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Should elderly patients with higher-risk myelodysplastic syndromes undergo allogeneic hematopoietic stem cell transplantation?

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Abstract

Myelodysplastic syndromes (MDS) include a group of hematopoietic malignancies characterized by dysplastic changes, ineffective hematopoiesis and variable risk of leukemic progression. At diagnosis, 86% of MDS patients are ≥60 years. Azacitidine, the only drug that prolongs life in high-risk (HR)-MDS patients, adds a median of only 9.5 months to life. Allogeneic stem cell transplantation (alloSCT) remains the only potentially curative approach. Despite recent improvements including use of reduced intensity conditioning (RIC) that decrease transplant-related mortality, alloSCT continues to be used rarely in elderly MDS. There is paucity of data regarding outcomes of RIC alloSCT in elderly MDS patients, especially in direct comparison with azanucleosides. In this paper, the authors discuss the recent Markov decision analysis by Koreth *et al.* in which investigators demonstrated superior survival of patients with HR-MDS aged 60–70 years who underwent RIC alloSCT in comparison with those who were treated with azanucleosides.

Keywords

allogeneic stem cell transplantation; decision analysis; myelodysplastic syndromes; reduced intensity conditioning

Myelodysplastic syndromes (MDS) include a group of hematopoietic neoplasms characterized by aberrant myeloid differentiation, dysplasia and ineffective hematopoiesis resulting in cytopenias and increased risk of leukemic progression [1,2]. At diagnosis, 86% of MDS patients are ≥60 years [3]. Reflecting a heterogeneous biology, outcomes are widely variable [2]. The most widely used prognostic instrument to guide therapeutic decisions is the International Prognostic Scoring System (IPSS). The IPSS generally classifies patients

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into a lower-risk (LR) group (low and intermediate-1 [INT-1]) and a higher-risk (HR) group (intermediate-2 [INT-2] and high) [4].

No drug has proven curative for MDS with only azacitidine proved to prolong overall survival (OS) in HR-MDS by a median of 9.5 months [5]. Allogeneic stem cell transplantation (alloSCT) currently offers the only hope for cure. Recent progress, including use of reduced intensity conditioning (RIC), has reduced transplantation-related mortality (TRM) significantly therefore increasing the applicability of RIC alloSCT for elderly patients [6,7]. Nonetheless, alloSCT is still performed in a small fraction of patients [8]. There are no randomized prospective data comparing alloSCT with azacitidine in MDS, retrospective data are few and conflicting and the two approaches are often used sequentially [1,9–11].

To address the appropriate choice of treatments for elderly MDS, Koreth *et al*. used decision analysis (DA); a flexible statistical technique that can assist clinical-decision making by allowing evaluation of potential outcomes given multiple scenarios and assumptions [10]. DA allows for evaluation of results under different sets of assumptions to observe whether the same conclusions are reached [12]. In a previous Markov DA predating the widespread use of AZA, better life expectancy (LE) in IPSS HR-MDS patients was observed among patients who underwent alloSCT soon after diagnosis [13]. By contrast, patients with LR-MDS achieved maximal gain of years of life if alloSCT was delayed [13]. The applicability of these results to elderly HR-MDS patients undergoing RIC alloSCT is not clear as they were based on data from patients younger than 60 years who underwent myeloablative conditioning (MAC) alloSCT from HLA-identical donors before the widespread use of azacitidine.

Summary of methods & results

Koreth *et al*. conducted another Markov DA using an international database of 514 patients with primary MDS aged 60–70 years collected over two decades [10]. One hundred thirty-two patients underwent RIC-alloSCT (median age, 64 years, median follow-up in survivors 30 months) while 165 were treated with azanucleosides (median age 66 years, median follow-up in survivors 20 months). The IPSS scores were calculated at pretransplantation and at initiation of azanucleosides, respectively, while survival was measured from date of transplantation and date of initiation of azanucleosides, respectively. Non-anemic LR-MDS patients were treated with best supportive care (n = 123) while the 94 anemic LR-MDS patients were treated with growth factors.

The outcomes were assessed in Markov DA models in which patients could transition between three Markov health states (MHS): alive with MDS, alive post-RIC-alloSCT or dead [10]. The probabilities of transition between different MHS were estimated using the observed survival data of the original cohorts. Patients could transition between MHS in three-monthly intervals. Patients were not censored at therapy cross-over therefore accounting for salvage therapy. LE was estimated as the area under the survival curve; adjustment for quality of survival was made to calculate quality-adjusted LE (QALE).

Monte-Carlo Simulation was used to plot Kaplan–Meier survival curves with a modeled 10-year follow-up. Results were validated by comparing them with the primary data [10].

The investigators found that for IPSS LR-MDS, RIC-alloSCT resulted in a significantly lower LE (38 vs 77 months) and QALE (35 vs 47 months) compared with non-transplantation strategies. By contrast, a benefit in LE (36 vs 28 months) and QALE (33 vs 15 months) was achieved with RIC-alloSCT for IPSS HR-MDS in comparison with non-transplantation therapies including azanucleosides. Across variable plausible assumptions, sensitivity analyses confirmed these conclusions [10].

Discussion & five-year view

Increasing the tiny cure rate for elderly MDS patients will require new effective targeted therapies that would be based on better understanding of the genetic landscape and the biologic underpinnings of MDS [11]. Another approach would be to increase the utilization of alloSCT. The low use of alloSCT in elderly MDS patients is related to multiple factors including concerns of excessive TRM, reduced physiologic reserve with advanced age and comorbidities, donor availability, patient preferences and other factors [7,12]. Age by itself has not been shown to compromise outcomes of RIC-alloSCT in patients with good performance status (PS) [14,15]. Although retrospective data suggest that RIC-alloSCT results in comparable OS with MAC-alloSCT in hematologic malignancies, MDS-specific data are scarce [9,14–17]. The reduced TRM with RIC-alloSCT is counterbalanced by increased relapse rates, resulting in long-term survival in 30–50% of patients [7,15].

Another potential reason for the low alloSCT utilization in the elderly might be the lack of evidence of a survival advantage with alloSCT over azacitidine [1,5]. No randomized study directly compared these modalities [1]. A retrospective study of elderly patients aged 60–70 years with HR-MDS and secondary acute myeloid leukemia compared two well-balanced cohorts of transplanted (n = 103) or azacitidine-treated patients (n = 75) [9]. The transplanted group had better 2-year OS rate (39%, 95% CI: 30–50% vs 23%, 95% CI: 14–40%) which persisted in multivariate analysis (hazard ratio [HR]: 0.3; p = 0.007) [9].

In the absence of prospective randomized data and high-quality retrospective studies comparing alloSCT with azanucleosides in elderly patients with HR-MDS, DA would be a reasonable approach to assess the question. Koreth *et al*. showed that for patients with primary MDS aged 60–70 years, non-transplantation strategies are associated with a survival advantage for IPSS LR-MDS, while RIC alloSCT results in survival benefit in patients with HR-MDS when compared with non-transplantation approaches, including azanucleoside therapy [10].

This study is limited by its retrospective nature and the lack of details regarding comorbidities, PS and other relevant clinical and biological data for many patients including details of prior therapy. Additionally, the various cohorts used in the DA come from wildly different time intervals; patients from the original International MDS Risk Analysis Working group date back to the 1970s. No attempts at matching the patients were made. Although azanucleoside-treated patients with PS >2 and those with renal and liver organ dysfunction (who would not have been candidates for alloSCT) were excluded, patients with

other significant comorbidities (e.g., cardiac) that might have otherwise prohibited RIC alloSCT were not excluded [10]. Moreover, HR-MDS patients who received decitabine were included in the assessment although this drug has not been shown to improve survival. Importantly, the IPSS calculation for transplanted patients was made at time of pretransplantation rather than at diagnosis (which is the only time point at which the IPSS has been validated). Thus, the transplanted patients may have been significantly time-censored compared with the non-transplanted patients, selecting for patients with more indolent natural histories. Lastly, only 59 patients (45%) of those who underwent RIC alloSCT had IPSS HR-MDS.

Despite the selection bias and other significant limitations, the robustness of the conclusions were confirmed by testing under multiple plausible assumptions in sensitivity analyses [10]. The LE of the HR-MDS patients who received non-transplantation therapies including azanucleosides was 28 months, which is slightly longer than the median survival of the azacitidine-treated patients in the landmark AZA001 trial (24.5 months) [5], therefore a lower than expected survival in non-transplanted patients probably did not account for the observed results. The benefit of RIC-alloSCT for HR-MDS was mainly due to a long-term survival plateau of 25% despite increased early mortality. The unfortunate news is that only 25% of the transplanted patients appear to be benefitting long-term from therapy, confirming previous studies [16,17]. In practice, azanucleosides and alloSCT are often used sequentially. Outcomes of patients who fail to respond or lose response to azanucleosides is dismal, including those who undergo subsequent alloSCT [18], therefore alloSCT should ideally be pursued in eligible patients before aza-nucleoside failure occurs. The authors did not specifically analyze the patients treated with azanucleosides followed by RIC-alloSCT, a treatment algorithm which many experts recommend.

Although physicians now have stronger evidence to consider RIC-alloSCT in elderly HR-MDS patients, a number of questions remain unanswered. Is pre-alloSCT cytoreduction always needed and if so, should chemotherapy or azanucleosides be used and what BM blast percentage should be targeted? What is the best alloSCT platform in terms of conditioning regimen intensity, drugs and graft-versus-host disease prophylaxis? With the wider use of alternative donors, can the results of this DA be applied to patients undergoing RIC-alloSCT using other graft sources such as umbilical cord blood or HLA-haploidentical donors?

Lastly, the IPSS has been shown to underestimate the risks in a significant minority of patients designated as LR [19,20]. Though newer prognostic schemes (e.g., MD Anderson low-risk score and the revised IPSS (IPSS-R)) and genetic biomarkers (e.g., *EZH2*) were reported to identify some of these patients, the optimal therapeutic approach is still not known as the benefits of alloSCT have not been demonstrated in these patients [1,19,21]. As the IPSS-R could potentially replace the IPSS, it would be important to study the benefit of RIC-alloSCT in elderly patients in the intermediate-risk group of the IPSS-R [12,21]. Lastly, effective pharmacologic and immunologic preventive, preemptive and therapeutic approaches for disease relapse will need to be developed as relapse becomes the main reason for treatment failure after RIC alloSCT for MDS [1,22].

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