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Advances in Transplantation

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Special MDS Edition

Welcome to a special issue of Advances in Transplantation, a National Marrow Donor Program series that summarizes the latest research in hematopoietic cell transplantation (HCT). This issue highlights recent research on transplant therapy for myelodysplastic syndromes (MDS) published in the medical literature in the past year.

In this issue:

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Hypomethylating agents as a "bridge to transplant" for MDS patients

Two studies examine the planned use of the hypomethylating agents azacitadine (AZA) or decitabine as a bridge to transplant with the goal of disease control prior to HCT.

The first study led by Dr. Aaron Gerds of the Fred Hutchinson Cancer Research Center (FHCRC) showed that patients receiving pre-transplant AZA had outcomes comparable to patients undergoing high-dose induction chemotherapy (IC), despite the significantly older age of the AZA patients. [1]

The study retrospectively compared two cohorts of patients with MDS or AML transformed from MDS: 35 patients who received AZA prior to allogeneic HCT, and 33 patients who had undergone high-dose IC before HCT.

The AZA/HCT cohort consisted of consecutive patients transplanted between 2004-2010 at FHCRC compared to a historical cohort of IC/HCT patients transplanted between 1992-2002 at the same institution. Patient demographics and study outcomes are summarized in Table 1.

Patient characteristics, selected outcomes

	AZA/HCT	IC/HCT	P-VALUE
N	35	33	
Median age (range)	60 yrs. (4-74)	47 (2-64)	<0.05
100-day mortality	29%	27%	NS
1-yr. survival	57%	36%	0.24

Table 1. Study outcomes of HCT recipients pre-treated with azacitidine (AZA/HCT) or induction chemotherapy (IC/HCT). NS=not significant

Hypomethylating agents: continued on page 3

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Myeloablative, reduced-intensity HCT comparable in AML/MDS

Reduced-intensity conditioning regimens allow older patients and those with more co-morbidities to undergo HCT. But do patients conditioned with reduced-intensity regimens experience inferior outcomes?

The answer suggested by a large, long-term retrospective study is no. The study found comparable outcomes for reduced-intensity and myeloablative regimens in patients transplanted for AML and MDS. [4] The study also demonstrated that truly non-myeloablative regimens (even less intense than reduced-intensity regimens) led to inferior outcomes, suggesting a minimum level of regimen intensity is needed to achieve optimal outcomes.

The study, led by Dr. Selina Luger of the Hospital of the University of Pennsylvania in Philadelphia, examined outcomes of 5,179 adults transplanted between 1997-2004. Transplant outcomes were reported to the CIBMTR (Center for International Blood and Marrow Transplant Research) from 223 transplant centers in 37 different countries.

All HCT recipients received myeloablative (MA; n=3,731), reduced-intensity (RI; n=1,041), or non-myeloablative (NMA; n=407) conditioning prior to transplantation with related (n=579) or unrelated donors (n=4,600). Other patient demographics are shown in Table 2.

Patient characteristics by conditioning regimen

	MA	RI	NMA	P-VALUE
Median age (range)	42 yrs. (18-68)	54 yrs. (18-70)	57 yrs. (18-70)	<0.001
AML (%)	2,814 (75%)	731 (70%)	289 (71%)	NS
MDS (%)	917 (25%)	310 (30%)	118 (29%)	NS
≥90 Karnofsky @ tx	63%	63%	52%	<0.001
% in 1st CR @ tx	32%	23%	31%	<0.001

Table 2. Major patient characteristics of patients with MDS or AML undergoing transplant between 1997-2004. MA=myeloablative, RI=reduced-intensity, NMA=non-myeloablative, CR=complete remission, NS=not significant.

In a multivariable analysis, treatment failure (relapse or death in remission) was significantly higher in the NMA cohort compared to the other patient groups ($p<0.001$).

Adjusted 5-year overall survival (OS) for MA, RI and NMA transplants was 34%, 33% and 26%, respectively, with the NMA group having significantly lower OS ($p<0.05$).

The authors concluded that "some level of conditioning intensity above typical NMA approaches may improve survival in AML/MDS" and that outcomes in MA and RI transplants are comparable. ■

BMT CTN MDS/AML Protocol 0901

The Blood and Marrow Transplant Clinical Trials Network (BMT CTN) is conducting a study examining outcomes for patients with MDS or AML randomized to receive either a full intensity or reduced intensity preparative regimen as part of an allogeneic HCT. The data to date suggest that both approaches are appropriate but no randomized comparison has been completed to date. For more information, visit BMTCN.net and look for the Protocols section.

HCT in children with advanced MDS

A recent multi-center study of 97 patients age 19 years and younger with advanced MDS demonstrated that transplantation using a myeloablative conditioning regimen can result in a 63% five-year overall survival in these patients. [5]

This observational study, led by Dr. Brigitte Strahm of the University of Freiburg, Germany, analyzed outcomes of patients with advanced primary MDS transplanted at 30 European transplant centers between 1998-2007. Median age at diagnosis was 10.7 (1.0-18.2).

HLA-matched sibling donors (MSD) were used in 39 patients (40%), 57 patients (59%) received unrelated donor (UD) grafts, and one patient (1%) had an alternative matched family donor.

All but two patients achieved sustained neutrophil engraftment, with the median time to engraftment being 16 days (range, 10-43). Median time to platelet recovery was 23 days (range, 7-148). Other results are shown in Table 3.

HSCT following a myeloablative preparative regimen offers a high probability of survival for children with advanced MDS.

Patients transplanted using an MSD had a significantly higher incidence of grade III–IV acute GVHD than those transplanted from a UD: 33% vs. 18%, respectively (p=0.04). (Of note, GVHD prophylaxis was different between the two groups).

HCT outcomes in patients 19 and under with MDS	
Day-100 grade III-IV acute GVHD	24%
Cumulative incidence chronic GVHD	37%
5-year cumulative TRM	21%
Relapse rate	21%
5-year overall survival	63%

Table 3. Selected HCT outcomes in 97 patients ≤19 years with advanced MDS. GVHD=graft-versus-host disease, TRM=transplant-related mortality.

Overall cumulative incidence of chronic GVHD was comparable in the MSD and UD cohorts: 43 vs. 33%, respectively (p>0.05).

In a univariate analysis, age at transplant >12 years, interval between diagnosis and transplant >4 months, and development of acute or extensive chronic GVHD were associated with significantly increased transplant-related mortality.

Five-year probability of event-free survival was 59%, with comparable survival in the MSD and UD cohorts: 67% vs. 53%, respectively (p>0.05). Overall survival probability was 63%.

The authors conclude that HCT following a myeloablative preparative regimen "offers a high probability of survival for children with advanced MDS." ■

Hypomethylating agents: continued from page 1

In a univariate analysis, AZA treatment was identified as a statistically significant predictor of reduced post-transplant relapse (hazard ratio [HR], 0.34; 95% CI, 0.12-0.94; p=0.04).

However, after adjusting for cytogenetic risk, IPSS score, and type of donor (related or unrelated), the post-transplant relapse rates for the two cohorts were comparable. In a commentary accompanying the research, Dr. David Steensma noted that this study confirms the feasibility of either preconditioning approach, and that AZA therapy can be a "relatively nontoxic outpatient bridge" to HCT. [2]

Another 2012 study examined 19 adults (median age 47 years, range 23-69) with MDS who received pre-transplant hypomethylating agents (AZA, n=10; decitabine, n=9) prior to undergoing HCT. [3] In this single-center retrospective study led by Dr. Dae-Young Kim of the University of Ulsan, Seoul, a non-myeloablative conditioning regimen was used in 18 of the 19 patients.

Following hypomethylating agent therapy, two patients achieved complete remission (CR), six marrow CR, three hematologic improvement, and six stable disease. Following transplantation, neutrophil and platelet engraftment was achieved in 95% and 79%, respectively, and incidence of acute and chronic GVHD were 42% and 26%, respectively.

Two-year overall survival (OS) was 68%. Outcomes of patients who achieved CR or marrow CR after receiving hypomethylating agents tended to be superior to those without CR or marrow CR, but this difference was not statistically significant. The high OS led the authors to conclude that hypomethylating agent therapy followed by HCT "may be feasible and effective as a bridging therapy strategy for patients with MDS." ■

Evidence-based transplant consultation guidelines for MDS

The NMDP and The American Society for Blood and Marrow Transplantation (ASBMT) have jointly developed guidelines based upon current clinical practice and medical literature, including comprehensive evidence-based reviews. [6]

These guidelines highlight disease categories that include patients at risk for disease progression and who should be referred for hematopoietic cell transplant (HCT) consultation.

For some patients, early transplant may be indicated; for others, transplant may be needed later or not at all. Because appropriate planning and early donor identification are critical for optimal outcomes, early consultation is appropriate, even for patients who may never need HCT. Table 4 shows an excerpt of these guidelines for patients with MDS. ■

Myelodysplastic Syndromes (MDS)
INTERMEDIATE-1 OR -2 (INT-1 OR INT- 2) OR HIGH IPSS SCORE
Any MDS with poor prognostic features, including:
• Older age
• Refractory cytopenias
• Adverse cytogenetics
• Transfusion dependent

Table 4. Excerpt from NMDP/ASBMT guidelines for transplant consultation for patients with MDS.

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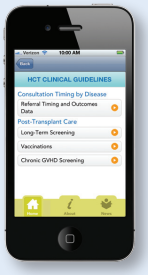

Quickly access the latest MDS referral timing recommendations and outcomes data through the *Transplant Guidelines* mobile app. The app also includes post-transplant care, vaccination, and GVHD screening recommendations.

Also available online and in print at **marrow.org/md-guidelines**

Download the free app now

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The National Marrow Donor Program (NMDP) is the global leader in providing marrow and umbilical cord blood transplants to patients with leukemia, lymphoma and other diseases. The nonprofit organization matches patients with donors, educates health care professionals and conducts research so more lives can be saved. The NMDP also operates Be The Match®, which provides support for patients, and enlists others in the community to join the Be The Match Registry®—the world's largest listing of potential marrow donors and donated cord blood units—contribute financially and volunteer. Learn more at marrow.org/md.

Review Publication: Allogeneic stem cell transplantation for elderly patients with MDS

In a June 2012 review published in Blood, Dr. Nicolaus Kröger of the University Medical Center Hamburg-Eppendorf, Hamburg, Germany, reviews evidence from large registry studies as well as prospective studies and summarizes current medical consensus on HCT in elderly patients with MDS. [7]

Influence of recipient age on outcome

- Recipient age alone cannot be considered as contraindication for allogeneic HCT

Impact of iron overload

- Can be considered as a comorbidity
- Is associated with a higher non-relapse mortality (NRM)
- There is no consensus on how to treat iron overload in HCT

Intensity of the conditioning regimen

- Patients up to 70 years of age can tolerate myeloablative regimens
- Age per se should not be a criterion for selecting the intensity of the conditioning regimen
- Performance status, comorbidity, and disease status should guide the choice of regimen

Donor selection strategies

- NRM is comparable in identical sibling and matched unrelated HCT, after adjusting for other risk factors
- Unrelated donors <30 years are more desirable than HLA-identical siblings
- HLA-identical donors should be preferred to an older (>30 years) matched unrelated donor

Role of pre-transplant cytoreduction

- While searching for a donor, hypomethylating agents should be initiated in elderly patients with INT-2 or high-risk IPSS

The role of cytogenetics and molecular genetics in outcomes

- Single abnormalities on chromosome 7 have significantly better survival than complex or monosomal karyotype

CIBMTR develops Medicare-approved study of HCT for MDS

In 2010, the Centers for Medicare and Medicaid Services (CMS) announced that allogeneic HCT for MDS will be covered by Medicare, but only for beneficiaries participating in a clinical study approved by CMS under the Coverage with Evidence Determination (CED) mechanism.

In response, the CIBMTR (Center for International Blood and Marrow Transplant Research) developed a study using data already being submitted by transplant centers to the Stem Cell Transplant Outcomes Database (SCTOD). This approach was subsequently approved by CMS, which opened in December 2010.

The primary objective of the study is to prospectively examine outcomes of allogeneic HCT in adults ≥65 years of age with MDS to determine whether their outcomes are similar to those in younger patients.

The CIBMTR protocol uses the existing infrastructure of the United States SCTOD, managed by the CIBMTR, to collect data on enrolled MDS patients. MDS patients with Medicare will therefore be eligible for claims coverage from the CMS by simply completing existing SCTOD forms and requesting enrollment in the CMS study on MDS.

Since the clinical trial opened in December 2010, more than 250 patients have been enrolled.

For information on eligibility and enrolling patients, visit CIBMTR.org or contact Christine Johnson, CIBMTR-Minneapolis, ckofstad@nmdp.org or 612-294-4386. ■

SUBMIT AN AML/MDS CASE

Have experts discuss your challenging AML or MDS case during the NMDP Friday Satellite Symposium Preceding the 54th ASH Annual Meeting.

Treatment of AML and MDS in Older Patients: A Case-Based Approach
- Friday, December 7, 2012, 7:00 - 11:00 a.m.

Visit **marrow.org/ASH-Symposium** to submit a case and register

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Long-term survival in MDS/AML better with HCT versus AZA

In a multi-center study of patients with high-risk MDS or secondary AML (sAML), HCT was associated with significantly better long-term overall survival compared to azacitidine (AZA) therapy alone. [8]

In this retrospective balanced-cohort study led by Dr. Uwe Platzbecker of the University of Dresden, Germany, 103 patients with high-risk MDS/sAML who underwent HCT were compared to 75 MDS patients receiving AZA.

At diagnosis, the AZA and HCT cohorts were comparable in terms of disease subtype (FAB or WHO), IPSS, cytogenetic characteristics, and gender. However, the AZA group was slightly older than the HCT group, median, 65 years (range 56-70) vs. 63 years (range 54-69; p=0.01).

> "Allogeneic HCT, in contrast to AZA treatment, can lead to long-term disease control and possibly cure in a substantial proportion of patients with advanced MDS in the seventh decade of life."

Allogeneic HCT was performed at a median of 7.6 months (range, 1.3-112 months) after the diagnosis of MDS. A conventional-intensity conditioning regimen was used in 45 patients (41%); the rest received a reduced-intensity conditioning regimen. Transplant grafts came from unrelated donors (n=63; 61%) or related donors (n=40; 39%).

The median time from diagnosis to first-line treatment with AZA was 6 months (range, 0 to 141 months), and AZA patients received a median of 6 cycles (range, 1-52 cycles) of therapy.

Outcomes at 2 years

RESULTS AT 2 YEARS	AZA	HCT
Overall survival	23%	39%
Event-free survival	14%	37%
Relapse	52% (relapse/progression)	30%
Non-relapse mortality	34%	33%

Table 5. Selected outcomes for 103 patients with high-risk MDS/sAML who underwent HCT compared to 75 MDS patients receiving AZA, in a retrospective comparison.

Non-relapse mortality (NRM) at two years was comparable in both cohorts: 33% (95% CI, 23%-42%) in the HCT group and 34% (95% CI, 22%-45%) in the AZA group.

There was no significant difference in overall survival in the first year following treatment: hazard ratio [HR] for HCT vs. AZA, 1.3; p=0.30. However, after one year, HCT was significantly associated with a strong protective effect: HR, 0.3; p=0.007.

The authors discuss possible limitations of the study, but conclude that "allogeneic HCT, in contrast to AZA treatment, can lead to long-term disease control and possibly cure in a substantial proportion of patients with advanced MDS in the seventh decade of life."

In a commentary accompanying the research, Dr. Corey Cutler noted that there did not seem to be a decrement in early survival in the transplantation arm, "possibly dispelling the myth that early, upfront non-relapse mortality is the price to be paid for the chance at cure with allogeneic transplantation." [9] ■