MEDICINE REPORTS

Published: 24 February 2009
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Hematopoietic stem cell transplantation in patients with myelodysplastic syndrome

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F1000 Medicine Reports 2009, **1**:11 (doi: 10.3410/M1-11)

The electronic version of this article is the complete one and can be found at: http://F1000.com/Reports/Medicine/content/1/11

Abstract

Hematopoietic stem cell transplantation (HSCT) is the only curative therapy for patients with myelodysplastic syndrome (MDS). However, the morbidity and mortality associated with conventional HSCT have traditionally prevented many patients from undergoing such treatment. Recent advances, including better prognostic algorithms, the introduction of reduced intensity conditioning regimens, and experience with alternative donors, have made HSCT a realistic option for an increasing number of patients with MDS.

Introduction and context

The myelodysplastic syndromes (MDSs) are a group of clonal hematological stem cell disorders characterized by defects in maturation resulting in cytopenias and a varied risk of transformation to acute myeloid leukemia (AML). Approximately 7,000–12,000 cases are diagnosed annually in the United States [1]. The majority of patients with MDS are older than 50 and the prognosis is quite variable, with some patients never requiring any intervention, and others needing treatment similar to patients with acute leukemia [2,3]. For many years, the French-American-British (FAB) classification distinguished five types of MDS [4]. The World Health Organization (WHO) proposed revisions in 1999 that included changing the definition of AML from 30% blasts to 20%, recognizing that the percentage of blasts is prognostic, stating that unilineage and multilineage dysplasia are separate entities, and recognizing the $5q^-$ syndrome [5]. The WHO system has again been recently revised; there are now eight types of MDS (Table 1).

While classification systems aid in diagnosis and communication, they are less helpful for predicting prognosis, which is essential for a disease with multiple therapeutic options. The International Prognostic Scoring System (IPSS) was based on information from 816 patients with MDS. In the IPSS, the number of cytopenias, percentage of blasts in the bone marrow, and cytogenetic abnormalities were used to define four risk groups (low, intermediate-1, intermediate-2, and high), which predicted overall survival and risk of AML transformation (Table 2) [6]. The IPSS has subsequently become the most widely used method to predict prognosis and assist in deciding which patients should receive aggressive treatment.

Clinical manifestations of MDS are usually related to cytopenias. The goals of treatment are to alleviate symptoms, improve quality of life, and prolong survival. Therapeutic options range from supportive care to aggressive therapy. Patients who are elderly or with significant comorbidities are usually supported with transfusions, antibiotics, and growth factors. Recently, three new therapies have been approved for treatment. Lenalidomide, an analog of thalidomide, showed a remarkable response in initial trials in patients with the $5q^-$ syndrome [7]. Studies in low-risk patients without loss of 5q have also shown a significant response [8,9]. For higher risk patients, 5-azacitidine and decitabine, which act through DNA demethylation, have been approved for use. Both are given safely to outpatients, but can induce significant cytopenias, especially during the first few cycles [10–13]. Even with these new agents,

Table 1. WHO classification for MDS [5]. Peripheral blood and bone marrow findings in myelodysplastic syndromes (MDS)

Disease	Blood findings	Bone marrow findings
Refractory cytopenias with unilineage dysplasia (RCUD): Refractory anaemia (RA); Refractory neutropenia (RN); Refractory thrombocytopenia (RT)	Unicytopenia or bicytopenia[1] No or rare blasts (<1%)[2]	Unilineage dysplasia: ≥10% of the cells in one myeloid lineage <5% blasts <15% of erythroid precursors are ring sideroblasts
Refractory anaemia with ring sideroblasts (RARS)	Anaemia No blasts	≥15% of erythroid precursors are ring sideroblasts Erythroid dysplasia only <5% blasts
Refractory cytopenia with multilineage dysplasia (RCMD)	Cytopenias(s) No or rare blasts (<1%)[2] No Auer rods $<1\times10^9$/L monocytes	Dysplasia in ≥10% of the cells in two myeloid lineages (neutrophil and/or erythroid precursors and/or megakaryocytes) <5% blasts in marrow No Auer rods ±15% ring sideroblasts
Refractory anaemia with excess blasts-1 (RAEB-1)	Cytopenias(s) <5% blasts[2] No Auer rods $<1\times10^9$/L monocytes	Unilineage or multilineage dysplasia 5–9% blasts[2] No Auer rods
Refractory anaemia with excess blasts-2 (RAEB-2)	Cytopenias(s) 5–19% blasts Auer rods ±[3] $<1\times10^9$/L monocytes	Unilineage or multilineage dysplasia 10–19% blasts Auer rods ±[3]
Myelodysplastic syndrome – unclassified (MDS-U)	Cytopenias ≤1% blasts[2]	Unequivocal dysplasia in less than 10% of cells in one or more myeloid cell lines when accompanied by a cytogenetic abnormality considered as presumptive evidence for a diagnosis of MDS <5% blasts
MDS associated with isolated del(5q)	Anaemia Usually normal or increased platelet count No or rare blasts (<1%)	Normal to increased megakaryocytes with hypobolated nuclei <5% blasts Isolated del(5q) cytogenetic abnormality No Auer rods

[1] Bicytopenia may occasionally be observed. Cases with pancytopenia should be classified as MDS-U.
[2] If the marrow myeloblast percentage is <5% but there are 2–4% myeloblasts in the blood, the diagnostic classification is RAEB 1. Cases of RCUD and RMCD with 1% myeloblasts in the blood should be classified as MDS, U.
[3] Cases with Auer rods and <5% myeloblasts in the blood and <10% in the marrow should be classified as RAEB 2.

hematopoietic stem cell transplantation (HSCT) remains the only curative therapy for MDS. However, HSCT historically possesses significant morbidity and mortality, and given the heterogeneous prognosis of MDS, it was not routinely offered to many patients.

Recent advances

Traditionally, only patients younger than 50 years of age with an HLA-matched donor were eligible for HSCT, however, improvements in prognostication, reduced intensity conditioning regimens, and experience with alternative donors have allowed physicians to consider many formerly ineligible patients as potential candidates for HSCT. Using registry data, investigators attempted to define the best time to perform HSCT for patients with MDS. Their findings showed that for patients with low and intermediate-1 IPSS risk disease, a strategy of delayed transplantation led to improved survival with the optimal time for HSCT being the development of a new cytogenetic abnormality, the appearance of a cytopenia, or the progression to a higher risk IPSS group. For patients with intermediate-2 and high IPSS disease, immediate transplantation led to maximal overall survival [14].

Reduced intensity conditioning (RIC) regimens were developed in the hope of decreasing acute transplant-related mortality (TRM) while allowing patients with advanced age or comorbidities to undergo HSCT. The therapeutic mechanism of RIC-HSCT is an immunological graft-versus-malignancy effect. Several different RIC regimens have been published showing reasonable toxicity in older patients [15–17]. There have also been retrospective analyses comparing myeloablative and RIC regimens in patients with MDS/AML with results suggesting that while TRM is indeed lower with RIC, relapse rates are higher, and overall and disease-free survival appear equivalent [18–21]. To date, no prospective randomized trials comparing conventional and reduced intensity transplants have been performed, however, it appears RIC-HSCT can offer approximately a 30–40% chance of long-term remission with an associated TRM between 15–40% for patients with MDS.

While the optimal HSCT donor remains a matched relative, alternative donors, such as unrelated donors (URDs) and umbilical cord blood (UCB), have become reasonable options. With the emergence of DNA-based

Table 2(a). International Prognostic Scoring System (IPSS) [6]

	Score value				
Prognostic variable	**0**	**0.5**	**1.0**	**1.5**	**2.0**
BM blasts (%)	<5	5–10	-	11–20	21–30
Karyotype*	Good	Intermediate	Poor		
Cytopenias	0/1	2/3			

Scores for risk groups are as follows: Low, 0; INT-1, 0.5; INT-2, 1.5–2.0; and High, ≥2.5.
* Good, normal, -Y, del(5q), del(20q); Poor, complex (≥3 abnormalities) or chromosome 7 anomalies; Intermediate, other abnormalities.
BM, bone marrow.

Table 2(b). International Prognostic Scoring System (IPSS). Survival and risk of acute myloid leukemia (AML) evolution [30]

	IPSS risk group			
	Low	**Int-1**	**Int-2**	**High**
Score	0	0.5–1.0	1.5–2.0	≥2.5
Lifetime AML Evolution	19%	30%	33%	45%
Median Years to AML	9.4	3.3	1.1	0.2
Median Survival (years)	5.7	3.5	1.2	0.4

HLA typing methods, outcomes of URD transplants have significantly improved, mainly due to decreased TRM. A few series of URD-HSCT in MDS have illustrated encouraging results that approach the outcomes of those with related donors [22–25]. In many centers, if a related or unrelated donor is not available, UCB has emerged as the preferred donor source. Several encouraging series of UCB-HSCT have been reported, including our own series, which shows a 14% 100-day TRM and a 67% 1-year disease-free survival in various hematological malignancies [26–29]. However, the experience with UCB-HSCT is early, and we eagerly await longer follow-up.

Implications for clinical practice

Even with the introduction of several new therapies, allogeneic HSCT remains the only curative treatment for patients with MDS. Historically, the majority of patients with MDS were not offered HSCT. Several recent advances have allowed physicians to consider HSCT for an increasing number of patients with MDS. Improved prognostic algorithms and analyses have allowed better prediction of disease outlook to permit aggressive therapies to be tailored to high-risk patients. Recognition of the graft-versus-malignancy effect in MDS and introduction of reduced intensity regimens have enabled many older patients to be considered for HSCT. In addition, the growing experience with unrelated donors and the use of umbilical cord blood has obviated the requirement for a matched sibling. Even with this progress, questions still remain. Future prognostic systems will no doubt incorporate genetic and molecular data in combination with the clinical information used in the IPSS. Moreover, more experience with reduced intensity regimens and alternative donors needs to be gained before they become standard of care.

Abbreviations

AML, acute myeloid leukemia; HSCT, hematopoietic stem cell transplantation; IPSS, International Prognostic Scoring System; MDS, myelodysplastic syndrome; RIC, reduced intensity conditioning; TRM, transplant-related mortality; UCB, umbilical cord blood; URD, unrelated donor; WHO, World Health Organization.

Competing interests

The authors declare that they have no competing interests.

References

1. Ma X, Does M, Raza A, Mayne ST: **Myelodysplastic syndromes: incidence and survival in the United States.** *Cancer* 2007, **109:**1536-42.
2. Williamson PJ, Kruger AR, Reynolds PJ, Hamblin TJ, Oscier DG: **Establishing the incidence of myelodysplastic syndrome.** *Br J Haematol* 1994, **87:**743-5.
3. Heaney ML, Golde DW. **Myelodysplasia.** *N Engl J Med* 1999, **340:**1649-60.
4. Bennett JM, Catovsky D, Daniel MT, Flandrin G, Galton DA, Gralnick HR, Sultan C: **Proposals for the classification of the myelodysplastic syndromes.** *Br J Haematol* 1982, **51:**189-99.
5. Brunning RD, Orazi A, Germing U, Le Beau MM, Porwit A, Baumann I, Vardiman JW, Hellstrom-Lindberg E. **Myelodysplastic Syndromes. In** *WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues.* 4th edition. Edited by Swerdlow SH, Campo E, Harris NL, Jaffe ES, Pileri SA, Stein H, Thiele J, Vardiman JW. Lyon, France: IARC Press; 2008:88-107.
6. Greenberg P, Cox C, LeBeau MM, Fenaux P, Morel P, Sanz G, Sanz M, Vallespi T, Hamblin T, Oscier D, Ohyashiki K, Toyama K, Aul C, Mufti G, Bennett J: **International scoring system for evaluating prognosis in myelodysplastic syndromes.** *Blood* 1997, **89:**2079-88.

7. List A, Kurtin S, Roe DJ, Buresh A, Mahadevan D, Fuchs D, Rimsza L, Heaton R, Knight R, Zeldis JB: **Efficacy of lenalidomide in myelodysplastic syndromes.** *N Engl J Med* 2005, **352:**549-57.

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8. List A, Dewald G, Bennett J, Giagounidis A, Raza A, Feldman E, Powell B, Greenberg P, Thomas D, Stone R, Reeder C, Wride K, Patin J, Schmidt M, Zeldis J, Knight R; Myelodysplastic Syndrome-003 Study Investigators: **Lenalidomide in the myelodysplastic syndrome with chromosome 5q deletion.** *N Engl J Med* 2006, **355:**1456-65.

   F1000 Factor 3.0 *Recommended*
   Evaluated by Andre Tichelli 13 Nov 2006

9. Raza A, Reeves JA, Feldman EJ, Dewald GW, Bennett JM, Deeg HJ, Dreisbach L, Schiffer CA, Stone RM, Greenberg PL, Curtin PT, Klimek VM, Shammo JM, Thomas D, Knight RD, Schmidt M, Wride K, Zeldis JB, List AF: **Phase 2 study of lenalidomide in transfusion-dependent, low-risk, and intermediate-1 risk myelodysplastic syndromes with karyotypes other than deletion 5q.** *Blood* 2008, **111:**86-93.

10. Fenaux P, Mufti GJ, Santini V, Finelli C, Giagounidis A, Schoch R, List AF, Gore SD, Seymour JF, Hellstrom-Lindberg E, Bennett JM, Byrd JC, Backstrom JT, Zimmerman LS, McKenzie DR, Beach CL, Silverman LR: **Azacitidine (AZA) treatment prolongs overall survival (OS) in higher-risk MDS patients compared with conventional care regimens (CCR): results of the AZA-001 Phase III study.** *Blood (ASH Annual Meeting Abstracts)* 2007, **110:**817.

11. Lübbert M, Wijermans P, Kunzmann R, Verhoef G, Bosly A, Ravoet C, Andre M, Ferrant A: **Cytogenetic responses in high-risk myelodysplastic syndrome following low-dose treatment with the DNA methylation inhibitor 5-aza-2'-deoxycytidine.** *Br J Haematol* 2001, **114:**349-57.

12. Silverman LR, Demakos EP, Peterson BL, Kornblith AB, Holland JC, Odchimar-Reissig R, Stone RM, Nelson D, Powell BL, Decastro CM, Ellerton J, Larson RA, Schiffer CA, Holland JF: **Randomized controlled trial of azacitidine in patients with the myelodysplastic syndrome: a study of the cancer and leukemia group B.** *J Clin Oncol* 2002, **20:**2429-40.

13. Wijermans P, Lübbert M, Verhoef G, Bosly A, Ravoet C, Andre M, Ferrant A: **Low-dose 5-aza-2'-deoxycytidine, a DNA hypomethylating agent, for the treatment of high-risk myelodysplastic syndrome: a multicenter phase II study in elderly patients.** *J Clin Oncol* 2000, **18:**956-62.

14. Cutler CS, Lee SJ, Greenberg P, Deeg HJ, Pérez WS, Anasetti C, Bolwell BJ, Cairo MS, Gale RP, Klein JP, Lazarus HM, Liesveld JL, McCarthy PL, Milone GA, Rizzo JD, Schultz KR, Trigg ME, Keating A, Weisdorf DJ, Antin JH, Horowitz MM: **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.

15. Ho AY, Pagliuca A, Kenyon M, Parker JE, Mijovic A, Devereux S, Mufti GJ: **Reduced-intensity allogeneic hematopoietic stem cell transplantation for myelodysplastic syndrome and acute myeloid leukemia with multilineage dysplasia using fludarabine, busulphan, and alemtuzumab (FBC) conditioning.** *Blood* 2004, **104:**1616-23.

16. Chan GW, Foss FM, Klein AK, Sprague K, Miller KB: **Reduced-intensity transplantation for patients with myelodysplastic syndrome achieves durable remission with less graft-versus-host disease.** *Biol Blood Marrow Transplant* 2003, **9:**753-9.

17. Kröger N, Shimoni A, Zabelina T, Schieder H, Panse J, Ayuk F, Wolschke C, Renges H, Dahlke J, Atanackovic D, Nagler A, Zander A: **Reduced-toxicity conditioning with treosulfan, fludarabine and ATG as preparative regimen for allogeneic stem cell transplantation (alloSCT) in elderly patients with secondary acute myeloid leukemia (sAML) or myelodysplastic syndrome (MDS).** *Bone Marrow Transplant* 2006, **37:**339-44.

18. Martino R, Iacobelli S, Brand R, Jansen T, van Biezen A, Finke J, Bacigalupo A, Beelen D, Reiffers J, Devergie A, Alessandrino E, Mufti GJ, Barge R, Sierra J, Ruutu T, Boogaerts M, Falda M, Jouet JP, Niederwieser D, de Witte T; Myelodysplastic Syndrome subcommittee of the Chronic Leukemia Working Party of the European Blood and Marrow Transplantation Group: **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.

   F1000 Factor 3.0 *Recommended*
   Evlauated by Marcie Tomblyn 11 Oct 2006

19. Scott BL, Sandmaier BM, Storer B, Maris MB, Sorror ML, Maloney DG, Chauncey TR, Storb R, Deeg HJ: **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.

20. Shimoni A, Hardan I, Shem-Tov N, Yeshurun M, Yerushalmi R, Avigdor A, Ben-Bassat I, Nagler A: **Allogeneic hematopoietic stem-cell transplantation in AML and MDS using myeloablative versus reduced-intensity conditioning: the role of dose intensity.** *Leukemia* 2006, **20:**322-8.

21. Alyea EP, Kim HT, Ho V, Cutler C, DeAngelo DJ, Stone R, Ritz J, Antin JH, Soiffer RJ: **Impact of conditioning regimen intensity on outcome of allogeneic hematopoietic cell transplantation for advanced acute myelogenous leukemia and myelodysplastic syndrome.** *Biol Blood Marrow Transplant* 2006, **12:**1047-55.

22. Anderson JE, Anasetti C, Appelbaum FR, Schoch G, Gooley TA, Hansen JA, Buckner CD, Sanders JE, Sullivan KM, Storb R: **Unrelated donor marrow transplantation for myelodysplasia (MDS) and MDS-related acute myeloid leukaemia.** *Br J Haematol* 1996, **93:**59-67.

23. Castro-Malaspina H, Harris RE, Gajewski J, Ramsay N, Collins R, Dharan B, King R, Deeg HJ: **Unrelated donor marrow transplantation for myelodysplastic syndromes: outcome analysis in 510 transplants facilitated by the National Marrow Donor Program.** *Blood* 2002, **99:**1943-51.

24. Kroeger N, Brand R, Martino R, Guardiola P, van Biezen A, Zander A, Niederwieser D, De Witte T: **Allogeneic stem cell transplantation from unrelated donors after reduced intensity conditioning in patients with MDS/sAML. A report from the Chronic Leukemia Working Party (CLWP) of the EBMT.** *Blood (ASH Annual Meeting Abstracts)* 2004, **104:**5176.

25. Lim Z, Ho A, Kenyon M, Devereux S, Duarte R, Pagliuca A, Mufti G: **Reduced intensity conditioned volunteer unrelated donor transplants using alemtuzumab are safe and effective in older patients with myelodysplastic syndromes.** *Blood (ASH Annual Meeting Abstracts)* 2005, **106:**444.

26. Ballen KK, Spitzer TR, Yeap BY, McAfee S, Dey BR, Attar E, Haspel R, Kao G, Liney D, Alyea E, Lee S, Cutler C, Ho V, Soiffer R, Antin JH: **Double unrelated reduced-intensity umbilical cord blood transplantation in adults.** *Biol Blood Marrow Transplant* 2007, **13:**82-9.

27. Barker JN, Weisdorf DJ, DeFor TE, Blazar BR, McGlave PB, Miller JS, Verfaillie CM, Wagner JE: **Transplantation of 2 partially HLA-matched umbilical cord blood units to enhance engraftment in adults with hematologic malignancy.** *Blood* 2005, **105:**1343-7.

28. Laughlin MJ, Eapen M, Rubinstein P, Wagner JE, Zhang MJ, Champlin RE, Stevens C, Barker JN, Gale RP, Lazarus HM, Marks DI, van Rood JJ, Scaradavou A, Horowitz MM: **Outcomes after transplantation of cord blood or bone marrow from unrelated donors in adults with leukemia.** *N Engl J Med* 2004, **351:**2265-75.

29. Rocha V, Labopin M, Sanz G, Arcese W, Schwerdtfeger R, Bosi A, Jacobsen N, Ruutu T, de Lima M, Finke J, Frassoni F, Gluckman E; Acute Leukemia Working Party of European Blood and Marrow Transplant Group; Eurocord-Netcord Registry: **Transplants of umbilical-cord blood or bone marrow from unrelated donors in adults with acute leukemia.** *N Engl J Med* 2004, **351:**2276-85.

30. List AF, Vardiman J, Issa JP, DeWitte TM. **Myelodysplastic syndromes.** *Hematology Am Soc Hematol Educ Program* 2004:297-317.