Myelodysplastic Syndromes

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73.1 Introduction

Myelodysplastic syndromes (MDS) are a heterogeneous group of clonal stem cell disorders characterized by hypercellular bone marrow, peripheral cytopenias, and dysplastic features in blood and bone marrow. The clinical progression of these diseases varies from an indolent course, over a number of years, to a more rapid transition into secondary AML. MDS is mainly diagnosed in elderly patients, with an annual incidence of 4.9/100,000, but this increases to between 20 and 50 cases per 100,000 persons annually after the age of 60. The current WHO classification (2016) distinguishes various MDS subtypes, which are detailed in Table 73.1 (Arber et al. 2016).

Due to the variable course the disease may take, a number of different *risk-scoring systems* have been developed. The most frequently used of these is the International Prognostic Scoring System (IPSS), introduced by Greenberg et al. (1997) (Table 73.2) and revised in 2012 (Greenberg et al. 2012) (Table 73.3). As a result, intensive treatment strategies are predominantly applied in patients with intermediate and higher-risk MDS. The importance of transfusion dependency is included in a WHO classification-based prognostic scoring system (WPSS) (Della Porta et al. 2015). The role of somatic mutations has been explored recently, highlighting the prognostic role of mutations. *SF3B1* mutations are commonly associated with refractory anemia with ringed sideroblasts and expected survival of more than 10 years. Poor prognostic mutations, such as *TP53* mutations, occur mainly in patients with higher-risk MDS and confer a higher risk of transition to acute leukemia (Makishima et al. 2017). In the setting of allo-HSCT, both somatic mutations and cytogenetic characteristics conserve their prognostic impacts after transplantation, and this aspect will be discussed further hereafter.

Allo-HSCT is increasingly performed, with 940 MDS patients transplanted in 2004 and 2646 patients transplanted in 2015 (EBMT registry). This increase is due to rising numbers of transplants in older patients (>60 years), from 22% of all transplants in 2004 to 44% in 2015, and more MURD, from 37% of all transplants in 2004 to 58% in 2015. The increasing use of unmanipulated haplo-HSCT using intensified IS therapy may also lead to a greater proportion of related donors in future.

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Table 73.1 World Health Organization classification (2016 revision) of MDS

Name	Dysplastic lineage	Cytopenia[a]	RS as % BME	BM and PB blasts, Auer rods (AR)	Cytogenetics[b]
MDS with single-lineage dysplasia (MDS-SLD)	1	1 or 2	<15%/<5%[b]	BM < 5%, PB < 1%, no AR	Any
MDS with multilineage dysplasia (MDS-MLD)	2 or 3	1–3	<15%/<5%[c]	BM < 5%, PB < 1%, no AR	Any
MDS with ring sideroblasts (MDS-RS)					
— MDS-RS SLD	1	1 or 2	≥15%/>5%[c]	BM < 5%, PB < 1%, no AR	Any
— MDS-RS-MLD	2–3	1–3	≥15%/>5%[c]		
MDS with isolated del(5q)	1–3	1–2	None or any	BM < 5%, PB < 1%, no AR	Del(5q)[d]
MDS with excess blasts (MDS-EB)					
— MDS-EB1	0–3	1–3	None or any	BM 5–9% or PB 2–4%, no AR	Any
— MDS-EB2	0–3	1–3	None or any	BM 10–19% or PB 5–19%, or AR	Any
MDS, unclassifiable (MDS-U)					
— With 1% blood blasts	1–3	1–3	None or any	BM < 5%, PB = 1%, no AR	Any
— With SLD and pancytopenia	1	3	None or any	BM < 5%, PB < 1%, no AR	Any
— Based on defining cytogenetic	0	1–3	<15%	BM < 5%, PB < 1%, no AR	Defining abnormality
Refractory cytopenia in childhood	1–3	1–3	None	BM < 5%, PB < 2%	Any

BM bone marrow, *PB* peripheral (blood) blast, RS as %BME, ring sideroblasts as a % of marrow erythroid elements
[a]Cytopenia defined as hemoglobin <10 g/dL, platelet count <100 g/L, absolute neutrophil count <1.8 g/L
[b]Cytogenetics by conventional karyotype analysis
[c]If *SF3B1* is present
[d]Alone or with one additional abnormality except −7 or del(7q)

Table 73.2 "Classic IPSS"

Points	*0*	*0.5*	*1*	*1.5*	*2*
Marrow blast	<5	5–10	>10	11–20	21–30
Cytogenetic[a]	Good	Intermediate	Poor		
Cytopenia[b]	0–1	2/3			
Risk	*Low*	*Intermediate-1*	*Intermediate-2*	*High*	
Number of points	0	0.5–1	1.5 or more		
Median OS (years)	5.7	3.5	1.2	0.4	
Median time to 25% AML transformation in years	9.4	3.3	1.1	0.2	

OS overall survival
[a]*Good*, normal, -Y, del(5q), del(20q); *poor*, complex karyotype (three or more abnormalities) or chromosome 7 anomalies; *intermediate*, other abnormalities
[b]Cytopenia was defined as follows: hemoglobin <10 g/dL, platelet <100 g/L, absolute neutrophil count <1 g/L

73.2 Indication of HSCT in MDS and Timing to Transplant

HSCT is an established procedure for MDS leading to long-term survival. The indications for HSCT may change following the introduction of new treatment strategies, and the HSCT approach itself has consistently evolved over time. TRM should always be balanced against the benefits associated with HSCT. Comparisons of several transplant and non-transplant cohorts show a gain in life expectancy in patients, with higher risks if they receive an allo-HSCT at MDS diagnosis, while in lower-risk MDS patients, a survival

Table 73.3 "Revised IPSS"

Points	*0*	*0.5*	*1*	*1.5*	*2*	*3*	*4*
Marrow blast	<3		3–4		5–10	11–20	
Cytogenetic[a]	Very good		Good		Intermediate	Poor	Very poor
Cytopenia[b]	No	Mild	Moderate	Severe anemia			
Risk	*Very low*	*Low*	*Intermediate*	*High*	*Very high*		
Number of points	≤ 1.5	2–3	4–4.5	5–6	>6		
Median OS (years)	8.8	5.3	3	1.6	0.8		
Median time to 25% AML transformation in years		10.8	3.2	1.4	0.73		

[a]Cytogenetics: *very good*, -Y, del(11q); *good,* normal, del(5q), del(12p), del(20q), double including del(5q); intermediate, del(7q), −8, −19, i(17q), any other single or double independent clones; *poor,* −7, inv.(3)/t(3q)/del(3q), double including −7/del(7q), complex, 3 abnormalities; *very poor*, complex, > 3 abnormalities

[b]cytopenia, *mild cytopenia*, platelet count <100 g/L or neutrophil count <0.8 g/L; *moderate cytopenia*, hemoglobin <10 g/dL but >10 g/dL, platelet count <50 g/L; *severe anemia*, hemoglobin <8 g/dL

advantage can be seen if HSCT is deferred (Cutler et al. 2004; Koreth et al. 2013; Della Porta et al. 2017; Robin et al. 2015). An international expert panel has also confirmed the indication of HSCT in higher-risk patients as well as lower-risk patients with specific poor prognostic features, including genetic alterations, failure to respond to usual treatment, life-threatening cytopenias, and high-intensity transfusions (de Witte et al. 2017). Figures 73.1 and 73.2 summarize transplant indications in MDS patients.

73.3 Post-HSCT Outcomes

Several recent registry studies including cytogenetic classification have reported outcomes for transplanted MDS patients (Table 73.4). Overall survival (OS) ranged from 35 to 50%, NRM from 30 to 40%, and relapse rates from 15 to 30%. Lower-risk MDS patients had better prognoses, and the EBMT cohort of low and intermediate-1 MDS patients showed that OS could reach 57%, with relapse incidence at 16% after 7 years (Robin et al. 2017a). Patients with poor and very poor risk cytogenetic characteristics, including monosomal karyotypes, were associated with poor outcomes. FAB classification, age, platelet count, stage at time of transplantation, and hematopoietic cell transplant-comorbidity index (HCT-CI) were prognostic clinical risk factors. Somatic mutations, i.e., *TP53, TET2, ASXL1, RUNX1*, and *RAS* pathways mutations, have been reported to be prognostic independent factors in several reports (Bejar et al. 2014; Della Porta et al. 2016; Lindsley et al. 2017; Yoshizato et al. 2017).

Due to the increase in patient age, transplantation results in these patients should be highlighted, as outcomes seem to be highly impacted by performance status and HCT-CI (McClune et al. 2010; Lim et al. 2010). The EBMT recently published two studies focusing on transplants in elderly patients. The first study included 1333 MDS patients above the age of 55, transplanted between 1998 and 2006 (Lim et al. 2010). Four-year OS was 31%, with NRM of 36%. The second study reported 313 MDS patients above the age of 70, transplanted between 2000 and 2013 (Heidenreich et al. 2017). The study findings showed 3-year OS of 34% and NRM of 42% confirming that transplant was feasible in this category of patients.

73.4 Alternative Donors and Donor Choice

In recent EBMT studies, HSCT from an URD did not appear to be a mortality risk factor compared with HSCT using MSD (Onida et al. 2014; Koenecke et al. 2015). Saber et al., on behalf of

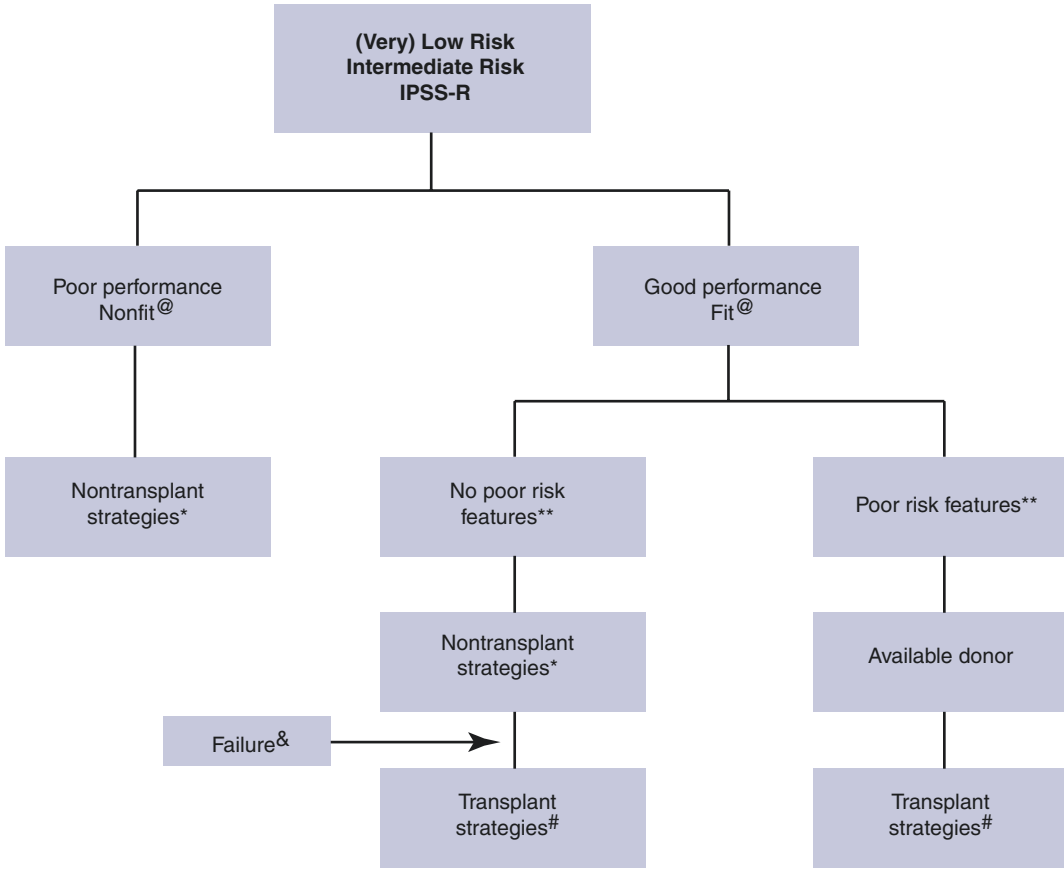

Fig. 73.1 Therapeutic flow chart for adult MDS patients with (very) low-risk or intermediate-risk IPSS-R scores @ indicates nonfit (patients with multiple comorbidities and/or poor performance) or fit (patients with no comorbidities and good performance status). * indicates nontransplant strategies according to most recent versions published by international MDS expert groups, including ELN and NCCN. & indicates failure of nontransplant strategies. ** indicates poor-risk features (defined as poor-risk cytogenetic characteristics, persistent blast increase [>50% or with >15% BM blasts], life-threatening cytopenias, high transfusion intensity >2 units per months for 6 months; molecular testing should be seriously considered, in case of absence of poor-risk cytogenetic characteristics or persistent blast increase). # indicates transplant strategies (all forms of HSCT, for details of the donor selection, type of conditioning, and post transplant strategies, see text; no upper age limit if patients are fit, without serious comorbidity, and with good Karnofsky status)

the CIBMTR, reported the results of HSCT in 701 MDS patients according to donor type: MRD, MUD (8 out of 8 high-resolution HLA compatibilities), and MMUD (Saber et al. 2012). Multiple-variable analysis showed that NRM was significantly lower with the use of MRDs compared with other donors, but that treatment failure (death or relapse) was similar to MUD, while it was significantly higher in patients transplanted from a MMUD (Saber et al. 2012).

The EBMT group reported outcomes for 631 MDS patients transplanted with a MUD (n = 379), a MMUD (n = 107), or a MMUCB (n = 129) (Robin et al. 2014). Patients transplanted with a MUD had better outcomes for OS, relapse-free survival, and NRM, while patients transplanted from MMUDs had similar outcomes, with a trend to a better DFS for MMUD compared with UCB. Recommendations are to choose an HLA-matched related or unrelated

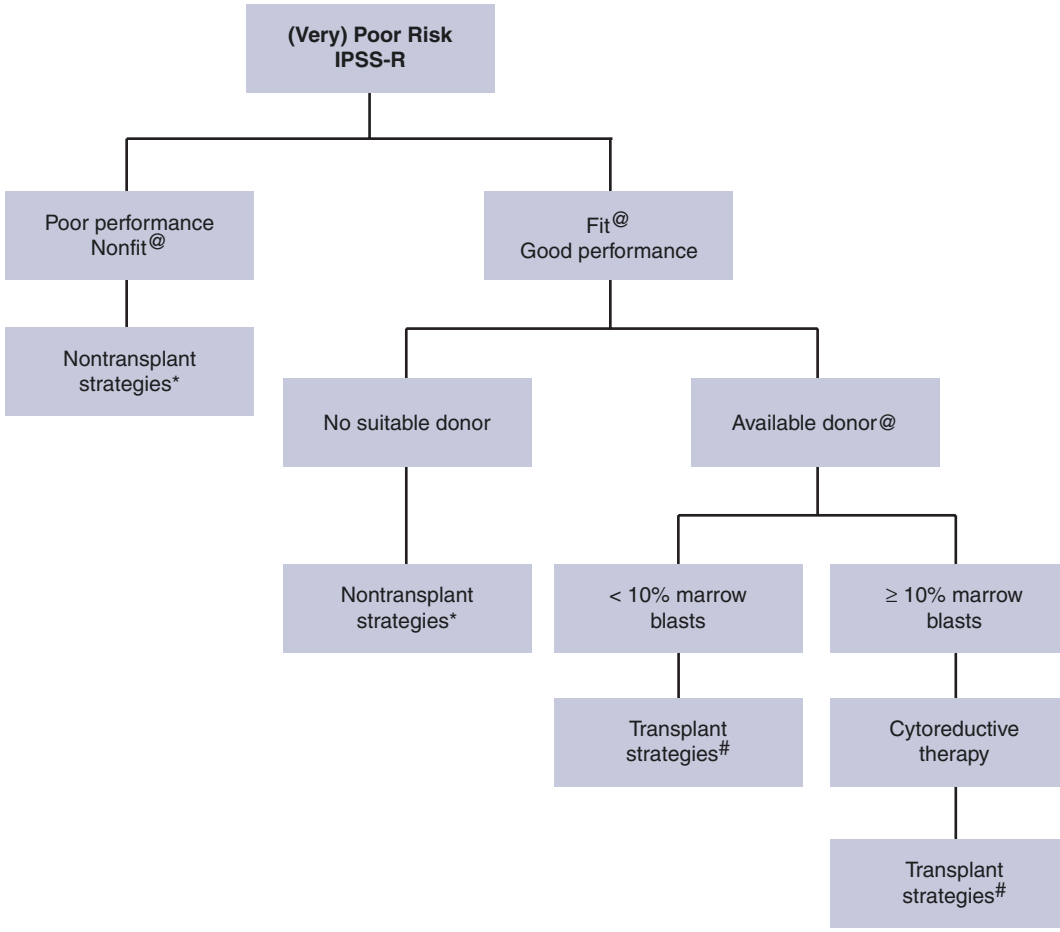

Fig. 73.2 Therapeutic flow chart for adult MDS patients with poor IPSS-R scores. @ indicates nonfit (patients with multiple comorbidities and/or poor performance) or fit (patients with no comorbidities and good performance status). * indicates nontransplant strategies according to most recent versions published by international MDS expert groups, including ELN and NCCN. & indicates failure of nontransplant strategies. ** indicates poor-risk features (defined as poor-risk cytogenetic characteristics, persistent blast increase [>50% or with >15% BM blasts], life-threatening cytopenias, high transfusion intensity >2 units per months for 6 months; molecular testing should be seriously considered, in case of absence of poor-risk cytogenetic characteristics or persistent blast increase). # indicates transplant strategies (all forms of HSCT, for details of the donor selection, type of conditioning, and post transplant strategies, see text; no upper age limit if patients are fit, without serious comorbidity,and with good Karnofsky status)

donor as both kinds of donor may lead to similar outcomes (Bowen 2017).

HSCT from haplo-identical related donors has been revisited due to new GVHD prophylaxis strategies, including the use of PT-CY. Little data has been published on MDS patients, although results in patients with other diseases are very promising (Bashey et al. 2013; Ciurea et al. 2015). A recent EBMT study reported 234 patients transplanted from haplo-donors between 2007 and 2014. Although NRM was relatively high, results were encouraging, with better results using PT-CY and RIC (Robin et al. 2017b). A recent issue is the impact of donor age on post transplant outcomes, suggesting that outcomes may be better with younger donors (Kollman et al. 2016; Kröger et al. 2013). This is particularly relevant in MDS, where both recipients and related donors are typically old.

Table 73.4 Patient outcomes in recent studies, including a large number of patients with cytogenetic data

HSCT centers; HSCT periods	Number of patients	Median age	RI	NRM	OS	RFS	Mortality risk factors in multiple-variable analysis
FHCRC[a] 1980–2010	1007	45	25	40	38	35	Blast count, CG, non-MAC, AML transformation, age, platelet count, HLA MM
EBMT[b] 1981–2006	523	43	25	36	43	38	CG, disease stage at HSCT, age, FAB, TCD[g]
EBMT[c] 1981–2012	903	50	36	33	36	32	Age, FAB, CG
SFGM-TC[d] 1999–2009	367	54	31–50	21–>31	32–>53		CG, marrow blast %, TBI in regimen, donor type
GITMO[e] 2000–2011	519	48	16–>41[f]	27–>35[f]	48–>15[f]		IPSS, HCT-CI, CG, disease stage at HSCT, donor type

FHCRC Fred Hutchinson Cancer Research Center, *SFGM-TC* Société Francophone de greffe de moelle et de thérapie cellulaire, *GITMO* Gruppo Italiano Trapianto di Midollo Osseo, *CG* cytogenetics, *RI* relapse incidence, *TBI* total body irradiation in conditioning regimen

[a]Deeg et al. (2012)

[b]Onida et al. (2014)

[c]Koenecke et al. (2015)

[d]Gauthier et al. (2015)

[e]Della Porta et al. (2014)

[f]According to cytogenetic risk

[g]Was assessed only in "untreated RA/RARS" because there were no prognostic factors in this group

73.5 Treatment Prior to HSCT

No randomized studies have compared pre-graft cytoreduction versus upfront transplants in MDS patients. Because hypomethylating agents (HMA) have been reported to improve survival in MDS patients, they are routinely used before considering a transplant procedure, leading to a delay in transplantation. It is very difficult from registry data to gain real insight into the risks or benefits of treatment with HMA. International guidelines generally recommend that patients with more than 10% marrow blast should receive cytoreductive treatment, which can be either intensive chemotherapy or HMA (de Witte et al. 2017b; Malcovati et al. 2013). The EBMT group reported that refractoriness to pre-graft treatment is associated with poor outcomes, confirming a French retrospective study (Potter et al. 2016; Damaj et al. 2012).

73.6 Preparative Regimen

The use of RIC regimens for HSCT has raised considerable interest. Multiple centers have developed novel RIC regimens that have reduced NRM and morbidity and subsequently expanded the curative potential of HSCT to older individuals who have historically not been considered to be HSCT candidates.

The EBMT group has compared outcomes for MDS patients treated by RIC or MAC (Martino et al. 2006; Martino et al. 2017). Studies show that relapse rates increased after RIC, while NRM was higher after MAC, in line with the findings of another study (Scott et al. 2006). Subsequent research by the EBMT group reported outcomes for 878 MDS or AML patients transplanted with less than 10% marrow blasts and classified according to the intensity of conditioning regimen considering four groups: non-MAC, RIC, standard regimen and hyperintensive regimen (Martino et al. 2013). OS after 7 years was 29, 53, 56, and 51%, respectively, for each regimen, with a disadvantage for the non-MAC. An EBMT prospective study comparing the use of RIC (FLU/BU) and MAC (CY/BU) in patients with MDS or secondary AML was published recently (Kröger et al. 2017). Multivariable analysis failed to show any impact of the regimen intensity in NRM, relapse, and RFS, while there was an advantage for RIC in OS, after adjustment for cytogenetics,

performance status, and disease stage. The BMT-CTN performed a prospective study on 272 patients with MDS or AML who were randomized between RIC and MAC. There was no difference in OS between the two groups, despite a higher relapse rate after RIC (Scott et al. 2017).

A novel RIC sequential regimen consisting of FLU 30 mg/m^2, Ara-C 2 g/m^2, and amsacrine 100 mg/m^2 (FLAMSA), followed 3 days later by 4 Gy TBI and CY 80–120 mg/kg showed promising results (Schmid et al. 2005; Schmid et al. 2006). Prospective randomized trials comparing sequential regimens with other regimens are ongoing.

73.7 Post-HSCT Treatment

MDS patients with relapse after HSCT are often refractory to treatment, or not fit enough to be treated. A German group recently reported outcomes for AML (n = 124) and MDS (n = 28) patients treated with AZA and DLI (Schroeder et al. 2015). The main risk factors for treatment response were molecular relapse only or marrow blast <13%. In these cases, OS was more than 60%, although it was below 10% in high-risk patients. An EBMT study of 181 patients treated with AZA for post transplant relapse of MDS confirmed that lower blast counts upon relapse and relapsing more than 6 months after HSCT were both good prognostic factors (Craddock et al. 2016a, b). In this study, the addition of DLI did not modify outcomes. Another EBMT study on cellular therapy after relapse (DLI or second transplant) showed that a second allo-HSCT performed in CR may rescue patients with relapse after initial HSCT, especially if they have no previous history of GVHD, and in cases where they may be transplanted from a new donor (Schmid et al. 2018). The French SFGM-TC group recently reported 147 MDS patients relapsing after transplant (Guieze et al. 2016). Only patients who received "cellular therapy" (DLI or second SCT) were able to achieve long-term survival (32% versus 6% for chemotherapy alone).

Other strategies involve preventive or preemptive treatment after transplantation to avoid morphological relapse. Preemptive strategies based on underlying risk or monitoring of minimal residual disease may be of use in these patients who present a high risk of post transplant relapse (Platzbecker et al. 2012). Although relapse remains the most common cause of transplant failure, particularly in patients with high-risk features, novel strategies such as the preemptive use of AZA or DLI may be effective in improving historically poor outcomes. Preventive post transplant treatment testing demethylating agents early after transplantation have also been reported in small prospective studies (de Lima et al. 2010; Pusic et al. 2015; Craddock et al. 2016a, b). This kind of treatment appears to be especially useful in patients with higher-risk MDS.

Key Points

- Allo-HSCT is the treatment of choice for all patients with (very) poor-risk MDS, or intermediate patients with high-risk features, who are fit enough to be considered for transplantation.
- Delayed HSCT is associated with reduced chances of prolonged relapse-free survival. Also, patients with less advanced MDS categories may benefit from deferred HSCT after they develop poor-risk features.
- Allo-HSCT outcomes have improved progressively in recent years, mainly due to a gradual reduction in non-relapse mortality. Reduced-intensity conditioning (RIC) regimens have extended the use of allo-HSCT to older patients, including those entering their eighth decade.
- However, a number of questions remain to be resolved by prospective studies, such as the choice of donor, including haplo-identical donors, the role of post transplant treatment, and the timing of transplantation in patients with lower-risk MDS.

References

Arber DA, Orazi A, Hasserjian R, et al. The 2016 revision to the World Health Organization classification of myeloid neoplasms and acute leukemia. Blood. 2016;127:2391–405.

Bashey A, Zhang X, Sizemore CA, et al. T-cell-replete HLA-haploidentical hematopoietic transplantation for hematologic malignancies using post-transplantation cyclophosphamide results in outcomes equivalent to those of contemporaneous HLA-matched related and unrelated donor transplantation. J Clin Oncol. 2013;31:1310–6.

Bejar R, Stevenson KE, Caughey B, et al. Somatic mutations predict poor outcome in patients with myelodysplastic syndrome after hematopoietic stem-cell transplantation. J Clin Oncol. 2014;32:2691–8.

Ciurea SO, Zhang M-J, Bacigalupo AA, et al. Haploidentical transplant with posttransplant cyclophosphamide vs matched unrelated donor transplant for acute myeloid leukemia. Blood. 2015;126:1033–40.

Craddock C, Jilani N, Siddique S, et al. Tolerability and clinical activity of post-transplantation azacitidine in patients allografted for acute myeloid leukemia treated on the RICAZA trial. Biol Blood Marrow Transplant. 2016a;22:385–90.

Craddock C, Labopin M, Robin M, et al. Clinical activity of azacitidine in patients who relapse after allogeneic stem cell transplantation for acute myeloid leukemia. Haematologica. 2016b;101:879–83.

Cutler CS, Lee SJ, Greenberg P, et al. A decision analysis of allogeneic bone marrow transplantation for the myelodysplastic syndromes: delayed transplantation for low-risk myelodysplasia is associated with improved outcome. Blood. 2004;104:579–85.

Damaj G, Duhamel A, Robin M, et al. Impact of azacitidine before allogeneic stem-cell transplantation for myelodysplastic syndromes: a study by the Societe Francaise de Greffe de Moelle et de Therapie-Cellulaire and the Groupe-Francophone des Myelodysplasies. J Clin Oncol. 2012;30:4533–40.

de Lima M, Giralt S, Thall PF, et al. Maintenance therapy with low-dose azacitidine after allogeneic hematopoietic stem cell transplantation for recurrent acute myelogenous leukemia or myelodysplastic syndrome: a dose and schedule finding study. Cancer. 2010;116:5420–31.

de Witte T, Bowen D, Robin M, et al. Use of hematopoietic cell transplantation for patients with myelodysplastic syndrome and chronic myelomonocytic leukemia. Blood. 2017;129:1753–62.

de Witte T, Bowen D, Robin M, et al. Allogeneic hematopoietic stem cell transplantation for MDS and CMML: recommendations from an international expert panel. Blood. 2017b;129:1753–62.

Deeg HJ, Scott BL, Fang M, et al. Five-group cytogenetic risk classification, monosomal karyotype, and outcome after hematopoietic cell transplantation for MDS or acute leukemia evolving from MDS. Blood. 2012;120:1398–408.

Della Porta MG, Tuechler H, Malcovati L, et al. Validation of WHO classification-based Prognostic Scoring System (WPSS) for myelodysplastic syndromes and comparison with the revised International Prognostic Scoring System (IPSS-R). A study of the International Working Group for Prognosis in Myelodysplasia (IWG-PM). Leukemia. 2015;29:1502–13.

Della Porta MG, Alessandrino EP, Bacigalupo A, et al. Predictive factors for the outcome of allogeneic transplantation in patients with MDS stratified according to the revised IPSS-R. Blood. 2014;123:2333–42.

Della Porta MG, Gallì A, Bacigalupo A, et al. Clinical effects of driver somatic mutations on the outcomes of patients with myelodysplastic syndromes treated with allogeneic hematopoietic stem-cell transplantation. J Clin Oncol. 2016;34(30):3627–37. https://doi.org/10.1200/JCO.2016.67.3616.

Della Porta MG, Jackson CH, Alessandrino EP, et al. Decision analysis of allogeneic hematopoietic stem cell transplantation for patients with myelodysplastic syndrome stratified according to the revised International Prognostic Scoring System. Leukemia. 2017;31:2449–57.

Gauthier J, Damaj G, Langlois C, et al. Contribution of revised International Prognostic Scoring System cytogenetics to predict outcome after allogeneic stem cell transplantation for myelodysplastic syndromes: a study from the French Society of Bone Marrow Transplantation and Cellular Therapy. Transplantation. 2015;99:1672–80.

Greenberg P, Cox C, LeBeau MM, et al. International scoring system for evaluating prognosis in myelodysplastic syndromes. Blood. 1997;89:2079–88.

Greenberg PL, Tuechler H, Schanz J, et al. Revised international prognostic scoring system for myelodysplastic syndromes. Blood. 2012;120:2454–65.

Guieze R, Damaj G, Pereira B, et al. Management of myelodysplastic syndromes relapsing after allogeneic hematopoietic stem-cell transplantation: a study by the SFGM-TC. Biol Blood Marrow Transplant. 2016;22:240–7.

Heidenreich S, Ziagkos D, de Wreede LC, et al. Allogeneic stem cell transplantation for patients age ≥ 70 years with myelodysplastic syndrome: a retrospective study of the MDS subcommittee of the chronic malignancies working party of the EBMT. Biol Blood Marrow Transplant. 2017;23:44–52.

Koenecke C, Gohring G, de Wreede LC, et al. Impact of the revised International Prognostic Scoring System cytogenetics and monosomal karyotype on outcome after allogeneic stem cell transplantation for myelodysplastic syndromes and secondary acute myeloid leukemia evolving from myelodysplastic syndromes: a retrospective multicenter study of the European Society of Blood and Marrow Transplantation. Haematologica. 2015;100:400–8.

Kollman C, Spellman SR, Zhang M-J, et al. The effect of donor characteristics on survival after unrelated donor transplantation for hematologic malignancy. Blood. 2016;127:260–7.

Koreth J, Pidala J, Perez WS, et al. Role of reduced-intensity conditioning allogeneic hematopoietic stem-cell transplantation in older patients with de novo myelodysplastic syndromes: an international collaborative decision analysis. J Clin Oncol. 2013;31:2662–70.

Kröger N, Zabelina T, de Wreede L, et al. Allogeneic stem cell transplantation for older advanced MDS patients: improved survival with young unrelated donor in comparison with HLA-identical siblings. Leukemia. 2013;27:604–9.

Kröger N, Iacobelli S, Franke G-N, et al. Dose-reduced versus standard conditioning followed by allogeneic stem-cell transplantation for patients with myelodysplastic syndrome: a prospective randomized phase III study of the EBMT (RICMAC Trial). J Clin Oncol. 2017;35:2157–64.

Lim Z, Brand R, Martino R, et al. Allogeneic hematopoietic stem-cell transplantation for patients 50 years or older with myelodysplastic syndromes or secondary acute myeloid leukemia. J Clin Oncol. 2010;28:405–11.

Lindsley RC, Saber W, Mar BG, et al. Prognostic mutations in myelodysplastic syndrome after stem-cell transplantation. N Engl J Med. 2017;376:536–47.

Makishima H, Yoshizato T, Yoshida K, et al. Dynamics of clonal evolution in myelodysplastic syndromes. Nat Genet. 2017;49:204–12.

Malcovati L, Hellstrom-Lindberg E, Bowen D, et al. Diagnosis and treatment of primary myelodysplastic syndromes in adults: recommendations from the European LeukemiaNet. Blood. 2013;122:2943–64.

Martino R, Iacobelli S, Brand R, et al. Retrospective comparison of reduced-intensity conditioning and conventional high-dose conditioning for allogeneic hematopoietic stem cell transplantation using HLA-identical sibling donors in myelodysplastic syndromes. Blood. 2006;108:836–46.

Martino R, de Wreede L, Fiocco M, et al. Comparison of conditioning regimens of various intensities for allogeneic hematopoietic SCT using HLA-identical sibling donors in AML and MDS with <10% BM blasts: a report from EBMT. Bone Marrow Transplant. 2013;48:761–70.

Martino R, Henseler A, van Lint M, et al. Long-term follow-up of a retrospective comparison of reduced-intensity conditioning and conventional high-dose conditioning for allogeneic transplantation from matched related donors in myelodysplastic syndromes. Bone Marrow Transplant. 2017;52:1107–12.

McClune BL, Weisdorf DJ, Pedersen TL, et al. Effect of age on outcome of reduced-intensity hematopoietic cell transplantation for older patients with acute myeloid leukemia in first complete remission or with myelodysplastic syndrome. J Clin Oncol. 2010;28:1878–87.

Onida F, Brand R, van Biezen A, et al. Impact of the International Prognostic Scoring System cytogenetic risk groups on the outcome of patients with primary myelodysplastic syndromes undergoing allogeneic stem cell transplantation from human leukocyte antigen-identical siblings: a retrospective analysis of the European Society for Blood and Marrow Transplantation-Chronic Malignancies Working Party. Haematologica. 2014;99:1582–90.

Platzbecker U, Wermke M, Radke J, et al. Azacitidine for treatment of imminent relapse in MDS or AML patients after allogeneic HSCT: results of the RELAZA trial. Leukemia. 2012;26:381–9.

Potter VT, Iacobelli S, van Biezen A, et al. Comparison of Intensive Chemotherapy and Hypomethylating Agents before Allogeneic Stem Cell Transplantation for Advanced Myelodysplastic Syndromes: A Study of the Myelodysplastic Syndrome Subcommittee of the Chronic Malignancies Working Party of the European Society for Blood and Marrow Transplant Research. Biol Blood Marrow Transplant. 2016;22:1615–20.

Pusic I, Choi J, Fiala MA, et al. Maintenance Therapy with Decitabine after Allogeneic Stem Cell Transplantation for Acute Myelogenous Leukemia and Myelodysplastic Syndrome. Biol Blood Marrow Transplant. 2015;21:1761–9.

Robin M, Ruggeri A, Labopin M, et al. Comparison of Unrelated Cord Blood and Peripheral Blood Stem Cell Transplantation in Adults with Myelodysplastic Syndrome after Reduced-Intensity Conditioning Regimen: A Collaborative Study from Eurocord (Cord blood Committee of Cellular Therapy & Immunobiology Working Party of EBMT) and Chronic Malignancies Working Party. Biol Blood Marrow Transplant. 2014;21:489–95.

Robin M, Porcher R, Ades L, et al. HLA-matched allogeneic stem cell transplantation improves outcome of higher risk myelodysplastic syndrome A prospective study on behalf of SFGM-TC and GFM. Leukemia. 2015;29:1496–501.

Robin M, Porcher R, Zinke-Cerwenka W, et al. Allogeneic haematopoietic stem cell transplant in patients with lower risk myelodysplastic syndrome: a retrospective analysis on behalf of the Chronic Malignancy Working Party of the EBMT. Bone Marrow Transplant. 2017a;52:209–15.

Robin M, Porcher R, Ciceri F, et al. Haploidentical transplant in patients with myelodysplastic syndrome. Blood Adv. 2017b;1:1876–83.

Saber W, Opie S, Rizzo JD, et al. Outcomes after matched unrelated donor versus identical sibling hematopoietic cell transplantation in adults with acute myelogenous leukemia. Blood. 2012;119:3908–16.

Schmid C, de Wreede LC, van Biezen A, et al. Outcome after relapse of myelodysplastic syndrome and secondary acute myeloid leukemia following allogeneic stem cell transplantation: a retrospective registry analysis on 698 patients by the Chronic Malignancies Working Party of the European Society of Blood and Marrow Transplantation. Haematologica. 2018;103:237–45.

Schmid C, Schleuning M, Ledderose G, et al. Sequential regimen of chemotherapy, reduced-intensity conditioning for allogeneic stem-cell transplantation, and

prophylactic donor lymphocyte transfusion in high-risk acute myeloid leukemia and myelodysplastic syndrome. J Clin Oncol. 2005;23:5675–87.

Schmid C, Schleuning M, Schwerdtfeger R, et al. Long-term survival in refractory acute myeloid leukemia after sequential treatment with chemotherapy and reduced-intensity conditioning for allogeneic stem cell transplantation. Blood. 2006;108:1092–9.

Schroeder T, Rachlis E, Bug G, et al. Treatment of acute myeloid leukemia or myelodysplastic syndrome relapse after allogeneic stem cell transplantation with azacitidine and donor lymphocyte infusions--a retrospective multicenter analysis from the German Cooperative Transplant Study Group. Biol Blood Marrow Transpl. 2015;21:653–60.

Scott BL, Sandmaier BM, Storer B, et al. Myeloablative vs nonmyeloablative allogeneic transplantation for patients with myelodysplastic syndrome or acute myelogenous leukemia with multilineage dysplasia: a retrospective analysis. Leukemia. 2006;20:128–35.

Scott BL, Pasquini MC, Logan BR, et al. Myeloablative versus reduced-intensity hematopoietic cell transplantation for acute myeloid leukemia and myelodysplastic syndromes. J Clin Oncol Off J Am Soc Clin Oncol. 2017;35:1154–61.

Yoshizato T, Nannya Y, Atsuta Y, et al. Genetic abnormalities in myelodysplasia and secondary acute myeloid leukemia: impact on outcome of stem cell transplantation. Blood. 2017;129:2347–58.