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REVIEW ARTICLE

Transplantation strategies for the management of patients with myelodysplastic syndromes

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Summary

Allogeneic stem cell transplantation (SCT) is the only therapeutic modality at present that may be delivered with curative intent in patients with myelodysplastic syndromes (MDS). Allogeneic CST replaces recipient dysplastic hemopoiesis with healthy donor haemopoiesis and immune system with an attendant graft-versus-leukemia (GvL) effect. Its applicability, however, is limited by the age of MDS patients, high rates of transplant-related mortality (TRM) and availability of a suitable HLA-matched donor. Results from several large centres indicated 3-year overall survival (OS) rates of 20-45%, which are almost equal with the results obtained by intensive chemotherapy alone. Failure was due primarily to TRM in patients with low-risk MDS and to disease recurrence in patients with high-risk MDS. Allogeneic SCT from matched unrelated donors produce poorer results than matched related siblings' transplantations. In an attempt to reduce TRM and deliver allogeneic SCT in a greater subgroup of MDS patients, many researchers used reduced-intensity allografts (RIC or "mini"-allograft) for MDS. Although differences in patient populations, preparative regimens, and graft-versus-host disease (GvHD) prophylaxis, as well as donor source (related vs. unrelated) have to be considered, OS of up to 40% at 3 years and disease-free survival (DFS) rates of almost 35% at 3 years have been reported in selected centres. However, randomized prospective studies are needed to further address the optimal choice of transplant conditioning intensity in MDS.

Autologous SCT has been extremely investigated in MDS. It is limited to patients who have achieved a complete remission (CR), can be harvested, and are candidates for the procedure. Autologous SCT after successful induction chemotherapy may increase the proportion of long-term survivors, thus improving CR duration in some patients with MDS, particularly in younger patients in remission. Results for older patients are unsatisfactory. The relapse rate is up to 75%, with a 2-year probability of DFS of only 25% for patients 40-60 years of age. Therefore, there is very limited enthusiasm for the future of autologous SCT in the management of MDS patients.

Key words: allogeneic stem cell transplantation, autologous stem cell transplantation, bone marrow transplantation, myelodysplastic syndromes, reduced conditioning allogeneic transplantation

Introduction

Definition and epidemiology

MDS are a group of clonal disorders of haemopoietic stem cells characterized by ineffective haemopoiesis that manifest clinically as anaemia, neutropenia, and/or thrombocytopenia of variable severity. The result often is transfusion-dependent anaemia, an increased risk of infection or haemorrhage, and a potential to progress to acute myelogenous leukemia (AML). Although progression to acute leukemia can lead to death in patients with MDS, many deaths are consequences of cytopenias and marrow failure in the absence of leukemia transformation. The incidence of MDS varies from 2.1 to 12.6 cases per 100,000 population per year, but approaches 50 cases per 100,000 per year in persons over 70 years of age [1-4]. Prevalence

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Table 1. Chromosomal abnormalities in MDS with conventional cytogenetics

Cytogenetic abnormality	*% in MDS/t-MDS*	*Risk of progression to AML*	*Region of chromosome (genes) involved*
Monosomy 5/5qdel	10-20 / 40	High	Two CDS regions: q31 and q33
5q- syndrome		Low	
Trisomy 8	10 / <1	Intermediate	Unknown
Monosomy 7/7qdel	~5 / 55	High	7q22and 7q32-33
17p-	~7	High	p53 gene
20qdel	5 / 7	Low	20q11.2-q12
11q23	5-6 / 2-3	Intermediate	MLL gene
Monosomy Y	<1	Low if isolated anomaly	Unknown
Complex	10-20 / 90	High	Multiple

MDS: myelodysplastic syndrome, t-MDS: therapy-related MDS, AML: acute myelogenous leukemia

is estimated to be 55,000 patients in the United States. The median age of patients is between 60 and 70 years with a male predominance. The increased incidence of MDS has been attributed to an improvement in geriatric medical care and diagnosis, as well as to a general aging of the population [1].

Etiology

Several risk factors have been implicated in the etiology of MDS, including age, male gender, alcohol, cigarette smoking, ionizing radiation, immunosuppressive therapy, viral infection, benzene and other environmental/occupational exposures [4-9]. These risk factors are seen infrequently and are estimated to account for disease development in only 20-30% of patients, who are often described as having secondary MDS [4,5]. The remainder of idiopathic cases constitute primary MDS. The major subset of secondary MDS is therapy-related MDS (t-MDS) that is increasingly frequent in patients previously treated with chemotherapy and/or radiotherapy [9,10]. In general, t-MDS usually presents as high-risk disease that frequently progresses to AML, and is associated with a poor prognosis regardless of therapy.

Biology

MDS is a clonal disorder of haemopoietic stem cells that results in excessive apoptosis, as reflected by the degree of dysplasia and proliferation and loss of differentiation of haemopoietic progenitors [11]. Cytogenetic analysis of MDS has been instrumental to confirming clonality and has led to further understanding of the disease [12]. Table 1 includes the most frequent chromosomal aberrations in MDS.

There is strong evidence supporting the view that MDS arises from an intrinsic or acquired genetic defect in stem cells, leading to clonal expansion of the abnormal population. It is also clear that aberrant cytokine production [including tumor necrosis factor-alpha (TNF-α), transforming growth factor-beta (TGF-β), interleukin-1beta (IL-1β), vascular endothelial growth factor (VEGF), etc], altered stem cell adhesion, and an abnormal marrow microenvironment contribute to the biology of the disease and may provide important therapeutic targets. Thus, a multistep sequence for the development of MDS has been proposed as a model of pathogenesis (Figure 1) [13]. As the numerous pathophysiologic pathways involved in MDS are being unravelled, new molecular targets are being identified. Novel and targeted therapeutic agents, including inhibitors of farnesyltransferases and receptor tyrosine kinases, more potent thalidomide analogs and epigenetic therapies, have produced encouraging results and might offer durable benefits to patients with MDS. These novel agents are depicted in Table 2.

MDS subtypes and prognostic systems

The French-American-British (FAB) classification, proposed in 1977, provided hematologists with the first consistent framework for morphologic classification of MDS (Table 3) [14]. Five MDS categories derived from morphologic criteria of marrow aspirates included refractory anaemia (RA), refractory anaemia with ringed sideroblasts (RARS), refractory anaemia with excess blasts (RAEB), refractory anaemia with excess blasts in transformation (RAEB-t), and chronic myelomonocytic leukemia (CMML). In the FAB classification, the two primary distinguishing features between the various MDS subtypes, CMML and AML, are blast cell percentage and the presence of dysplastic features. CMML was considered a myeloproliferative/leukemic-like disorder, which was frequently associated with t(5;12)(q33;p13), and AML was defined as ≥30% marrow blasts with the various MDS subtypes ranging from <5% to <30% blasts. However, this first clas-

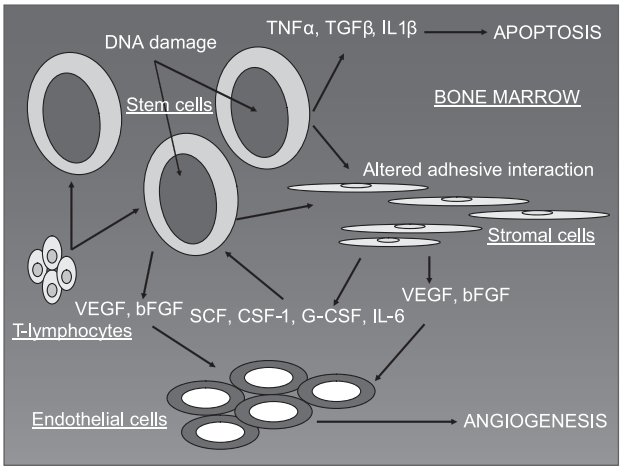

Figure 1. Mechanisms leading to myelodysplastic syndromes (MDS) development: The figure illustrates components that contribute to the development of MDS and their relationships. Mutations in critical growth-regulating genes in the haemopoietic progenitor cells block the cells' normal differentiation and maturation. Cytokine imbalances and aberrant signal transduction that result from these mutations in the affected myeloid cells lead to accelerated apoptosis and altered adhesive interactions with marrow stromal cells. Increased production of angiogenic factors leads to neo-angiogenesis. Dysregulation of the immune response has also been implicated in a proportion of patients with early-stage MDS, mainly with hypoplastic bone marrow. After an initiating event affects a pluri/multipotent progenitor marrow cell, a growth advantage is required for the clone to establish ineffective haematopoiesis. As MDS clinically progresses, apoptotic signals decrease, while anti-apoptotic signals increase. Events that then increase genomic instability likely include telomere shortening, abnormal methylation and silencing of DNA mismatch repair genes (MMR) and tumor suppressor genes. Genomic instability leads to clinical disease progression, increased cytogenetic abnormalities, leukemic transformation with increased blasts, and thereby, a poor prognosis.

Table 2. Novel agents for the treatment of myelodysplastic syndromes

Class of drug	*Name of drug*
Angiogenesis inhibitors	thalidomide
IMIDs	lenalidomide (revlimid™)
anti-VEGF monoclonal antibodies	bevacizumab (avastin™)
VEGFR tyrosine kinase inhibitors	AG013736, SU11248, SU5416,
MMPs	PTK787
	AG3340 (prinomastat™)
Hypomethylating agents	5-azacytidine (vidaza™)
	decitabine (dacogen™)
Histone deacetylase inhibitors	valproic acid, sodium phenylbutyrate,
	FK2228, SAHA, MS275
Farnesyltransferase inhibitors	R115777 (tipifarnib, zarnestra™)
	SCH66336 (lonafarnib, sarasar™)
	BMS-214662
Anticytokine therapy	
Soluble recombinant TNF receptor fusion protein	etanercept (enbrel™)
Anti-TNF monoclonal antibody	infliximab (remicade™)
Arsenicals	As_2O_3 (Trisenox™)
	As_4S_4
Proteasome inhibitors	bortezomib (velcade™)
Tyrosine kinase inhibitors	imatinib (gleevec™)
Nucleoside analogs	clofarabine
Flt-3 inhibitors	MCN512, PKC412, BAY43-9006
Glutathione analog inhibitors of GST	TLK199

IMIDs: immunomodulatory drugs, SAHA: suberoylanilide hydroxamic acid, MMPs: matrix metalloproteinases, Flt-3: fms-like tyrosine kinase 3, GST: glutathione S-transferase, VEGF: vascular endothelial growth factor, VEGFR: VEGF receptor, TNF: tumor necrosis factor

Table 3. Classification systems for MDS (adapted from [4])

FAB	*IPSS*		*WHO*
(1) RA: cytopenia of one PB lineage; normo-or hypocellular marrow with dysplasias; <1% blasts in PB and <5% BM blasts	(1) Marrow blast percentage: *Blast %* <5 5-10 11-20 21-30	 *IPSS score* 0 0.5 1.5 2.0	Myelodysplastic syndromes: (1) RA (2) RCMD
(2) RARS: cytopenia, dysplasia and the same % blast involvement as RA; >15% ringed sideroblast in BM	(2) Cytogenetic features[e]: *Karyotype* Good prognosis (-Y, 5q-, 20q-, normal) Intermediate prognosis (trisomy 8) Poor prognosis (abn 7, complex)	 *IPSS score* 0 0.5 1.0	(3) RARS (4) RCMD - RS
(3) RAEB: cytopenia of two or more PB lineages; dysplasia involving all 3 lineages; <5% BM blasts and 5-20% BM blasts	(3) Cytopenias[f]: *Cytopenia* None or 1 lineage 2 or 3 lineages	 *IPSS Score* 0 0.5	(5) RAEB 1: 5-10% blasts (6) RAEB 2: 10-20% blasts (7) MDS with isolated 5q-: (5q- syndrome) (8) MDS unclassified
(4) RAEB-t: hematologic features identical to RAEB. >5% blasts in PB or 21-30% blasts in BM or the presence of Auer rods in blasts	(4) Overall IPSS score and survival: *Overall score* Low (0) Intermediate 1 (0.5 or 1.0) 2 (1.5 or 2.0) High (2.5 or more)	 *Median survival (yrs)* 5.7 3.5 1.2 0.4	Acute Myelogenous Leukemia: (1) AML with recurrent genetic abnormalities (2) AML with multilineage dysplasia (3) t-AML and t-MDS (4) AML not otherwise categorized
(5) CMML: monocytosis in PB; <5% blasts in PB and up to 20% BM blasts			Myelodysplastic/myelo-proliferative diseases: (1) CMML (2) aCML: (atypical chronic myelogenous leukemia) (3) JMML: (juvenile myelomonocytic leukemia)

sification had several problems. The recognition that MDS and AML are part of the same continuous biologic and genetic spectrum of disease, the use of arbitrary "thresholds" for the distinction of AML from MDS for the purposes of disease classification and therapeutic decision-making has become particularly problematic. At what blast cell percentage should a clinician institute AML-based therapies in an MDS patient progressing to RAEB-t and from RAEB-t to AML? Should AML-based therapies be instituted in a patient whose marrow has dysplastic morphologic features, a blast cell percentage <20%, and a t(8;21)-containing clonal population of cells? Should we treat a patient with RA and hypoplastic bone marrow with similar therapies used for patients with hypercellular bone marrow? Therefore, WHO proposed a novel classification system, which is also depicted in Table 3 [15]. However, no agreement was reached whether or not to expand the original 3 myeloid diseases consisting of myeloproliferative disorders (MPD), MDS, and AML, with the addition of a new category MDS/MPD that included CMML, atypical CML, and juvenile myelomonocytic leukemia.

Another significant change compared with FAB classification is that in WHO system RAEB-t patients were placed in one of the 4 new AML categories, lowering the blast threshold to 20% for diagnosing AML. With respect to MDS, in addition to the elimination of RAEB-t, refinements were made within the lower risk RA and RARS that distinguish pure erythroid lineage vs. refractory cytopenia with multilineage dysplasia (RCMD) with or without RS. RAEB was separated into 2 groups and the 5q-syndrome was identified as a distinct entity.

Several prognostic scoring systems were developed based on retrospective studies during 1980s to the mid 1990s, using various methods and combinations of

observed clinical features. An International MDS Risk Analysis Workshop was convened in 1996 that developed the International Prognostic Scoring System (IPSS) (Table 3) [16]. The IPSS identified 3 critical variables: (a) percent bone marrow blasts, (b) specific cytogenetic abnormalities, and (c) the number of cell lineages with dysplasia and cytopenia (0 or 1, and 2 or 3). Scores were combined to place an individual patient into 4 groups: low, intermediate-1, intermediate-2, and high. The IPSS stratification defined survival and freedom from AML evolution better than the FAB classification or any prior scoring system. Limitations to the IPSS are that the choice of treatment depends on age, performance status, and donor availability for marrow transplant.

Treatment strategies for MDS

Treatment strategies for MDS include mainly supportive care, growth factors, 5-azacytidine, low intensity treatment, acute myeloid leukaemia (AML)-type therapy, and SCT (Figure 2) [17-19]. The decision about how to deal with the morbidity of the disease vs. the potential benefits and toxicities from treatment is very complex. This decision is based on age, performance status, type of MDS and available data for disease biology and prognostic factors. Although the possibility of curing MDS has increased with improved transplant strategies, the majority of MDS patients will die of their disease. Severe anemia leading to the need for chronic transfusions and markedly reduced quality of life is often the major clinical problem for patients with low risk MDS or with IPSS of low or intermediate-1 risk. Progressive cytopenia, which is more common in the other MDS subtypes, may predict for transformation to AML but may also be a feature of RCMD without an increase of blasts. Severe pancytopenia is linked to markedly increased morbidity and reduced quality of life. The life expectancy of patients with high and intermediate-2 risk MDS, according to IPSS, is very short (≤12 months), and approaches to prevent transformation from low to high-risk disease are urgently needed. The better understanding of MDS pathophysiology has led to the development of novel agents that target both MDS cell and its interactions with the abnormal marrow microenvironment. Hypomethylating agents, immunomodulatory drugs and farnesyltransferase inhibitors have produced very promising results in MDS (Table 2). Azacytidine is the only agent which has been licensed by Food and Drug Administration of the USA for the treatment of all subtypes of MDS [20,21], while lenalidomide has been licensed for use in MDS patients with 5q- anomaly [22,23]. Despite the use of older and novel therapeutic regimens, MDS remains incurable. High-dose therapy followed by stem cell support has given some promising results and certainly has a significant role in the management of MDS.

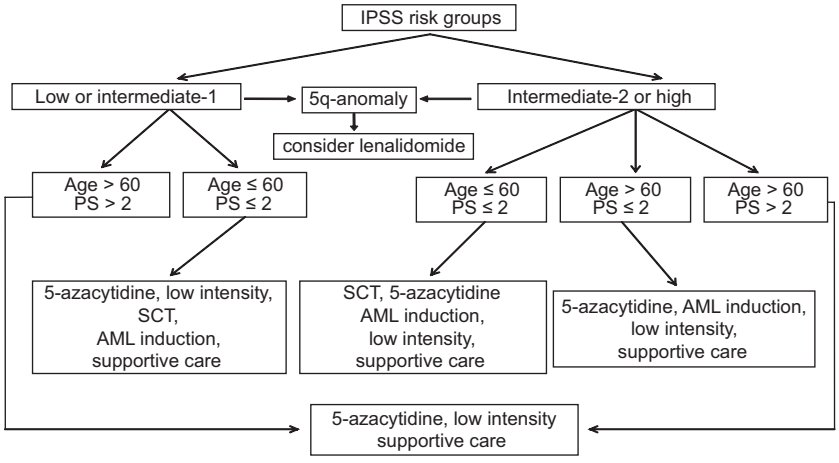

Figure 2. Treatment algorithm, which illustrates the decision to use low-intensity vs. high-intensity treatment, based on the IPSS score, patient age, and performance status (PS). Low-intensity treatment includes predominantly the use of growth factors (erythropoietin and/or G-CSF), immunosuppressive drugs (antithymocyte globulin, antilymphocyte globulin, cyclosporine A; mainly in hypocellular MDS), and low-dose chemotherapy (cytarabine, melphalan). 5-azacytidine may be used in all MDS subtypes as it is the only agent which has been approved for such use. Patients with 5q-anomaly may be given lenalidomide if it is available (adapted from the NCCN MDS treatment algorithm – Http://www.nccn.org). SCT: stem cell transplantation, AML: acute myelogenous leukemia.

Allogeneic stem cell transplantation for MDS

Standard allograft regimens

Allogeneic SCT incorporating myeloablative regimens in the management of MDS has been described since 1984 both as single-centre and registry reports. Conditioning regimens including busulfan, cyclophosphamide, with or without total body irradiation (TBI) are the mainstay of treatment with some centres incorporating T-cell depletion. Allogeneic SCT has an attendant increased risk of treatment-related mortality (TRM) of near 40%. Therefore, it is usually reserved for patients with high-risk MDS, because their prognosis is as unfavorable as in AML. Age and performance status have also to be considered in the treatment decision. High-intensity therapy with allogeneic stem cell support is most appropriate for patients aged <60 years, who have a good performance status (Figure 2). Allogeneic SCT replaces recipient dysplastic haemopoiesis with healthy donor haemopoiesis and immune system with an attendant GvL effect. The outcome of treatment is highly dependent on the selection of patients, and it is therefore difficult to evaluate the effect of different conditioning regimens and other treatment approaches.

In a review from Fred Hutchinson Cancer Research Centre, the results of allogeneic SCT in 251 patients with MDS showed an overall median DFS of 40% after a median follow-up of 6 years [24]. Important predictors for long-term survival were age, morphology and cytogenetics. While patients < 20 years of age (i.e. paediatric MDS and young secondary MDS) showed a DFS of almost 60%, DFS in patients >50 years of age was below 20%, mostly due to high TRM. Increasing disease duration before transplant significantly increased the risk for non-relapse mortality but did not influence DFS.

A Canadian study reported the outcome of 60 adult patients with MDS [25]. The 7-year event-free survival was 29% for all patients, > 60% for patients with RA/RARS, 20% for patients with ≥5% blasts, and 6% for patients in the poor cytogenetic subgroup.

The Chronic Leukemia Working Party of the European Blood and Marrow Transplantation (EBMT) retrospectively analyzed 131 patients who underwent SCT from HLA-identical siblings without prior remission induction chemotherapy [26]. At the time of SCT 46 patients had RA or RARS, 67 patients had more advanced MDS subtypes and 18 patients had progressed to secondary AML (sAML). The 5-year DFS and OS for the entire group of patients was 34 and 41%, respectively. Fifty patients died from transplant-related complications, most commonly GvHD and/or infections. Relapse occurred in 28 patients between 1 and 33 months after SCT, resulting in an actuarial probability of relapse of 39% at 5 years. DFS and OS were dependent on pre-transplant bone marrow blast counts. Patients with RA/RARS, RAEB, RAEB-t and sAML had a 5-year DFS of 52, 34, 19 and 26%, respectively. The 5-year OS for the respective patient groups was 57, 42, 24 and 28%. In the multivariate analysis, younger age, shorter disease duration, and absence of excess of blasts were associated with improved outcome. From these results we conclude that patients with myelodysplasia who have appropriate marrow donors, especially those aged < 40 years and those with low medullary blast cell count should be treated with SCT as the primary treatment early in the course of their disease. Transplantation early after establishing the diagnosis of MDS may improve prognosis due to a lower treatment-related mortality and a lower relapse risk

An update of the EBMT group experience of SCT in 1378 patients with MDS has reported an estimated DFS and relapse risk at 3 years of approximately 36% for 885 patients transplanted with stem cells from matched siblings [27]. DFS and relapse rate in RA/RARS was 55% and 13%, respectively, while the corresponding figures for more advanced MDS was 28% and 43%. DFS in patients with advanced MDS treated to CR was 44%. This analysis did not indicate a significantly better DFS in patients transplanted <1 year from diagnosis. The response criteria used for the evaluation of therapy in MDS are depicted in Figure 3 [28].

Deeg et al. also reported results on 50 MDS patients, aged 55-66, receiving allogeneic SCT with stem cells from matched siblings (n=36), unrelated volunteers (n=6), HLA-nonidentical family members (n=4), and identical twins (n=4) [29]. The Kaplan-Meier estimate of relapse-free survival at 3 years was 39% for all patients and 47% for patients with primary MDS transplanted with stem cells from an HLA-identical sibling. As in previous studies, cytogenetic risk group and IPSS score were highly predictive for the outcome of treatment. Moreover, conditioning regimen with cyclophosphamide and targeted busulfan showed an advantage compared to other conditioning regimens. The study shows that results in selected groups of older patients are beginning to improve.

Allogeneic SCT seems to be suitable even for selected patients aged > 60 years. Wallen et al. treated 52 patients from 1979 to 2002 with a median age of 62.8 years using ablative preparative regimens followed by allogeneic SCT from sibling donors [30]. Diagnoses included MDS (n=35), chronic myeloid leukemia (CML; n=8), AML (n=6), and other (n=3). Conditioning regimens included cyclophosphamide and busul-

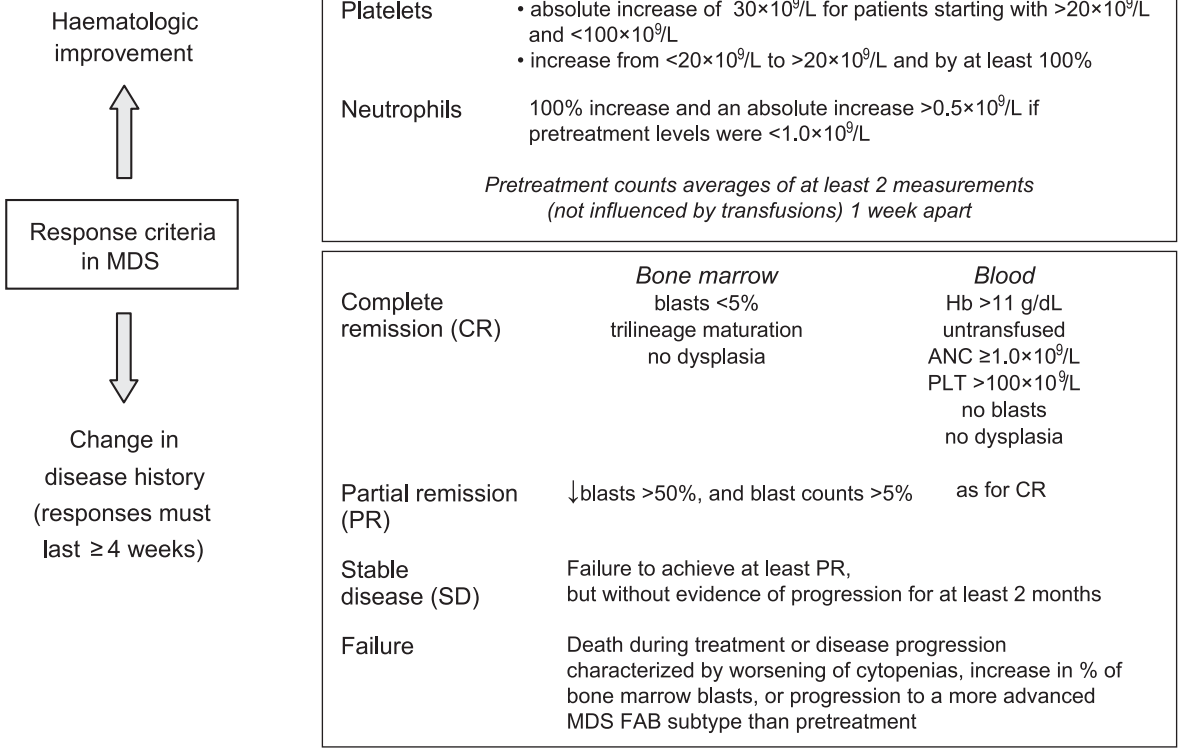

Figure 3. Novel International Working Group modified response criteria for MDS by Cheson et al [28].

fan (67%), TBI and cyclophosphamide (21%), busulfan-fludarabine (10%), and cyclophosphamide (2%). Eighteen (35%) of 52 patients were alive at a median of 4.6 years (range 0.8-9.1) after transplantation. Median OS and progression-free survival (PFS) were 300 and 218 days, respectively. Three-year OS and relapse rates were estimated to be 34% and 24%, respectively. Non-relapse mortality rates at 100 days and 3 years were 27% and 43%, respectively. Grade 3-4 acute GvHD occurred in 20% of patients, and chronic extensive GvHD was described in 53% of patients. Fourteen (40%) of 35 patients with MDS were alive at a median of 2.8 years (range 0.8-8.2). Patients who underwent transplantation after 1993 had improved survival.

In an update of the International Bone Marrow Transplant Registry, 452 patients who underwent HLA-identical sibling transplantations had an OS rate at 3 years equal to 42% [31]. The median patient's age was 38 years, and most patients (60%) had high-risk MDS. Favorable prognostic factors included age <50 years and platelet counts >100×10^9/L. The incidence of relapse was higher in patients who had high percentages of bone marrow blasts at the time of transplantation, high IPSS scores, and received T-cell depleted SCT. The possibility of being alive at 5-years was 60% in the low-risk group, 36% in the intermediate-1 risk group, and 28% in the intermediate-2 risk group. This was compared with 5-year survival rates of 55%, 35%, and 7%, respectively, for unselected patients who did not undergo SCT. The authors concluded that allogeneic SCT mostly benefited patients with high-risk MDS. However, the appropriate timing and optimal bone marrow ablation regimen remain disputed.

As less than a third of patients have a suitable HLA-matched related donor, transplant centres have increasingly explored the use of volunteer unrelated donors (VUD). Allogeneic SCT from matched VUD produces poorer results than matched related siblings' transplantations. The Chronic Leukemia Working Party of the EBMT collected data on 118 patients of median age 24 years who underwent an allogeneic SCT from unrelated donors for treatment of MDS or sAML (RA/RARS, n=24; RAEB, n=26; RAEB-t, n=34; CMML, n=12; sAML, n=22) between 1986 and 1996 [32]. The data were reported from 49 EBMT centres. Thirty-four of 118 patients were alive, relapse was the cause

of death in 19 of 84 patients and the remaining patients died of TRM. For the whole group the actuarial probability of survival at 2 years was 28%, DFS 28%, relapse risk 35% and TRM was 58%. TRM was significantly influenced by the age of the recipient (<18 years 40%, 18-35 years 61%, >35 years 81%). The relapse rate after SCT was influenced by FAB classification of the disease at transplantation. Patients with a low blast count (RA, RAEB) had a lower probability of relapse (13 and 15%, respectively) compared to patients with RAEB-t or sAML (29 and 45%, respectively). Furthermore, there was evidence of a GVL effect in MDS/sAML. Patients with acute GvHD, grade II-IV, had a probability of relapse of 26% vs. 42% in patients with no acute GvHD or grade I only.

In an update from the USA National Marrow Donor Program in MDS, 510 patients with MDS underwent unrelated donor bone marrow transplantation [33]. The median age was 38 years (range <1-62). Several conditioning regimens and GvHD prophylaxis methods were used, and T-cell depletion was used in 121 patients. Donors were serologically matched for HLA-A, -B, and -DRB1 antigens for 74% of the patients. Of 437 patients evaluable for engraftment, 24 (5% cumulative incidence, with 95% confidence interval [CI] of 3-7) failed to engraft, and an additional 33 (8% cumulative incidence; 95% CI 6-10) had late graft failure. Grades II-IV GvHD developed in 47% of the patients (95% CI 43-49), and limited and extensive chronic GvHD developed at 2 years in 27% (95% CI 24-30). The incidence of relapse at 2 years was 14% (95% CI 11-17). Higher relapse was independently associated with advanced MDS subtype and no acute GvHD. The estimated probability of DFS at 2 years was 29% (95% CI 25-33). Improved DFS was independently associated with less advanced MDS subtype, higher cell dose, recipient cytomegalovirus (CMV) seronegativity, shorter interval from diagnosis to transplantation, and transplantation in recent years. Common causes of death were treatment-related complications accounting for 82% of fatalities. The 2-year cumulative incidence of TRM was 54% (95% CI 53-61). Sixty-nine percent of TRM occurred within the first 100 days, and 93% occurred within the first year of transplantation. Higher TRM was independently associated with older recipient and donor age, HLA-mismatched, and recipient CMV seropositivity. This study demonstrated that unrelated donor SCT cures a significant proportion of patients with MDS. TRM is the major problem limiting the success of unrelated donor SCT in MDS.

Better survival rates have been reported by the Seattle group using conditioning regimens with targeted busulfan and cyclophosphamide [34]. A total of 109 patients (aged 6-66 years; median 46 years) with MDS were treated with busulfan targeted to plasma concentrations of 800-900 ng/mL plus cyclophosphamide 2×60 mg/kg, and haemopoietic SCT from related (n=45) or unrelated donors (n=64). At the time of transplantation, 69 patients had < 5% myeloblasts in the marrow, and 40 patients had more advanced disease. All but 2 evaluable patients had engraftment. The Kaplan-Meier estimates of 3-year RFS were 56% for related and 59% for unrelated recipients. The cumulative incidences of relapse were 16% for related and 11% for unrelated recipients. The non-relapse mortality rate among all patients was 16% by day 100 post-SCT, and 31% by 3 years, 12% and 28%, respectively, for HLA-identical sibling transplants, 13% and 30%, respectively, for matched unrelated donor transplants, and 36% and 52%, respectively, for recipients of HLA-nonidentical transplants. The only factor significant for RFS was the etiology of MDS (*de novo* better than treatment-related). Factors significantly correlated with relapse were advanced FAB classification and IPSS score, poor-risk cytogenetics, and treatment-related aetiology. None of the factors examined was statistically significant for non-relapse mortality. Patient age and donor type had no significant impact on outcome. RFS tended to be superior in patients receiving transplants with peripheral blood rather than marrow stem cells.

In an attempt to improve these results, a matched cohort study was designed to test the efficacy of polyclonal rabbit antiserum specific for human T cells (thymoglobulin), administered *in vivo* on days 1-5 (2 mg/kg/day) before T cell-replete unrelated donor marrow transplantation [35]. Thymoglobulin was given to 52 leukemia patients at Huddinge Hospital. Control patients matched for diagnosis, disease stage, age and treated with a similar regimen, apart from the omission of thymoglobulin, were selected in Seattle during the same period (n=104). All received conditioning with cyclophosphamide and TBI. In the study group all patients received 10 Gy single dose TBI, while the controls were given 12-14.4 Gy fractionated TBI. GvHD prophylaxis was cyclosporine and methotrexate. Patients were treated for grade I acute GvHD in the study group, and for grade II GvHD in the control group. Multivariate analyses were adjusted for patient and donor age and CMV serology, HLA matching, donor gender and marrow cell dose. Non-relapse mortality was lower in the study group of patients. The 5-year cumulative incidence of non-relapse mortality was 19% in the study cohort, and 35% in the control cohort. Overall mortality was also lower in study patients. This study showed that thymoglobulin during conditioning

may reduce non-relapse mortality after unrelated donor marrow transplantation.

In conclusion, allogeneic SCT is a treatment option for MDS patients. However, the high TRM reported between 40-55% has restricted the use of standard allograft regimens to those < 50 years of age, although in few selected older patients with good performance status allogeneic SCT has outcome comparable to younger patients. In general, outcome following allogeneic SCT is adversely affected by disease progression, poor risk cytogenetics and older age. A lower incidence of GvHD and improved survival is documented with HLA-identical sibling donors. The application of IPSS incorporating morphological disease stage and cytogenetics has aided the identification of patients where transplantation is most valuable. As TRM is the major problem in allogeneic SCT procedures, further methods to reduce toxicity have been explored.

Allogeneic SCT with reduced intensity conditioning regimens

In an attempt to reduce TRM and deliver allogeneic SCT in a greater subgroup of MDS patients, many researchers tried to use reduced-intensity allografts (RIC or "mini"-allograft). The better understanding of the alloimmune processes that govern the GVL response and GvHD has led to the development of several RIC protocols [36-39]. Lower toxicity with TRM documented at 9%, has resulted in the ability to expand its use to patients of older age with co-morbid illnesses whilst maintaining the balance in favor of GVL effect and minimising GvHD. A multitude of RIC protocols have been developed, regimens usually incorporate combinations of low dose TBI, fludarabine, busulfan, melphalan, anti-thymocyte/anti-lymphocyte globulin (ATG/ALG), Campath 1-H (alemtuzumab) or Campath-1G. Campath-1H, a humanized IgG_1 monoclonal antibody, and Campath-1G, a rat IgG_2 monoclonal antibody, are directed against the CD52 antigen expressed on all lymphoid cells, circulating dendritic cells and cells of the monocyte lineage. In addition Campath-1G has been shown to deplete host dendritic cells, therefore contributing to a lower incidence of GvHD [40]. The long half-life of alemtuzumab also results in depletion of donor CD52 positive cells with persistence of lympholytic levels for up to 56 days post-transplant [41]. Serum levels of ATG/ALG also remain high for several weeks post-transplant, resulting in a reduction of donor T-cells [42]. GvHD remains a major cause of morbidity and mortality following allogeneic SCT. T-cell depletion achieved with the use of Campath or ATG has resulted in a significant reduction in the incidence of GvHD following RIC transplantation [43,44], with acute (grade II-IV) and chronic GvHD reported as high as 60% and 46% respectively, without T-cell depletion [45-47].

Although differences in patient populations, preparative regimens, and GvHD prophylaxis, as well as donor source (related vs. unrelated) have to be considered, OS of up to 40% at 3 years and DFS rates of almost 35% at 3 years have been reported in selected centres [48-51]. The M.D. Anderson group reported its experience comparing the outcomes after a truly non-ablative regimen (120 mg/m^2 fludarabine, 4 g/m^2 cytarabine, and 36 mg/m^2 idarubicin [FAI]) and a more myelosuppressive, reduced-intensity regimen (100-150 mg/m^2 fludarabine and 140 or 180 mg/m^2 melphalan [FM]) in 94 patients with MDS (n=26) and AML (n=68) [49]. Sixty-two patients were given FM and 32 were given FAI. The FAI group had a higher proportion of patients in CR at transplantation (44 vs. 16%, p=0.006), patients in first CR (28 vs. 3%, p=0.008), and HLA-matched sibling donors (81 vs. 40%, p=0.001). The median follow-up of that study was 40 months. FM was significantly associated with a higher degree of donor cell engraftment, higher cumulative incidence of TRM, and lower cumulative incidence of relapse-related mortality. Relapse rate after FAI and FM was 61% and 30%, respectively. Actuarial 3-year survival rate was 30% after FAI and 35% following FM [49].

In a recent multicenter retrospective study, the outcomes of 836 patients with MDS who underwent transplantation with a HLA-identical sibling donor were analyzed according to 2 types of conditioning regimens: RIC in 215 patients, and standard myeloablative (or high-dose) conditioning (SMC) in 621 patients. In multivariate analysis, the 3-year relapse rate was significantly increased after RIC (hazard ratio [HR], 1.64; 95% CI 1.2-2.2; p=0.001), but the 3-year nonrelapse mortality rate was decreased in the RIC group (HR 0.61; 95% CI 0.41-0.91; p=0.015). The 3-year probabilities of PFS and OS were similar in both groups (39% after SMC vs. 33% in RIC; and 45% vs. 41%, respectively) [48].

The Birmingham group reported their results in 76 patients with high-risk AML or MDS who received an allograft using a fludarabine/melphalan RIC regimen incorporating alemtuzumab [50]. The median age of the cohort was 52 years (range 18-71). The 100-day TRM rate was 9%, and no patient developed greater than grade 2 GvHD. With a median follow-up of 36 months, 27 patients were alive and in remission, with 3-year actuarial OS and DFS rates of 41% and 37%, respectively. The 3-year OS and DFS rates of patients with AML in CR at the time of transplantation were 48% and 42%, re-

spectively. Disease relapse was the most common cause of treatment failure and occurred at a median time of 6 months after transplantation.

Results from King's College (UK) group in 115 patients with MDS (63% with IPSS of intermediate-2 or higher, median age of 53 years, who received either sibling [n=40] or VUD [n=75] FBC conditioning) showed a day-100 TRM of 8%, 1- and 2- year DFS of 51 and 41%, respectively and 1- and 2-year OS of 59 and 50%, respectively. Outcome correlated strongly with IPSS and disease status at the time of the transplant [52].

Hallemeier et al. analyzed outcomes of patients with MDS or sAML who were treated with a RIC regimen of 550 cGy TBI and cyclophosphamide followed by sibling or VUD transplantation [53]. Fifty-one consecutive patients with MDS or sAML received this RIC regimen and VUD (n=30) or sibling (n=21) stem cells. GvHD prophylaxis consisted of cyclosporine alone (sibling transplant) or with corticosteroids and methotrexate (VUD transplant). Median patient age was 44 years. With a median follow-up of 3.7 years after transplantation in the 19 (37%) surviving patients, Kaplan-Meier estimates of OS were 88, 46, 33, and 11% for patients transplanted with sAML in remission, RA, RAEB, RAEB-t, or sAML refractory/untreated, respectively. Kaplan-Meier estimates of RFS were 75, 46, 33, and 11%, respectively. Overall, the cumulative incidence of relapse and TRM were 27% and 37%, respectively.

Life-threatening infections in the post-transplant period occurred as a consequence of delayed immune reconstitution. Inadequate thymic function secondary to conditioning agents, GvHD, or age resulted in delayed or incomplete establishment of normal donor immunity [54,55]. In addition, the use of *in vivo* T-cell depletion delayed lymphoid engraftment, increasing the susceptibility to infections [56]. Chakrabati et al. reported an increased incidence of CMV, adenovirus and respiratory viruses following the use of Campath-1 H [57,58]. A high incidence of CMV reactivation was reported (50% reactivation at a median of 27 days). Adenovirus isolates were exclusively identified in those receiving T-cell depleted transplants with an incidence of 19.7%.

In a recent study 40 patients with *de novo* MDS, 25 patients with treatment-related MDS and 7 patients with CMML underwent allogeneic SCT using a conditioning regimen of low-dose TBI alone (200 cGy) on day 0 or with the addition of fludarabine 30 mg/m^2/day on days -4 to -2. Postgrafting immunosuppression consisted of cyclosporine and mycophenolate mofetil. By day +28, 75% of the patients demonstrated mixed T-cell chimerism. Graft rejection was seen in 15% of the patients. With a median follow-up of 47 months (range 6-89), the 3-year RFS and OS were both 27% for all patients, with a relapse incidence of 41%. The 3-year RFS for the patients with *de novo* MDS, t-MDS, and CMML were 22, 29, and 43%, respectively, and the 3-year OS was 20, 27, and 43%, respectively. The 3-year nonrelapse mortality was 32%. Factors associated with a lower risk of relapse were the development of extensive chronic GvHD and having a low or intermediate-1 IPSS risk for the *de novo* MDS patients. Nonmyeloablative SCT conferred remissions in patients who otherwise were not eligible for conventional allogeneic SCT but for whom relapse was the leading cause of treatment failure [59].

These studies suggest that RIC-SCT has been demonstrated to be a rather safe and feasible procedure as an alternative to standard conditioning regimens. The main cause for treatment failure in patients who underwent a RIC-transplant is disease recurrence, which is greater compared with patients who underwent allogeneic SCT, especially in patients who had advanced-stage disease [48]. Overall, the preliminary experience suggests that RIC-SCT may become a valuable alternative for older patients or for patients who are at high risk for complications after undergoing standard allogeneic SCT. However, the optimal choice of transplant conditioning intensity in MDS has not clearly defined yet. A comparison between nonmyeloablative regimens (2 Gy TBI alone or with fludarabine 90 mg/m^2) and myeloablative regimen (busulfan 16 mg/kg, and cyclophosphamide 120 mg/kg) showed no difference in MDS patients with respect to OS, PFS and non-relapse mortality [60]. GVL effects may be more important than conditioning intensity in preventing progression in patients in chemotherapy-induced remissions at the time of transplantation. Randomized prospective studies are needed to further address the optimal choice of transplant conditioning intensity in MDS.

Autologous stem cell transplantation for MDS

Autologous SCT has been extremely investigated in MDS. Autologous SCT is applicable only to a minority of younger patients with MDS because of the difficulty in harvesting adequate CD34+ cells from MDS patients. Even in low risk cases, adequate numbers of CD34+ cells are not collected [61]. However, Carella et al. reported successful mobilisation of CD34+ cells from high-risk MDS patients following chemotherapy [62]. In addition, lack of GVL effect results in a high risk of relapse.

In a EBMT trial the 3-year DFS of the 173 patients transplanted with SCT was 30%. The TRM was 29% and the relapse rate 55%. Non-relapse mortality was 25%. The DFS of patients transplanted beyond first CR was 18%. Age had a borderline significant effect on treatment outcome. The relapse incidence was similar for all age groups [27]. In a recent study with long-term follow-up of 53 patients with MDS autografted in first CR, 5 (9.4%) died from the procedure whereas haematological reconstitution occurred in all the remaining patients. Forty patients (75%) relapsed, with 87.5% of the relapses occurring within 2 years of the autologous transplant. With a median follow-up of 6.2 years, the median actuarial DFS and OS were 8 and 17 months after autograft, respectively. Karyotype was the only prognostic factor for DFS and OS. The 8 (15%) survivors, including 2 patients with unfavorable or intermediate karyotype, remained in first complete remission 50+ to 119+ months after transplantation and are probably cured [63]. The source of stem cells (peripheral blood or bone marrow) seemed not to influence survival [64]. Therefore, given the more rapid haemopoietic recovery peripheral blood is the preferred source of stem cells.

In general, autologous SCT is limited to patients who have achieved a CR, can be harvested, and are candidates for the procedure. Autologous SCT after successful induction chemotherapy may increase the proportion of long-term survivors, thus improving CR duration in some patients with MDS, particularly in younger patients in remission. Results for older patients are unsatisfactory. Therefore, there is very little enthusiasm for the future of autologous SCT in the management of MDS patients [65].

Umbilical cord blood transplantation

With an increasing number of patients referred for allogeneic SCT and the difficulty in finding a suitable HLA-matched donor in a significant number of cases, interest in umbilical cord blood transplantation (UCB) has risen. However, despite the reduction in the incidence of GvHD and the ability to utilise UCB with increasing HLA disparity, the lower haemopoietic stem cell dose retrieved has led to concern over engraftment in adults and hence limited its use. The most recent report by the Eurocord and Netcord registries analysed 682 adults with AML or ALL, 98 of which received UCB and 584 SCT. A lower incidence of acute grade II-IV GvHD was reported following UCB (26 vs. 39%), with 94% receiving UCB from a HLA-mismatched donor, whereas bone marrow recipients were fully HLA-matched. No significant difference in TRM, DFS or OS was noted between the groups [66].

A multi-centre study reported by Laughlin et al. compared the outcome following UCB from both one (34 patients) and two (116 patients) HLA-antigen mismatched unrelated donors, to recipients of bone marrow from HLA-matched (367 patients) and one antigen-mismatched (83 patients) donors in patients with haematological malignancies including MDS. Improved outcome was only demonstrated following transplantation using fully compatible bone marrow recipients, with no significant differences between those receiving mismatched UCB or mismatched bone marrow. A higher rate of acute GvHD was identified following HLA-mismatched bone marrow and higher incidence of chronic GvHD following UCB transplantation [67].

The incidence of grade III-IV acute GvHD is low (7-27%) despite the fact that the majority of patients receive HLA-mismatched units, although a significant day 100 TRM of 43-56% is documented. All reports document a correlation between poorer outcome and advanced disease at the time of transplantation.

The toxicity reported from the use of myeloablative regimens and UCB transplantation prompted a study of engraftment potential with reduced intensity conditioned regimens by Barker et al. Two conditioning regimens were assessed, busulfan, fludarabine and low dose TBI (Bu/Flu/TBI) vs. cyclophosphamide, fludarabine and low dose TBI (Cy/Flu/TBI) with 93% receiving one or two HLA antigen-mismatched units. Sustained donor engraftment was achieved in 76% and 94% of patients, respectively, with a low incidence of acute grade III-IV GvHD (9%) and 39% 1-year OS [68].

Reports to date confirm UCB transplantation as a feasible alternative to SCT in patients where a suitable HLA-matched donor is unavailable. Despite low stem cell doses and slow engraftment, similar outcome is observed to that of SC allografts using HLA-mismatched donors.

Donor lymphocyte infusion

The GVL effect can be harnessed by the use of donor leukocyte infusions (DLI) in the post-transplant setting. DLI has been used both for mixed chimerism and relapsed disease, to induce remission in patients with relapsed haematological malignancies [69,70]. Durable remissions have been documented in cases of relapsed MDS/AML post-transplant [70-72]. However, uncertainty still remains about the optimal timing and

dose of DLI. Administration of DLI in the early post-transplant period (3-4 months) is associated with an increased risk of GvHD [73], therefore current protocols tend to reserve its use until at least day+100 post-transplant. A report by the EBMT registry noted a 41% risk of GvHD following DLI in patients with a variety of haematological malignancies [70]. A multicentre analysis of the use of DLI in the UK following RIC transplantation, the majority being T-cell depleted, showed the median dose of DLI capable of inducing remission was 1×10^7/kg (lowest 1×10^6/kg), with a strong association between response and occurrence of GvHD [31]. The incidence of acute grade II-IV GvHD was 25% and chronic GvHD 33% following the use of DLI. Whether the lower incidence of GvHD is related to previous T-cell depletion is uncertain. The knowledge that patients can develop GvHD with mixed donor chimerism and demonstrate disease relapse following the use of DLI, makes the optimal timing and dosage of DLI difficult to ascertain. Larger studies of the use of DLI in patients with MDS/AML are necessary to determine more precisely the role of DLI post-RIC allograft.

Conclusion

Allogeneic SCT is a treatment with curative potential but is restricted to younger, healthier patients with a histocompatible donor. DFS rates are approximately 30–50%, with the greatest benefit for those who may least need treatment, i.e. younger patients with low-risk MDS treated within one year of diagnosis. Treatment failure is attributed to TRM in low-risk patients and relapse in high-risk patients. When IPSS groups were compared, Intermediate-2 risk groups benefited the most from SCT. In addition, combining IPSS and WHO criteria identified the RCMD group to benefit most from SCT among low-risk patients, highlighting the necessity to assess which disease group will benefit from which form of treatment.

The lower toxicity associated with RIC regimens has allowed allogeneic transplantation to be expanded to a much wider cohort of patients with MDS. An improved knowledge of the alloimmune processes that govern GvHD and the GVL response provide greater potential for antitumor specificity. Transplantation across HLA-boundaries using haplo-identical siblings or unrelated donors have been achieved through the use of T-cell depletion, and umbilical cord transplantation. Longer follow-up is however required to assess whether a survival advantage of RIC conditioning over standard conditioning regimens will be identified, while further development of precise prognostic classification systems, including an accurate evaluation of cytogenetic/molecular response to initial chemotherapy, is needed to develop a risk-adapted strategy for individual patients.

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