

# \* CHAPTER 22

## HSCT for myelodysplasia in adults

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## 1. Introduction

Myelodysplasia (MDS) consists of a heterogeneous group of clonal stem cell disorders. The spectrum of MDS varies from a disease with an indolent course over several years to a form with rapid progression to acute myeloid leukaemia (AML). Since 1982, myelodysplasia has been classified according to the French–American–British (FAB) criteria (1). The new World Health Organization (WHO) classification system for MDS corrected several limitations of the original FAB classification in 1997 (2). An international workshop generated an International Prognostic Scoring System (IPSS) in 1997 (3). MDS usually occurs without a preceding provoking event (primary MDS), but treatment with radiotherapy and certain chemotherapeutic agents promotes the development of therapy-related (t-)MDS. Both alkylating substances and drugs targeted at topoisomerase II are capable of inducing t-MDS and t-AML.

The majority of MDS patients are older than 60 years. For these patients supportive care, including new biologic response modifiers, is the mainstay of therapy. Allogeneic haematopoietic stem cell transplantation (HSCT) is usually considered the treatment of choice for most young MDS patients who have a histocompatible donor. Long-term disease-free survival (DFS) can be attained by these patients. For patients who lack a compatible donor, the outcome with autologous HSCT appears comparable with allogeneic SCT. Many clinicians consider allogeneic HSCT as the only curative treatment option. However, a retrospective study evaluating intensive chemotherapy alone versus chemotherapy followed by HSCT did not show a clear benefit for either chemotherapy alone or chemotherapy followed by HSCT.

## 2. Role of reduced-intensity conditioning (RIC) regimens in myelodysplasia

The general age of patients with MDS is higher than 60 years and co-morbidity is rather common. For these reasons, RIC regimens have recently been increasingly used in MDS. The initial reports in MDS showed an encouraging low TRM compared with conventional conditioning. Kröger et al. reported on 37 MDS patients who were ineligible for conventionally conditioned HSCT. The actuarial DFS rate at 3 years was 38%, with a median follow-up of 20 months (4). More favourable results were reported following conditioning with fludarabine, busulfan, and alemtuzumab in 62 MDS patients. The 1-year DFS rates were 61 and 59% in patients with matched sibling donors (n=24) and unrelated donors (n=38), respectively (5). The EBMT analysed the outcomes of 215 RIC patients, and standard myeloablative conditioning (SMC) in 621 patients. In a multivariate analysis, the 3-year relapse rate was significantly increased after RIC (hazard ratio [HR] 1.61, P=0.001), but the 3-year non-relapse mortality (NRM) was decreased after RIC (0.61, P=0.015) (6).

It is difficult to evaluate the contribution of RIC regimens to the improved outcome of allogeneic HSCT for MDS patients in view of the recently improved outcomes of HSCT with marrow ablative regimens and the heterogeneity of the patient populations (age, comorbidity, stage of disease). Therefore, the EBMT has launched a prospective randomised study comparing RIC regimens with standard conditioning regimens (for details, see: <http://www.ebmt.org/5WorkingParties/CLWP/clwp8.html>).

### 3. Role and outcome of autologous stem cell transplantation

In view of the high relapse rate after chemotherapy alone, transplantation with autologous stem cells has been applied in an attempt to intensify post-remission therapy. One of the first reports by the EBMT on autologous HSCT in MDS showed a 2-year DFS of 34%. In a prospective study, 24 of the 39 candidates received an autologous HSCT, resulting in a median DFS of 29 months from transplantation (7). A European study compared the results of 100 patients who had entered CR after remission-induction chemotherapy and who were candidates for allogeneic and autologous HSCT, depending on the availability of an HLA-identical sibling. The 4-year DFS rates in the group of patients with or without a donor were 31 and 27%, respectively (HR 0.93, 95% CI 0.57–1.52). This outcome suggested that patients with high-risk MDS might benefit from either allogeneic or autologous HSCT (8). A successful autograft is theoretically restricted to patients who achieve CR following induction chemotherapy, and in whom a suitable autologous harvest can be collected. Stem cell mobilisation was feasible in only 44/102 patients (43%) in the recovery phase after chemotherapy with G-CSF (9). This relatively low yield of a sufficient number of stem cells might reflect the low number of residual normal stem cells or the damage to the bone marrow stroma caused by pro-apoptotic cytokines produced by the MDS clone. It is clear that better mobilisation schedules and approaches should be developed before autologous peripheral HSCT can be recommended as part of the post-remission treatment of MDS patients treated with intensive anti-leukaemic therapy.

### 4. Role and outcome of HLA-identical sibling transplants

Results of allogeneic HSCT have improved over time. The International Bone Marrow Transplant Registry (IBMTR) reported a 3-year DFS rate of 40% for 452 patients who underwent HLA-identical sibling HSCT for MDS performed between 1989 and 1997 (10). Deeg et al. reported favourable results in MDS patients treated with a busulfan-based regimen in which the busulfan dosage was adjusted to maintain blood levels at 800–900 ng/mL. The 3-year non-relapse mortality (NRM) rate was 28% with related donors (11).

Cytogenetic abnormalities have a major influence on the outcome after HSCT. Using cytogenetic risk categories defined by the IPSS, the event-free survival rates for the poor-risk, intermediate-risk, and good-risk groups were 6, 40, and 51%, respectively (12). More advanced age (continuous variable) and long disease duration (>12 months) before HSCT were associated with an increased risk for treatment-related death after HSCT. This mandates consideration of HSCT early in the disease course. However, Cutler et al. showed that delayed HSCT results in maximised overall survival (OS) for low and intermediate-1 IPSS groups. They hypothesised that the optimal timing of HSCT in this cohort is at the time of development of a new cytogenetic abnormality, the appearance of a clinically important cytopenia, or an increase in the percentage of marrow blasts (13). Whether patients with advanced stage MDS should receive remission-induction chemotherapy prior to HSCT conditioning remains a point for debate. Retrospective analyses have reported conflicting data. Interpretation of the data is hampered by different selection biases in the two treatment approaches. Details regarding the type of chemotherapy administered are lacking in most studies. Preliminary analysis of the Criant study presented in 2005 showed that the majority of patients with an identified donor who were treated with remission-induction and consolidation chemotherapy received the planned HSCT (47/50). The 4-year DFS rate of the donor group was 46% – encouraging when compared with large-registry data (9). However, only prospective randomised studies can prove the benefit of remission-induction therapy prior to transplant conditioning. The EBMT launched such a study in December 2006 (see <http://www.ebmt.org/5WorkingParties/CLWP/clwp8.html> for full details).

### 5. Role and outcome of matched unrelated allogeneic transplants

Several reports have demonstrated that transplantation from matched unrelated donors (MUD) is a feasible and curative strategy for MDS patients. The National Marrow Donor Program (NMDP) reported on 510 MDS patients, transplanted between 1988 and 1998. At 2 years, the probability of DFS was 29%, and the cumulative incidence of TRM was 54% (14). A more recent report described the results obtained with a conditioning regimen of oral busulfan targeted to plasma concentrations of 800–900 ng/mL plus cyclophosphamide. The 3-year relapse-free survival of 64 MDS patients who underwent HSCT from MUDs was 59% and the NRM was 30% (11).

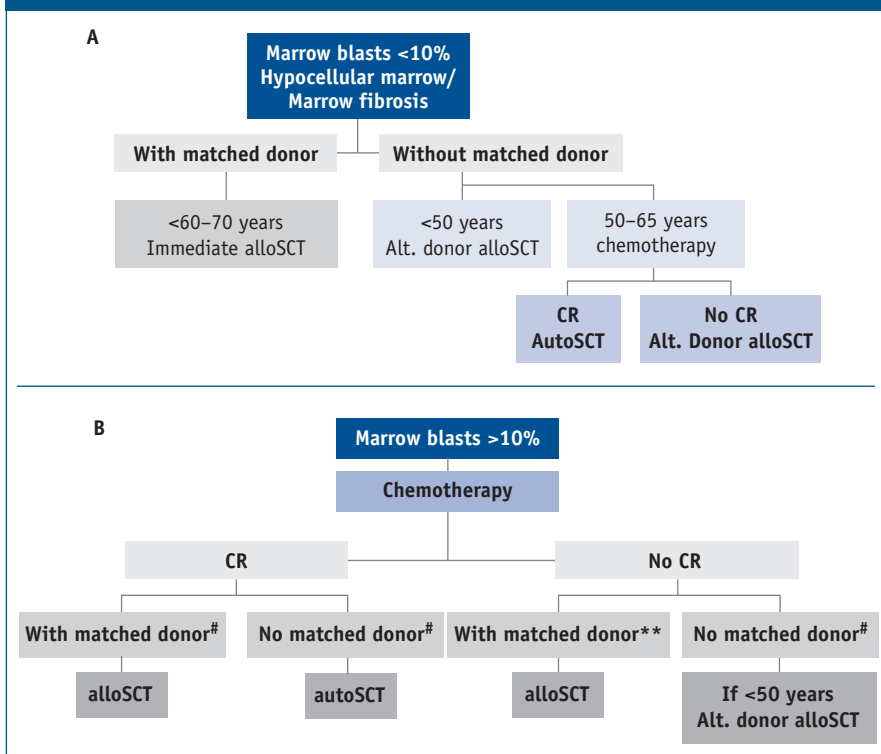
The status of the disease at transplantation and the time from diagnosis to transplantation have shown close relationships with DFS after MUD transplantation for MDS. Patients with MDS secondary to chemo/radiotherapy have poorer DFS rates than patients with *de novo* MDS. There also appears to be an improvement in DFS

rates in patients who have been transplanted in recent years (>1992). Other characteristics that have been associated with better DFS rates in some series are younger recipient age (continuous variable), greater cell dose, CMV seronegativity, and grades 0–I acute GvHD.

## 6. Role and outcome of cord blood transplants

Experience with CB transplantations from unrelated donors for MDS patients is still very scarce. Ooi et al. from the University of Tokyo have published the outcomes of 13 patients with advanced MDS with a median age of 40 years (15). Despite the

**Figure 1: Algorithm for the management of MDS patients candidates for intensive therapy**



\* Matched donor: HLA-identical sibling or HLA-matched unrelated donor; Alt. donor: all stem cell sources except stem cells from HLA-identical sibling or HLA-matched unrelated donor; # exception: good risk cytogenetics; \*\* exception: progressive disease after chemotherapy

very advanced disease status at transplantation, 10/13 patients were alive and in CR, with an estimated 76% DFS rate at 2 years. The Eurocord Cooperative Group has reported their preliminary experience with CB transplantation in 50 MDS patients. With a median follow-up of 21 months, 2-year probability of DFS is 29%. These preliminary results suggest that CB transplantation could constitute an alternative approach to transplantations from MUD in MDS patients.

## 7. Conclusions

Allogeneic HSCT is the treatment of choice for the majority of young patients with MDS who have a histocompatible donor (sibling or unrelated). For patients who lack an HLA-compatible sibling donor, the outcomes with autologous HSCT or chemotherapy appear comparable. These might be good alternatives for MDS patients with good-risk cytogenetic characteristics. Achievement of CR and the harvest of a sufficient number of autologous stem cells are prerequisites for autologous SCT.

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## Multiple Choice Questionnaire

To find the correct answer, go to <http://www.esh.org/ebmt-handbook2008answers.htm>

1. **A male patient, 40 years age old, diagnosis: refractory anaemia without multilineage dysplasia, normal cytogenetics, platelet count  $130 \times 10^9/L$ , neutrophil count,  $1.2 \times 10^9/L$ . Transfusion need: two units every 4 weeks.**

**What is the best treatment approach?**

- a) Immediate allogeneic stem cell transplantation if a histocompatible sibling has been identified . . . . .
- b) Supportive care with transfusion and iron chelation . . . . .
- c) Treatment with lenalinomide . . . . .
- d) Other treatment options . . . . .

**2. Allogeneic stem cell transplantation with reduced intensity conditioning regimens is usually applied in:**

- a) Patients >55 years . . . . .
- b) Patients with advanced stages of myelodysplasia . . . . .
- c) Both patient categories . . . . .
- d) Neither of these patient categories . . . . .

**3. Autologous haematopoietic stem cell transplantation is a reasonable treatment option for patients:**

- a) With refractory anaemia or refractory anaemia with ring sideroblasts . . . . .
- b) In complete remission with high risk cytogenetics before treatment . . . . .
- c) In complete remission with low risk cytogenetic characteristics before treatment . . . . .
- d) All 3 patient categories . . . . .

**4. The optimal timing of allogeneic stem cell transplantation in a patient with refractory anaemia and excess of blasts (RAEB), 7% marrow blasts and a platelet count of  $15 \times 10^9/L$  is:**

- a) Immediate allogeneic stem cell transplantation with histocompatible sibling donor . . . . .
- b) Allogeneic stem cell transplantation after intensive remission induction therapy (AML-type) . . . . .
- c) Supportive care followed by allogeneic stem cell transplantation if there is disease progression . . . . .
- d) Alternative options . . . . .

**5. The outcome of matched unrelated donor transplantation is comparable with that of transplantation with a histocompatible sibling in:**

- a) Patients <50 years . . . . .
- b) Patients <60 years . . . . .
- c) All ages . . . . .
- d) None of these three . . . . .