]. Younger age and shorter disease duration were associated with better outcome. Another EBMT trial included 118 patients (69 conditioned with TBI) who received HLA-matched unrelated donor transplants. RFS at 2 years was 27, 8, and 27% for patients with RAEB, RAEB-T and tAML, respectively[4]. A report from the International Bone Marrow Transplant Registry (IBMTR) on 452 patients transplanted from HLA-identical siblings (44% conditioned with TBI regimens) between 1989 and 1997 showed an overall survival of 42% at 3 years[46]. Corresponding figures for RFS and NRM were 40 and 37%, respectively. The proportion of marrow blasts at transplantation was the strongest predictor for relapse and RFS, and younger age correlated with higher probability of survival (Fig. 5).

In an attempt to decrease the relapse rates of patients with "advanced" MDS, increased conditioning intensity has been employed. CY is not stem cell toxic, but it contributes to non-hemopoietic toxicity. Thus, in another trial, 60 patients with RAEB, RAEB-T, CMML, or tAML (20 related, 40 unrelated donors) were conditioned with BU plus TBI (without CY), aimed at reducing the relapse rate[26]. The Kaplan-Meier estimate of survival at 3 years was 26%, while the relapse incidence of 25% was comparable to that observed previously with a regimen combining BUTBI with CY (BUCYTBI; see above)[1]. Overall NRM was 38% at 100 days. Particularly disappointing were results with unrelated donors. The data showed that CY was not required to achieve engraftment of donor cells, and suggested that high-dose TBI may not be the optimum modality for conditioning, given the relatively high TRM.

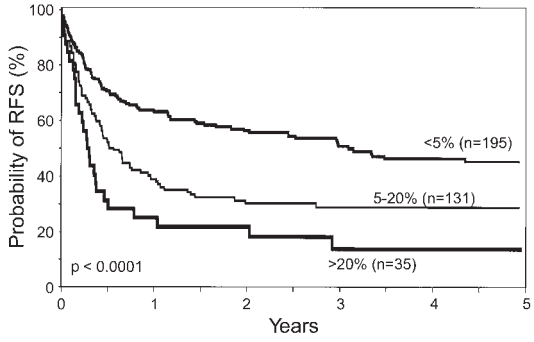

Figure 5. RFS after HCT according to blasts in bone marrow before transplantation.

RIC and optimization of transplant regimens

Other trials have evaluated toxicity and efficacy of conditioning regimens that combine (targeted) BU with fludarabine (Flu) rather than CY[8]. The transplant team in Calgary used a regimen of intravenous (i.v.) Flu, given over 5 days, and i.v. BU, 3.2 mg/kg, given once a day over 3 h on 4 consecutive days, combined with rabbit ATG (Thymoglobulin [THY]), 4.5 mg/kg, plus MTX and CSP. The study enrolled 70 patients with various diagnoses, including MDS, and patients were given marrow or PBPC from related or unrelated donors. There were two cases of graft failure (from unrelated donors), and the incidence of acute GVHD was 8%, and chronic GVHD 36%. The day 100 mortality was 2% with related, and 8% with unrelated donors. Projected RFS at 2 years was 74% for low-risk and 65% for high-risk disease[41]. A recently concluded FHCRC trial of targeted BUCY in patients with high-risk MDS also incorporated THY in a dose escalation design[13]. While the rates of GVHD observed at FHCRC were higher than in the Calgary study, they were lower than in concurrent trials not using THY. A trial in 96 patients at the M.D.

Anderson Cancer Center in Houston, including 22 patients with MDS, also used a FluBU regimen (without THY)[18]. While results for patients with MDS were difficult to separate out, the incidence of acute GVHD (grades II–IV) was 15% for related and 68% for unrelated transplant recipients. These data suggest excellent tolerability of FluBU regimens, and additional trials with these agents are warranted.

A major drawback of HCT has been the high rate of TRM. The development of NMA or RIC transplant regimens ("mini-transplants") has therefore met with considerable interest[9]. The rationale for RIC is that a reduction in the intensity of cytotoxic conditioning regimens will be associated with lower early toxicity and thereby reduce TRM. The post-transplant administration of immunosuppressive drugs (e.g. cyclosporine plus mycophenolate mofetil or tacrolimus plus methotrexate) facilitates donor cell engraftment and enhances the allogeneic (immunologic) effect of donor lymphocytes against the patients' clonal stem cells (graft-versus-MDS effect)[31]. Such an approach should be particularly attractive for the treatment of generally older patients with MDS and for patients with co-morbid medical conditions. RIC regimens may also hold promise for patients who relapse after conventional transplantation, since second transplants using more standard approaches have generally not been very successful because of TRM.

For many years transplant strategies focused on intensification of conditioning regimens to eradicate the underlying disease and prevent post-transplant relapse. The use of RIC regimens represents a dramatic departure from that approach, relying heavily on immunologic effects of allogeneic donor T cells directed against the patient's disease. The field is developing rapidly[27, 28, 37, 46, 49, 50]. It would be inappropriate, however, to simply contrast NMA or RIC with more conventional (ablative) regimens. All efforts are directed at achieving the best results with the least toxic regimens. Thus, as already described above, we are also witnessing progressive modifications of conventional (ablative) regimens. Finally, because of problems with sustained engraftment of donor cells and, in parallel, disease progression following NMA transplants, steps at "re-intensification" of NMA regimens are being taken. Research in this area, therefore, has resulted in a spectrum of regimens (with increasing or decreasing intensity), the goal of which is to determine the optimum regimen for a given disease and patient which optionally balances the competing risks of TRM and relapse.

Kroger et al.[27] have used a regimen of fludarabine combined with a reduced dose of BU and showed a RFS of 38% at 3 years among 37 patients with MDS or tAML (transplanted from related (n=19) or unrelated HLA-matched (n=18) donors). The cumulative incidence of relapse was 32%. De Lima et al.[17] recently reported the M.D. Anderson experience with two regimens: Flu, 120 mg/m^2, plus cytosine arabinoside, 4 g/m^2, and idarubicine, 36 mg/m^2 (FAI), compared with Flu 100–150 mg/m^2, plus melphalan, 140 or 180 mg/m^2 (FM)[17]. There were 26 patients with AML included in this study of 94 patients. The FM regimen was significantly associated with a higher degree of donor cell engraftment and a lower incidence of relapse (30 vs. 61%), but also a higher incidence of TRM (p=0.036; Fig. 6). The 3-year overall survival rates were 30 and 35% for the FAI and the FM regimens, respectively.

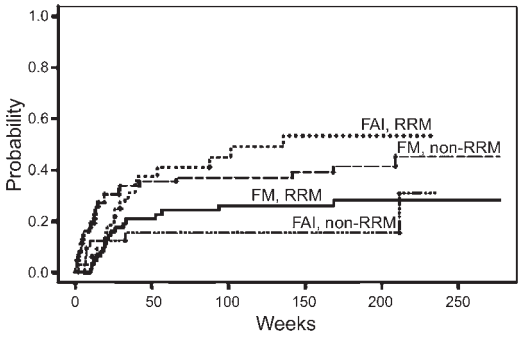

Figure 6. Cumulative incidence of relapse-related (p=0.029) and relapse-unrelated mortality (p=0.036). FAI – fludarabine, ara C, indirubin, FM – fludarabine and melphalan, RRM – relapse related mortality (from de Lima et al.[17]; copyright American Society of Hematology, used with permission).

An update on NMA regimens by the Seattle consortium included 78 patients with MDS (45 related, 33 unrelated transplants; 46 were IPSS low/intermediate--1, and 32 intermediate-2/high or unknown). These patients were conditioned with Flu (3×30 mg/m^2) plus 200 cGy of TBI. Graft failure occurred in 6% of patients and 43% of patients relapsed. The NRM was 14% at day 100 and 25% at 1 year. Approximately 20% of patients were surviving at 3 years (25% with low-risk and less than 10% with high-risk disease)[50].

Ho et al.[25] reported on 62 patients (24 with HLA--identical siblings, and 38 with matched unrelated donors) conditioned with a FluBU/campath regimens. The day 100 NRM was 0% for HLA-identical siblings and 11% for unrelated donor transplants. The incidence of relapse ranged 7–50% for intermediate-1 to high IPSS risk groups. There were 26 patients who received donor lymphocyte infusions at a median of 273 days after HCT. RFS ranged from 86% for IPSS low-risk patients to 33% among patients with IPSS high-risk MDS.

It appears, therefore, that a standard regimen for allogeneic transplants in patients with MDS has yet to be established. Early studies indicate that a reduction in conditioning intensity reduces TRM, but at the expense of an increased relapse incidence. It is important to note, of course, that patients prepared with RIC regimens tended to be older and often suffered from co-morbid conditions. The optimum balance between a reduction in TRM without an increase in relapse has yet to be achieved. Phase III randomized studies comparing different regimens in well-defined patient populations should be helpful in achieving that goal.

Is autologous HCT an option?

Autologous HCT generally does not lead to GVHD and is associated with lower TRM than conventional allogeneic transplants. It may hold promise in patients in whom a "pure" population of normal hemopoietic stem cells is obtainable. The ability to obtain a pure population of normal hemopoietic stem cells remains a controversial issue in diseases like MDS, which by nature are stem cell disorders.

The EBMT reported results in 79 patients with MDS (and tAML), showing RFS of 34% at 2 years after autologous HCT. TRM was 9% in patients 40 years of age or older[21]. These results were restricted, however, to patients who were in a first complete remission after induction chemotherapy. Wattel et al.[52] prospectively assessed feasibility of autologous HCT (either with bone marrow [16 patients] or PBPC [8 patients]) after conditioning with BUCY in 24 of 39 patients who achieved complete remissions after induction chemotherapy. Of the 15 patients who did not receive autologous HCT, 4 had poor stem cell harvests. Among the 24 patients who did receive autologous HCT, 50% were alive 8–55 months after transplantation, and the median RFS was 29 months from time of autologous HCT[52]. Again, autologous HCT was only performed in patients who were able to obtain a complete remission following induction chemotherapy.

De Witte et al.[20] presented data on 184 patients with MDS/tAML who received induction chemotherapy with a plan to proceed to consolidation with either autologous or allogeneic HCT if complete remission was obtained. One hundred patients achieved remissions, 39 were transplanted with allogeneic, and 61 with autologous cells. The rate of continuous complete remission was 33% for allogeneic and 31% for autologous transplants. The 4-year RFS (expressed as proportion of the total cohort) was 25% for allogeneic and 15% for autologous transplants[20].

The same authors recently reported results in patients with or without HLA-identical sibling donors[36]. There were 159 patients with advanced MDS who received remission induction and consolidation chemotherapy. Sixty-five patients had no donor available and, among these, 33 ultimately received autologous transplants. RFS was 23% for patients with and 21% for patients without a donor ($p=0.66$). This intention-to-treat analysis failed to show a survival advantage for patients with HLA-identical sibling donors compared with those without such a donor[36]. The data indicate, however, that outcomes with autologous transplantation are superior to those with chemotherapy alone (without a transplant) in a selected population of MDS patients with high-risk features.

SPECIAL CONSIDERATIONS

The "older" patient

On average, patients with MDS are in their early 70s at the time of diagnosis. Transplantation for these patients has been viewed with great skepticism. Results show, however, that many older patients do quite well, and the age "ceiling" for transplantation has been raised progressively.

In an FHCRC trial, 50 patients with MDS, 55–66 years of age, were conditioned with either BU (7 mg/kg)/CY plus fractionated TBI or targeted BU (prescribed dose: 16 mg/kg)/CY[15]. Donors were HLA-identical siblings in 34, HLA-nonidentical family members in 4, identical twins in 4, and unrelated volunteers in 6 patients. The RFS at 3 years was 53% for RA, 46% for RAEB, and 33% for RAEB--T/tAML or CMML. The overall survival and relapse rate was 44 and 20%, respectively, at 3 years (Fig. 7). When only transplants from HLA-identical siblings were considered, RFS for patients with RA was 67%. Survival in all FAB categories was highest among patients conditioned with targeted BUCY[15]. A recent

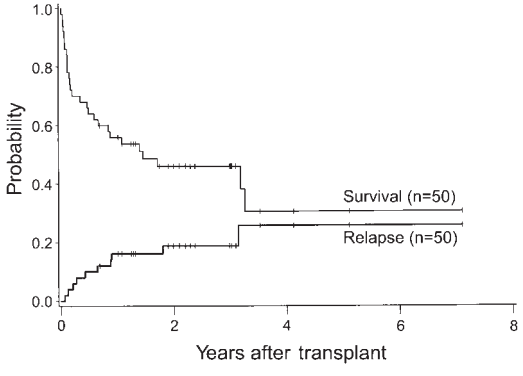

Figure 7. Overall probability of survival and relapse in patients more than 55 years of age with MDS.

analysis in a larger cohort of patients confirmed those results and showed no significant negative impact of age up to 66 years on transplant outcome[16].

In view of the concern about TRM, it was in this older patient population that NMA/RIC regimens were developed and are being exploited. The average age of patients in those studies has generally been a decade or more above that of patients treated with more conventional regimens such as targeted BU/CY. We analyzed retrospectively data on 172 patients more than 40 years of age with MDS/tAML who were transplanted at the FHCRC and conditioned with targeted BUCY (age 40–65 [median 52] years) or conditioned with a regimen of 200 cGy of TBI with or without the addition of Flu (age 40–73 [median 62] years). Patients with RA/RARS fared slightly better with targeted BUCY; however, no significant differences were observed among patients with more advanced MDS[43]. It is important to note, however, that all of the patients with advanced MDS who received an NMA regimen were in complete remission at the time of transplantation, indicating that conditioning intensity is not an important factor in preventing relapse in MDS patients who are in complete remission at the time of transplantation. The data suggest that various regimens are acceptable in older patients. However, toxicity still is a problem, and patients must be selected carefully.

Other parameters

Numerous MDS disease parameters are not considered in currently used classification schemes, but may well be relevant for prognosis and treatment outcome. For example, we have shown that the severity of immunophenotypic aberrancies and scatter properties of myeloid and monocytic marrow cells pre-transplant correlates directly with the probability of post-transplant relapse, and inversely with RFS[54]. One should consider HCT in patients in whom sequential marrow aspirates show worsening of flow parameters, even if by established classification schemes the disease is "stable."

Patients with MDS and associated marrow fibrosis tend to have more rapid disease progression than patients without fibrosis[30]. Preliminary transplant data suggest, however, that fibrosis does not have a negative impact on transplant outcome[42]. Thus in these patients one may want to consider HCT early in the disease course, even if by other criteria, such as IPSS classification, the patients remain in the good or intermediate-1 risk categories. The impact of factors such as cellularity or neo-angiogenesis in the marrow also remains to be determined.

Treatment-related MDS

Treatment-related (secondary) MDS occurs in various settings. At 10 years after autologous HCT for Hodgkin disease or non-Hodgkin's lymphoma, incidence figures of 1–20% have been reported[22, 32, 48]. The median time from primary disease to secondary MDS ranges 2–9 years[22, 32]. Abnormal, usually poor-risk karyotypes (monosomy 7; complex abnormalities) are present in 80–90% of patients[22, 32, 48]. Irradiation and chemotherapy given for the patient's original disease are thought to be the major causes, although a genetic predisposition cannot be excluded. As prior therapy (given for the original disease) is expected to result in tissue damage, such damage is likely to predispose the patient to substantial morbidity and mortality with a later transplant.

Among 552 patients who had received autologous HCT for non-Hodgkin's lymphoma, Friedberg et al.[22] observed 41 who developed MDS at a median of about 4 years, for an actuarial incidence of 19.8% at 10 years. Thirteen patients underwent allogeneic HCT and all died, with a median survival of 1.8 months. A French group reported on 70 patients receiving allogeneic HCT (after various conditioning regimens) for therapy-related MDS and AML[56]. Overall, 54 patients died, 19 of relapse, 34 of TRM, and one of relapse of the primary disease. Age greater than 37 years, absence of complete remission at HCT, and intensive schedules for conditioning were associated with poor outcome. RFS, relapse incidence, and NRM rates at 2 years were 28, 42, and 49%, respectively. All patients had received pre-transplant induction chemotherapy, and patients who achieved CRs had a significantly higher RFS compared with patients not in remission at transplantation.

We analyzed results in 111 consecutive patients with secondary MDS transplanted at the FHCRC between 1971 and 1998 from either related or unrelated donors. The primary diagnoses included Hodgkin disease, non-Hodgkin's lymphoma, carcinoma of the breast, aplastic anemia, multiple myeloma, polycythemia vera, and other malignancies or immunologic disorders. RFS at 5 years was 8% for patients prepared with TBI regimens, 19% for those given fixed-dose BUCY, and 30% for those prepared with targeted BUCY. Relapse rates at 5 years were 40% for tAML, 40% for RAEB-T, 26% for RAEB, and 0% for RA and RARS[55]. Thus, as with *de novo* MDS, disease stage was the most important risk factor for relapse, and the type of conditioning regimen had a major impact on TRM.

Results obtained with allogeneic HCT for treatment-related MDS are currently not satisfactory, although

transplantation may be the only viable option for many of these patients. Efforts must be directed first at the prevention of secondary MDS and secondly at improved tolerability of transplant conditioning. Some preliminary studies with induction chemotherapy followed by RIC regimens have yielded encouraging results.

Post-transplant relapse

Post-transplant relapse remains a problem in patients with a high myeloblast count, poor-risk cytogenetics, or both. Reports on the efficacy of donor lymphocyte infusions in patients with MDS are still limited; however, there is evidence that this approach may be effective[5, 7, 10, 25, 45]. A Japanese series noted complete remissions in 5 of 11 MDS patients[45]. Similar results have been presented by Ho et al.[25] and Depil et al.[19] We have given donor lymphocytes to 7 patients with MDS (5 with RAEB and 2 with RA), and three (all with RAEB) achieved complete remissions. Two patients are alive, disease free, at more than 2 years (Flowers et al., unpublished observations). Some patients with relapse have undergone successful second transplants. Conceivably, RIC transplants are effective in these patients, particularly if carried out before disease evolution. Another treatment strategy currently being employed is "debulking" chemotherapy followed by donor lymphocyte infusion. Further studies are needed to determine the superior approach.

CONCLUSIONS AND OUTLOOK

HCT offers potentially curative therapy for patients with MDS. Patients with intermediate-2 or high-risk MDS by IPSS criteria who have HLA-identical related or matched unrelated donors should be transplanted at time of diagnosis. Patients with less advanced MDS by FAB criteria (<5% marrow blasts) but with poor-risk IPSS cytogenetic findings or severe multilineage cytopenias according to IPSS, and platelet transfusion dependence or severe neutropenia should also be considered for early transplantation. Patients with good-risk cytogenetic features and without severe cytopenias may do well for extended periods of time with more conservative management. However, these patients should be followed closely for any signs of disease progression and offered transplantation at that time. HCT can be successful, even in the seventh decade of life. Overall, regimens not incorporating high-dose TBI appear to be better tolerated than TBI-containing regimens, primarily due to a reduction in TRM. The use of PBPC may offer an advantage over marrow cells, although at the price of a higher incidence of chronic GVHD. A scale of regimens with different conditioning intensities is evolving, aimed at optimizing transplant strategies for a given disease stage and patient.

Improved survival with transplants from unrelated volunteer donors in part reflects selection of donors on the basis of high-resolution (allele-level) HLA typing. Autologous transplants are an option for patients without a suitable donor if a remission can be induced pre-transplant and if stem cells can be harvested. The role of pre-transplant induction chemotherapy is currently not clear. Future investigations will focus on identification of additional prognostic parameters as well as on determination of the optimal timing of HCT.

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