

Mini-review

Bone marrow transplantation for myelodysplastic syndrome – who? when? and which?

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Summary:

Although allogeneic transplantation has resulted in long-term disease-free survival in some patients with myelodysplastic syndromes (MDS), the morbidity and mortality of this approach remains high. Additionally, many patients are not candidates for such an approach because of their age or comorbid factors. Autologous transplantation and the use of reduced intensity conditioning prior to allogeneic stem cell transplantation has provided less toxic alternatives as well as increased the numbers of patients eligible for some form of transplantation. While bone marrow transplantation clearly has a role in the treatment of MDS, the decision to proceed to transplantation is not always easy and the optimal approach has not been clearly defined. Improvement in patient selection and novel approaches to transplantation will hopefully allow for more effective, less toxic results.

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The myelodysplastic syndromes (MDS) are a heterogeneous group of clonal hematologic disorders, which are characterized by abnormal cellular maturation resulting in cytopenias and a variable risk of progression to acute leukemia.¹ Patients have traditionally been classified into groups according to a 1982 French–American–British consensus (FAB), based primarily on percentage of bone marrow blasts.^{2,3} In addition to facilitating diagnosis, this classification system is somewhat useful in determining prognosis. More recently, however, an international prognostic scoring system (IPSS) was devised following a risk analysis study.⁴ Median life expectancy for patients with MDS ranged from a few months to several years, and prognosis depended on several factors: the marrow blast percentage, the karyotype of the clone, and the number of cytopenias present. For the low-risk patients with few blasts, normal

karyotype, and 0 or 1 cytopenias the median survival was 5–6 years; for those with higher risk features estimates of survival ranged from 4 to 14 months.

While advances are being made in the biology of MDS, which will hopefully allow for more effective therapies in the future, the only treatment that has been shown to alter the natural history of the disease is allogeneic bone marrow transplantation. With leukemic induction chemotherapy alone, a proportion of patients achieve complete remission (CR), but this is rarely durable. Furthermore, 40–45% of patients with MDS die of complications of cytopenias (infections or hemorrhage) without ever developing leukemia. This is the justification for the use of a high-risk treatment strategy in early stages of the disease. This review summarizes the data from recent studies of stem cell transplantation in MDS.

Allogeneic bone marrow transplant

Allogeneic BMT is considered the only curative approach for patients with MDS. Table 1 summarizes several recent studies of allogeneic bone marrow transplant for MDS. A formal meta-analysis of results is precluded by the multiple sources of variability in these retrospective trials. The patient populations in these studies have varying proportions of *de novo* MDS, treatment-induced MDS (t-MDS), AML arising from MDS, treatment-induced AML, and *de novo* AML. These are categories of patients that can be quite different in their biology, natural history, and response to treatment. In some instances the outcomes for these distinct groups are not reported separately. Even among patients with *de novo* MDS, studies of prognosis based on the FAB classification and the IPSS, indicate that this a heterogeneous group, for whom transplant will have variable success. Furthermore, ages of the patients, pre-transplant treatments (ranging from none to successful induction of CR), duration of disease before transplant, conditioning regimens, type of GVHD prophylaxis, donor's relation and match (ranging from syngeneic to unmatched-unrelated), and the source of stem cells vary considerably both within and between studies. This degree of variability in approaches is indicative of the many unresolved issues in this field, which we discuss below.

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Table 1 Trials of allogeneic BMT in MDS

Author/Accrual period	Size (n) age	Diagnosis at BMT	Protocol	Donor	Follow-up (yrs)	Results
de Witte ²⁴ 11/92–4/97	n = 184 m = 47 y	RA/RARS 8 RAEB 54 RAEBt 60 CMML 16 sAML 46	TBI+Cy 51% Bu+Cy 29% other 20%	HLA-match rel 56 AUTO 128	1.1 y	OS 26% DFS 29% Relapse 54%
Bibawi ³⁸ 5/91–5/98	n = 12 15–55 y	—	thiotepa+Bu+Cy 12	HLA-matched 1 relative	5.5 y	OS 17% at 3 y
Yakoub-Agha ³⁴ 6/80–2/98	n = 31 m = 37 y	RA 9 RAEB 13 RAEBt 8 CMML 1	TBI+Cy 11 Bu+Cy 26 Melph+Cy 4 other 4	HLA-matched 1 relative	7.9 y	OS 30% at 2 y
Deeg ⁸ 11/89–1/98 2 patients: 78 and 83	n = 50 range 55–66 y	RA 13 RAEB 19 RAEBt/sAML 16 CMML 2	TBI+Cy 15 TMI+Cy 4 TBI+Bu 4 Bu+Cy 27	HLA match rel 36 mismatch rel 4 syngeneic 4 MUD 6	—	OS 46% at 3 y Relapse 19%
Copelan ¹⁵ 3/84–5/99	n = 42 m = 46 y	RA 6 RAEB 8 RAEBt 7 CMML 2 sAML 19	Bu+Cy 29 By+Etop+Cy 13	match sib 35 mismatch rel 3 MUD 4	—	DFS 35% at 4 y Relapse 46% TRM 36%
Okamoto ⁵ 5/91–8/96	n = 13 m = 43 y	RAEB 4 RAEBt 1 sAML 8	TBI+Ara-C+ continuous infusion G-CSF 13	HLA match sib 13	3.2 y	OS 75% at 5 y Relapse 8%
Witherspoon ³⁷ 1971–1997	n = 99	RA 11 RARS 1 RAEB 11 RAEBt 15 sAML 52	Chemo+/-TBI	Match or mismatch rel 65 MUD 34	—	OS 13% Relapse 47% NRM 78%
Neville ³⁹	n = 60 m = 40 y	RA 14 RAEB 11 RAEBt 14 sAML 12	TBI+Cy 12 Bu+Cy 35 Other 13	HLA match sib 37 match rel 1 MUD 22	5.8 y	DFS 29% Relapse 52% NRM 50%
Appelbaum ⁷ 1981–1996	n = 251 med = 38 y	RA 108 RAEB or RAEBt or CMML 143	TBI+Cy 173 Bu+Cy 78	HLA match 148 HLA partial 33 unrelated 70	—	OS 40%
Runde ¹⁶ 1983–1994	n = 131 m = 33 y	RA or RARS 46 RAEB 35 RAEBt 28 CMML 4 sAML 18	varied by center 70% included TBI 12% TCD	HLA match sib 131	2.2 y	OS 41% at 5 y Relapse 39% TRM 44%
Arnold ¹⁷ 1986–1996	n = 118 m = 24 y	RA/RARS 24 RAEB 26 RAEBt 34 CMML 12 sAML 22	varied by center 58% included TBI.	MUD 105 minor-mismatch UD 13	1.6 y	OS 28% a 2 y Relapse 35% TRM 58%
Mattijssen ³⁶ 4/86–12/94	n = 35 m = 41	RA 13 RAEB 7 RAEBt 11 CMML 1 sAML 3	TBI+Cy 9 TBI+Cy+ida 22 Other 4 All TcDepleted	HLA match sib 32 mismatch rel 1 MUD 2	1.7 y	DFS 39% at 2 y Relapse 34% TRM 28%
Ballen ³⁵ 1/80–6/94	n = 43 med = 32–36	RA 13 RARS 3 RAEB 9 RAEBt 9 sAML 9	TBI+Cy 1 TBI+Cy+Ara-C 31 CBV 4 Bu+Cy 7 TCD 7	syngeneic 2 match sib 33 mismatch rel 4 MUD 2 mismatch UD 2	3–4y	t-MDS: DFS 24% TRM 50% Relapse 22% de novo: DFS 43% TRM 60% Relapse 8%

Table 1 Continued

Author/Accrual period	Size (n) age	Diagnosis at BMT	Protocol	Donor	Follow-up (yrs)	Results
Sutton ¹⁰ 7/82–11/91	n = 71 med = 37 y	At diagnosis: RA 16 RAEB 27 RAEBt 28 At transplant: 17 progressed 11 had sAML	TBI+Cy 26 Bu+Cy 17 Other high-dose chemo +/- TBI 28 6/71 T cell-depleted graft	HLA-identical sib 71	6 y	OS 32% Relapse 48% TRM 39%
Demuyneck ¹³ 12/81–3/94	n = 24 m = 30 y	RA 4 RAEB 4 RAEBt 9 CMML 1 sAML	TBI+Cy	HLA match sib 16 mismatch sib 5 MUD 3	1.6–11 y	OS 40% at 5 y Relapse 28%
O'Donnell ⁴⁰	n = 38 m = 35 y	blasts <10% 20 blasts ≥10% 18	Bu+Cy	HLA match sib 38	2 y	DFS 38% Relapse 24%

RA = refractory anemia; RAEB = refractory anemia with excess blasts; RAEBt = refractory anemia with excess blasts in transformation; CMML = chronic myelomonocytic leukemia; sAML = secondary AML; Bu = busulfan; Cy = cyclophosphamide; VO16 = etoposide; Ara-C = cytarabine; CBS = cyclophosphamide, BCNU, etoposide; TBI = total body irradiation; TCD = T cell depleted; sib = sibling; MUD = matched unrelated donor; Auto = autologous; rel = relative; DFS = disease-free survival; OS = overall survival; TRM = treatment-related mortality.

Survival

Survival rates in these studies ranged from 13% to 75%, mostly in the 20–40% range. The lowest rate of 13% was seen in Witherspoon's study;³⁷ all of these patients had t-MDS, and 34 of the 99 patients received bone marrow from volunteer unrelated donors (VUD). This is likely reflected in the high non-relapse mortality rate of 78%. An unusually high survival rate of 75% is reported in a small study of 13 patients all of whom had HLA-matched sibling donors.⁵ This was the only study that reported the use of infusional G-CSF in the conditioning regimen, with the theoretical goal of selectively increasing the chemosensitivity of the leukemic cells to the conditioning regimen.

The largest experience in allogeneic bone marrow transplant comes from a report of the European Group for Blood and Marrow Transplantation.⁶ This retrospective analysis reports on 1087 patients with MDS who underwent allogeneic transplantation between 1983 and 1998. They report a 36% disease-free survival (DFS) at 3 years, 37% non-relapse mortality in the 885 patients who had HLA-identical sibling donors. DFS and relapse-free survival (RFS) rates were 55% and 13%, respectively, in patients with RA/RARS, while corresponding figures for more advanced disease were 28% and 43%. The largest single-center study from Seattle reported their experience in allogeneic transplant of 251 MDS patients.⁷ DFS at 6 years was 40% with an 18% relapse rate. Age as well as IPSS were highly predictive for DFS. Patients under age 20 had a 60% DFS as compared to that of 20% for those over age 50, which was secondary to high transplant-related mortality in the older age group.

Since 75% of patients with MDS are over age 60 there is a particular interest in the use of BMT in older patients, who have generally been excluded from transplant trials. The median ages for these trials hovers around 40; however, one trial reports 50 patients aged 55 to 66.⁸ Overall

survival was 46% and DFS 42% at 3 years, with improved outcomes in patients with low IPSS scores, and/or HLA-identical sibling donors. Of note, patients with targeted busulfan dosing fared better. This trial suggests that the age limits in transplant trials may be too strict.

Conditioning regimen

The variety of treatment protocols listed in Table 1 demonstrates that there is little consensus on the appropriate conditioning regimen for patients undergoing transplant. The challenge is that of balancing regimen-related toxicity against relapse risk. The two most common regimens used in the studies reviewed were busulfan/cytosine or cytosine/total body irradiation (TBI). Sutton *et al*'s study¹⁰ suggested that TBI plus cyclophosphamide performed better when compared to busulfan plus cyclophosphamide. The use of busulfan targeting may provide a regimen that reduces toxicity, while maintaining adequate efficacy. This was addressed in Deeg *et al*'s study⁸ of older patients, which showed that patients who received cyclophosphamide and busulfan targeted to plasma levels of 600–900 ng/ml lived longer than those who received other regimens (either busulfan at 16 mg/kg and cyclophosphamide, or busulfan and TBI, or cyclophosphamide and TBI). For busulfan targeting, busulfan was initiated at a dose of 1 mg/kg every 6 h. The target was achieved by serial assessments of individual patient plasma levels after dosing, and then adjusting the dose to achieve the desired target serum level. In an updated publication of 109 patients with a median age of 46 treated in this fashion, Deeg *et al*⁹ report a 3 year RFS of 58%, and a 100 day TRM of 12%. A recent phase II trial¹¹ of intravenous busulfan included nine patients with MDS, five of whom had t-MDS. These patients received 0.8 mg/kg every 6 h for 16 doses followed by cyclophosphamide at 60 mg/kg daily for 2 days. The pharmacokinetic

studies demonstrated good interdose reproducibility. The authors observed that the toxicity was similar to oral busulfan-based conditioning regimens, but that there was a lower overall incidence of serious veno-occlusive disease, and no serious CNS toxicity. A retrospective analysis of unrelated donor transplants for MDS was recently published by the NMDP. In a group of 510 patients transplanted between 1988 and 1998, unrelated donor transplant resulted in a 29% 2 year DRS, with a 54% TRM and a 14% relapse rate at 2 years.²²

Use of TBI varies by center, and modifications of TBI have been studied. Attempts at decreasing toxicity by shielding of the liver and lung have led to unacceptable relapse rates.¹² Anderson *et al*¹² studied 14 patients with refractory anemia undergoing allogeneic BMT who had customized cerrobend blocks designed to shield the lungs and the right lobe of the liver. Compared to 46 historical controls, the shielded patients had similar non-relapse mortality (29% vs 37%), but a higher relapse rate. The authors conclude that the shielding strategy is associated with an unacceptably high risk of relapse. A few studies included T cell depletion of the allograft. These patients appeared to have higher rates of graft failure, and of relapse.

Pre-transplant treatment and timing of transplant

All the trials included patients with variable treatment histories. The trial data offer conflicting answers to the question of whether transplant is more effective for patients who have obtained CR. For instance in Demuyneck *et al*'s trial¹³ of 24 patients, those in CR had higher overall survival rates. However, in the Sutton *et al* trial,¹⁴ prior intensive chemotherapy did not show a benefit. The data from 44 of the EBMT centers showed an overall survival rate of 41% at 5 years, and none of these patients had undergone prior induction. It is likely that those patients who obtain remission have favorable characteristics that would bode well for success with transplant, regardless of prior treatment strategies. It is also difficult to draw conclusions from these trial data about the timing of transplant. In Applebaum and Anderson's review⁷ of 251 patients, longer disease duration was associated with higher relapse rates and higher NRM. Longer disease duration was associated with shorter survival in some studies,¹⁵⁻¹⁷ but did not affect outcome in others.¹⁴ Again, the outcomes in these mostly non-randomized studies likely reflect patient features rather than transplant protocol procedures

Predictors of outcome after alloBMT

Given the multiple sources of variability in these trials, is it possible to identify which patients are most likely to benefit from allogeneic BMT? Table 2 outlines the results of prognostic factor analyses from the study reviews. Although these studies are rarely powered for statistical comparisons of subsets, several trends emerge. Factors which consistently appear to influence survival, transplant-related mortality and relapse, are (1) FAB classification, cytogenetics, (2) IPSS score, (3) age, and (4) donor avail-

ability. The largest statistically meaningful analysis of univariate and multivariate predictors comes from a retrospective review of the first 250 consecutive patients who underwent allogeneic BMT in Seattle.⁷ In this population, the 5-year cumulative incidences of relapse, non-relapse mortality, and DFS were 17.9%, 43.8% and 38.2%, respectively. Features that predicted relapse were a higher blast percentage, and poor risk karyotype, while higher non-relapse mortality (NRM) was predicted by disease duration, older age, t-MDS, male sex, and mismatched or unrelated donors.

The decision to perform an allogeneic bone marrow transplant is not always clear. Characteristics which define the patients who do best with transplant are the same as those characteristics which determine those who do best with standard therapy (Table 3). While the results of allogeneic transplant are improving, there remains a high transplant-related mortality and relapse rate. In patients without a suitable allogeneic donor, as well as in patients who are deemed unsuitable for allogeneic transplant, alternative options are necessary. This is particularly relevant in this disease which primarily affects older patients who often have multiple co-morbidities.

Autologous transplantation

The utility of autologous transplantation depends on the collection of healthy hematopoietic progenitor cells. A few studies have been published that indicate that polyclonal, karyotypically normal peripheral blood stem cells can be successfully collected from patients with MDS.¹⁸ Hence, autologous transplant is theoretically justified, and has been studied in patients for whom allogeneic transplant was not an option.^{19,20} In a later prospective phase II European trial of the EBMT and ERTC, DeWitte *et al*²¹ have reported results on 184 patients with MDS with transformed AML who underwent stem cell transplantation after remission induction therapy, of whom 61 received autografts. Fifty-four percent of all enrolled patients attained a complete remission. After one course of consolidation therapy, those patients with an HLA-identical sibling were to undergo allogeneic stem cell transplantation. Those without an HLA-identical donor, or over age 50 to 60, were to receive an autologous stem cell transplantation. Of these 57 patients without a donor, 35 were autografted. The remaining patients had prolonged hypoplasia, or insufficient stem cell harvest, or early relapse. The 4 year disease-free and overall survival for the 57 patients (27.3% and 32.7%, respectively), was not significantly different from the results of those with a donor (30.8% and 36.4%). However, the study was not powered to evaluate that comparison. The IPSS cytogenetic risk groups were of prognostic importance, however, the IPSS score did not correlate with survival.

Wattel *et al*²³ reported a prospective study of autologous stem cell transplant for patients with myelodysplastic syndrome drawn from a randomized controlled trial of mito/Ara-C chemotherapy with or without quinine. Forty-two of the original 132 patients were eligible to proceed to autologous transplantation after achieving a CR from induc-

Table 2 Predictors of outcome after allogeneic bone marrow transplantation for MDS

Author (n)	Increased survival	Increased relapse rate	Increased NRM
Anderson ³³ (250)		higher % blasts, poor risk karyotype	longer disease duration, older, t-MDS, male, mismatched or unrelated donors
Yakoub ³⁴ (31)	improved survival: age ≤ 37 , < 2 cytopenias at BMT, CMV neg. recipient		
Applebaum ⁷ (251)	younger age, early stage morphology, low-risk cytogenetics	longer disease duration, advanced morphology, poor risk cytogenetics	older, longer disease duration, mismatched donors, male, t-MDS
Sutton ¹⁰ (71)	age ≤ 37 , female, single karyotype abnormality	FAB subtype, higher % blasts	
Ballen ³⁵ (43)	matched sibling donor, age ≤ 30		
Runde ¹⁶ (125)	early morphology, disease duration < 3 months		
Arnold ¹⁷ (118)	interval < 6 months from diagnosis to transplant	age > 35 , advanced stage	
Copelan ¹⁵ (42)	younger, shorter disease duration, fewer blasts, no prior chemotherapy		
Deeg ⁸ (50)	<i>de novo</i> MDS, low risk karyotype, targeted busulfan dosing		
Mattijssen ³⁶ (35)	RA with HLA matched sibling, CR before transplant		
Witherspoon ³⁷ (99)	less advanced stage		

Table 3 Characteristics which may affect decision to proceed to allogeneic bone marrow transplant for MDS

Favorable	Unfavorable
Younger	$>$ age 60
HLA matched sibling donor	Mismatched donor
Good performance status	Poor performance status
Early stage disease	Advanced or secondary MDS
Disease of short duration	Prolonged course of disease

tion chemotherapy. Of these, 16 patients received an autologous bone marrow transplantation and eight received an autologous peripheral stem cell transplantation with busulfan and cytoxan. Median disease-free and overall survival were 29 and 33 months, respectively, with a median follow-up of 19 months following autografting. In a retrospective review of autologous transplantation in MDS, the EBMT reported on 79 patients who underwent autologous transplantation in first CR.²⁴ They reported a 34% 2 year DFS with a 51% relapse rate and a $< 10\%$ TRM. The DFS for patients under age 40 was significantly better than for older patients (39% vs 25%, $P = 0.04$) mainly due to increased relapse rate in younger patients (59% vs 72%, $P = 0.05$).

The role of monoclonal antibodies in the treatment of hematologic malignancies is under active investigation. A phase I study of 131-I-anti-CD45 antibody plus cyclophosphamide and TBI for patients with high-risk leukemia included three patients with MDS.²⁵ The delivery of sup-

plemental doses of radiation to the marrow and spleen should theoretically decrease the risk of relapse, and thereby improve the cure rate. The authors demonstrated that the approach is feasible, and phase II studies are ongoing.

These studies suggest that there is a subset of MDS patients who can attain durable remission with an autologous transplantation. Although it is not proven whether autologous transplantation is better than traditional consolidation following CR, it is a reasonable strategy for younger patients without an appropriate donor, or for older patients who may not tolerate allogeneic transplantation. New techniques that can better identify residual disease in patients thought to be in CR may improve our capacity to appropriately recommend this treatment strategy.

Reduced intensity allogeneic stem cell transplantation

While both autologous and allogeneic transplantations rely on the efficacy of myeloablative chemotherapy, there has more recently been a growing interest in exploiting the graft-versus-leukemia effect associated with allogeneic transplantation. Several small studies and case reports²⁶ demonstrate the feasibility of donor leukocyte infusion (DLI) to treat MDS patients who have relapsed after allogeneic transplantation. In Shiobara's report five of 11 patients with relapsed MDS achieved CR after a dose of $3 \times 10^7/\text{kg}$ of recipient's body weight.

In order to exploit this phenomenon, reduced intensity allogeneic stem cell transplantation has recently been

developed for patients with hematologic malignancies. Given the advanced age of most patients with MDS, the potential reduced toxicity of these regimens has made this approach of particular interest. While a variety of conditioning regimens has been used, this approach focuses on the immune-mediated effects of the allograft rather than the myeloablative effects of the conditioning regimen. For this reason, preparative regimens are chosen which focus on pregrafting immunosuppression. Agents commonly used include fludarabine, cytoxan and low-dose total body irradiation²⁶⁻³¹ Variable rates of response and toxicity have been observed. In general, non-myeloablative stem cell transplantation was much better tolerated when compared to conventional myeloablative allogeneic transplantation, transplanted-related morbidity and mortality being much decreased. Toxicity is generally related to GVHD and infection. While acute GVHD greater than grade II is less frequent, rates of up to 40% for chronic GVHD have been reported.

Slavin *et al*²⁸ have reported results of nonmyeloablative transplantation on patients with AML or MDS. All patients engrafted; of the eight patients with MDS, DFS was 100% in three patients with RAB, and 40% in those with RAEBT. Kroger *et al*³² reports 12 patients with high-risk MDS who were treated with a fludarabine-based reduced intensity conditioning regimen followed by HLA-matched allogeneic stem cell transplantation. Seven of the patients had unrelated donors. All patients engrafted. Four of the patients died due to treatment, and four had grade II-IV GVHD. Two-year DFS was 12%, and the overall survival was 26%. Morbidity and mortality rates were high in this study, but these were high-risk patients who were ineligible for conventional allogeneic treatment.

A novel conditioning regimen employing photopheresis, pentostatin and low-dose total body irradiation has been employed in a pilot study of non-myeloablative allogeneic stem cell therapy at the New England Medical Center.⁴¹ Although the exact mechanism of photopheresis is not known, the treatment is both immunosuppressive and cytotoxic. Photopheresis has been shown to augment monocyte function and to induce the malignant T cells to undergo a high rate of apoptosis, exerting an anti-tumor effect through cytokine modulation and modification. Photopheresis is also active in the treatment of acute and chronic GVHD. In a prospective randomized trial in cardiac transplant recipients, photopheresis was shown to decrease the incidence of organ rejection and the need for additional immunosuppressive drugs. Photopheresis has also been used for patients with various collagen vascular diseases. Photopheresis may induce autoreactive T cell clones that may attenuate the allogeneic response and ameliorate the incidence of acute and chronic GVHD.

2-Deoxycoformycin (pentostatin; dCF; Nipent) is a third-generation purine analogue that is currently used in the treatment of hairy cell leukemia (HCL), chronic lymphocytic leukemia and mycosis fungoides. The drug is a potent inhibitor of the enzyme adenosine deaminase (ADA), which catalyzes the deamination of adenosine and deoxyadenosine to inosine and deoxyinosine. Most prevalent in lymphocytes, ADA deficiency leads to the accumulation of adenosine and deoxyadenosine leading to cell death. The

rationale for the use of pentostatin in the NEMC protocol is that this drug is active against memory T cells, which may be an important mediator of GVHD. Moreover, pentostatin has demonstrated activity in acute and chronic GVHD. Pentostatin administered by continuous infusion was well tolerated. Total body irradiation has been used in preparative regimens for allogeneic bone marrow transplantation. The Seattle group found that 9.5 Gy in a single fraction was required to obtain sustained engraftment in experimental animals. Low-dose TBI, 2-4 Gy in a single fraction, has been used as part of less intensive preparative regimen.

In the pilot study at the New England Medical Center over 50 patients, including 10 with MDS, median age 48 years (range 23-72), underwent conditioning with extracorporeal photopheresis \times 2 days, CI pentostatin (4 mg/m²/d \times 2 days), and TBI (200 cGy \times 3). Patients received BM harvested from an HLA-identical sibling, 5/6 antigen matched related donor, or matched unrelated donor. GVHD prophylaxis consisted of CsA and methotrexate. Donor hematopoiesis in sex mismatched transplants was 100% at the time of engraftment and was durable to day 100. Median time to ANC $>$ 500 was 17 days (range 13-26) and median time to platelets $>$ 20 000/ μ l was 20 days (range 13-38).

The 100 day overall survival was 100% and progression-free survival is 62% at a mean follow-up of 280 days. The preparative regimen was well tolerated in all patients. All patients experienced grade 4 neutropenia and thrombocytopenia. None of the patients developed veno-occlusive disease. All patients engrafted, and all surviving patients remain in clinical and cytogenetic remission (K Miller, personal communication). Based on these results ECOG is planning to initiate a phase II trial of photopheresis, pentostatin and TBI as a reduced intensity regimen for stem cell transplant in patients with myelodysplastic syndromes.

Conclusions

The myelodysplastic syndromes are a heterogeneous group of disorders with a risk of life-threatening complications secondary to cytopenias and a variable rate of progression to leukemia. Although criteria have been developed which allow us to estimate the risk of leukemic progression as well as median survival, this is not always helpful in determining appropriate treatment options. While allogeneic bone marrow transplantation appears to offer the lowest risk of relapse, it also carries with it the highest rate of transplant-related mortality. Of note, those patients who do the best with allogeneic transplantation (young, RA, RARS, normal cytogenetics) are also those who are the most likely to do well without transplantation. Additionally, since the median age of patients with this disease is over 60, most patients are not candidates for this procedure. Autologous transplantation has been performed with some encouraging results in patients who are able to attain complete remission with standard induction chemotherapy. Using autologous bone marrow broadens the population for whom transplantation is a possibility. The lack of risk of GVHD also allows us to consider older patients.

More recently, in an attempt to decrease the toxicity of

allogeneic transplantation, several reduced intensity regimens have been developed. These allow patients to benefit from the allogeneic graft vs tumor effect without suffering the complications of the traditional myeloablative regimens. This also allows us to treat patients who would otherwise not be eligible for allogeneic transplantation because of age or co-morbidity. While the risk of acute GVHD may be significantly decreased with this approach, there remains significant toxicity secondary to infection and chronic GVHD. Long-term results of this approach remain unknown.

Many new approaches are under study for the treatment of MDS. Immunosuppressive therapy has been of some success, particularly in patients with a hypocellular bone marrow and normal cytogenetics. Other novel agents include thalidomide, retinoids, arsenic, amifostine, and methylating agents. The optimal role of these agents in the treatment paradigm is unclear; they may work alone or in combination as alternatives to transplantation, or function as long-term maintenance agents.

Although it is clear that young patients with HLA-identical siblings, who have an increased number of blasts should undergo allogeneic transplantation, the role of bone marrow or stem cell transplantation is still not well defined in other populations. The optimum source of stem cells, preparative regimen, timing of transplant and pretransplant therapy are not well defined. Patients should be enrolled in appropriate clinical trials when possible. While bone marrow transplantation should always be considered in the management of a patient with myelodysplastic syndrome, we must continue to try and improve upon the technique by developing ways of increasing the efficacy while decreasing toxicity.

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