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Transplantation for Myelodysplastic Syndrome in the Era of Hypomethylating Agents

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Abstract

Purpose of Review—To summarize the available data on the role of hypomethylating agents in the setting of hematopoietic cell transplantation (HCT) for myelodysplastic syndrome (MDS).

Recent Findings—Although hypomethylating agents have been established as standard of therapy for MDS in the non-transplant setting, the role of these agents in patients who are candidates for HCT or are undergoing HCT is less well defined. Hypomethylation therapy has been investigated in both the pre-HCT and post-HCT setting. Patients who are transplant candidates and are given pre-HCT hypomethylating therapy should proceed with HCT when “best response” is achieved; HCT when hypomethylation has failed is associated with inferior outcome. Only limited data have been presented on the use of hypomethylating agents after HCT setting. While this approach may prove to be useful in reducing post-HCT relapse, such therapy should only be given in the setting of clinical trials.

Summary—Treatment planning for patients with MDS who are HCT candidates should comprise the entire treatment arc including pre-HCT debulking, possibly with hypomethylating agents, condition regimen, and potential post-HCT treatment, be it prophylactic, pre-emptive or therapeutic.

Keywords

Hypomethylating therapy; MDS; hematopoietic cell transplantation; debulking therapy; preemptive therapy

Introduction

Hematopoietic cell transplantation (HCT) is currently the only therapeutic modality with curative potential for patients with myelodysplastic syndrome (MDS). The lead patients are currently surviving in unmaintained remission more than two decades after HCT [1,2]. However, success is not uniform as a result of complications related to the conditioning regimen used in preparation for HCT, transplant-related side effects such as graft versus host disease (GVHD) and infections, and the inability to consistently eradicate the underlying disease even with HCT. While GVHD is an important risk for all allogeneic transplant recipients, relapse is a major cause of HCT failure primarily in patients with high-risk karyotype or advanced disease [1,3–5]. These observations, naturally, lead to the question of who should be transplanted and when?

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Results of a Markov analysis almost a decade ago showed that patients with MDS categorized in the International Prognostic Scoring System (IPSS) as intermediate-2 or high risk, had the best life expectancy if transplanted early after diagnosis, whereas more conservative management appeared appropriate in patients with low-risk MDS and even with intermediate-1 risk disease [6]. However, that analysis involved patients transplanted before the era of hypomethylating agents and included only patients less than 60 years of age who were conditioned with high intensity regimens and transplanted from HLA-matched related donors. The results of this analysis are difficult to apply to all patients with MDS as the median age at diagnosis is in the early 70s, and HCT in older individuals has generally been possible only with reduced-intensity conditioning (RIC) regimens to prevent prohibitive toxicity [7]. Though with the use of RIC regimens, the incidence of relapse has tends to be higher than with high dose conditioning. The use of pre-transplant “debulking” with induction type chemotherapy in an attempt to reduce the risk of relapse has been associated with treatment-related mortality in the range of 10–15% [8–10]. The availability of two hypomethylating agents, 5-azacitidine (azacitidine) and 5-aza-2'-deoxycytidine (decitabine), has provided the opportunity to offer chemotherapy with limited toxicity as a more gentle approach to debulking. In contrast to classic induction chemotherapy, hypomethylating therapy typically achieves the intended goal of remission, or at least disease control, only after multiple courses [11,12]. On the other hand, patients can be maintained on this minimally toxic regimen for extended periods of time.

This therapeutic option brings with it some important questions: Should patients who are candidates for HCT and who respond to hypomethylating therapy be maintained on that treatment as long as they respond and come to HCT only when failing treatment or should they be transplanted when the optimum response has been achieved [13]? Will prolonged therapy with hypomethylating agents, while debulking the disease, lead to the selection of clones with greater resistance, even to the modalities used in HCT conditioning regimens? Will such treatment lead to an increase in co-morbid conditions that may have a negative impact on post-HCT outcome?

An additional prospect has been raised by the low toxicity profile of hypomethylating agents: Since the post-HCT relapse probability is high for certain categories of MDS, and since hypomethylating agents have been shown to be effective in treating MDS, should they be administered prophylactically or preemptively *after* HCT in an attempt to reduce the incidence of post-HCT relapse [14,15]?

Hypomethylating Therapy before Transplantation

There are no controlled trials investigating the impact of pre-HCT hypomethylating therapy on post-HCT outcome. All reported data are derived from retrospective analyses. Field et al. presented data in 54 consecutive patients with MDS or CMML (chronic myelomonocytic leukemia) who underwent HCT from HLA-matched donors [16]. Thirty patients had received azacitidine for 1–7 (median 4) cycles, and 24 patients had not received azacitidine. At 1 year after HCT with conditioning involving high-dose busulfan and fludarabine, 47% of azacitidine-treated patients were alive, compared to 60% of patients not given azacitidine. The corresponding figures for relapse-free survival were 41% and 51%, and for relapse 20% and 32%, respectively. Non-relapse mortality in the 11 azacitidine-treated patients who died in remission was primarily due to GVHD (n=4) and infections (n=3). NRM in patients not given azacitidine was due to GVHD (n=2), infection (n=2), pulmonary hemorrhage (n=2), and multi-organ failure (n=1). The authors concluded that outcome was comparable with a trend towards a lower incidence of relapse in azacitidine-treated patients. It was not clear, however, why a given patient had received the drug and another had not. It is possible that patients considered at high risk for relapse *did* receive azacitidine, while the remaining patients did not. If this were the case, then the trend for a lower relapse rate would be

encouraging, although there was no survival advantage. In fact, overall survival was apparently inferior in azacitidine-treated group, suggesting that the severity of the underlying disease or side effects of therapy contributed to death.

De Padua Silva et al. presented results in 17 patients with MDS who underwent HCT after having received decitabine [17]. At 1 year, 11 patients were alive, while 6 had died, four from disease progression, one from GVHD, and one with septicemia. Lubbert et al. presented data on 15 similarly treated patients who then underwent allogeneic HCT following RIC [18]. At the time of reporting, six patients were alive in remission while four had died from progressive disease and five from transplant-related complications while in remission.

We reviewed results in 68 patients who underwent HCT for MDS or AML transformed from MDS at our Center. Thirty-five patients had received cytorreduction with azacitidine prior to HCT following either a high-dose (40%) or RIC (60%) regimen, while 33 patients had undergone induction-type chemotherapy followed by HCT with high-dose conditioning. The one-year overall survival was 57% in the azacitidine group, and 36% in the group given induction chemotherapy. While the risk of post-HCT relapse and non-relapse mortality was lower in the azacitidine group, none of the differences were statistically significant (unpublished).

As alluded to already, one central question is whether patients given pre-transplant hypomethylating therapy should continue to receive that treatment until treatment fails, or whether HCT should be carried out while patients are still responding. Jabbour et al. analyzed outcome in 67 patients with MDS and 20 patients with CMML who had received decitabine therapy [19]. The median survival was 4.3 months, and the estimated 12-month survival rate 28%. With a median follow-up of 21 months after decitabine failure, 13 patients (15%) were alive. There was no significant difference between patients in different MDS risk categories (defined by IPSS).

In a similar study [13], Prebet et al. determined the prognosis of patients who were treated on protocols that required azacitidine for at least 4 or 6 months and either showed disease progression [20] or were intolerant of azacitidine. The prognosis was generally poor. However, with “investigational therapy,” the median survival among 44 patients so treated was 13.2 months, compared to 4.1 months with best supportive care. The best results were obtained with allogeneic HCT. This subcohort included 37 patients (14% of all patients) who underwent HCT at 1–26 (median 5) months after azacitidine failure was declared; 9 received other salvage therapy before HCT, whereas 28 (14 of whom had progressive disease) went directly to HCT. The median survival for all patients was 19.5 months, 14 months for those with progressive disease, while it was not reached for those with stable disease. Survival at 3 years was approximately 40%.

These data indicate that patients whose disease progresses on or after hypomethylating therapy have a poor prognosis with a median survival of approximately 4 months (remarkably similar in azacitidine and decitabine treated patients). The data also suggest that patients who are candidates for HCT should be transplanted before there is evidence of disease progression.

Hypomethylating Therapy After Hematopoietic Cell Transplantation

Post-HCT relapse has remained a major cause of failure, particularly with high-risk MDS, i.e. in patients with advanced MDS or high-risk karyotypes [5,21]. While earlier studies had shown that intensification of the transplant conditioning regimen reduced the relapse frequency, the associated increase in non-relapse morbidity and mortality was prohibitive

[22]. Therefore, rather than adding toxicity by intensifying the transplant regimen, it may be advantageous to allow for recovery from the conditioning-related effects, and delay the administration of additional agents, be it in a prophylactic or preemptive fashion. The use of hypomethylating agents in that setting offers an attractive option. Firstly, even though some myelosuppression is expected, these agents are generally well tolerated and marrow recovery typically occurs quickly. Secondly, the use of hypomethylating agents may lead to increased expression of various gene products, including cancer testis genes, that would represent targets for immune-mediated effects of donor cells, possibly leading to an enhanced graft versus tumor (GVT) reaction and eradication of residual MDS cells [23].

In a phase I dose-finding study, de Lima and colleagues at the MD Anderson Cancer Center started azacitidine at 6–7 weeks after HCT and determined that a dose of 32 mg/m² given for 5 consecutive days, was well tolerated [15]. They treated 45 patients with high-risk MDS/AML and observed a 1-year relapse-free survival of 58%, which in their assessment justified further studies. In addition, the authors noted that the incidence of chronic GVHD was lower in 5-azacitidine-treated patients than in historical controls. This observation was confirmed in a study at Washington University, which emphasized, in addition, the beneficial effect on GVHD did not compromise the GVT effect [23].

The MD Anderson team conducted an additional phase II trial which enrolled 17 patients with acute leukemia (16 AML and 1 ALL), 8 of whom were given 5-azacitidine (16, 24 or 40 mg/m² for 5 consecutive days, every 4 weeks) as maintenance, and 9 as salvage. All patients were high risk and 11 were transplanted from unrelated donors. Various conditioning regimens were used. The median follow-up was 16 months after HCT and 11 months after 5-azacitidine. Five of 9 patients receiving azacitidine as salvage therapy responded. Relapse-free survival and overall survival at one year were 55% and 90%, respectively.

Platzbecker and colleagues conducted a trial in which they administered azacitidine for “imminent relapse” in patients transplanted for MDS or AML [24]. This was a prospective, open-label study enrolling patients 18 years of age or older with MDS or AML expressing CD34. Patients were screened after HCT for CD34⁺ donor chimerism. If donor chimerism fell below 80%, patients were offered treatment with 5-azacitidine. This event occurred in 25 of 59 screened patients at a median of 169 days, and azacitidine was initiated at 75 mg/m²/day for 7 days. Sixteen patients responded with an increase in CD34⁺ donor chimerism or stabilization at 80%. Eleven patients were given additional 1–11 (median 4) cycles of azacitidine. Hematologic relapse eventually occurred in 13 patients (65%), but was delayed to days 56–558 (median 231) after the initial documentation of a decrease in donor CD34 chimerism to below 80%. The authors concluded that this strategy of preemptive azacitabine treatment was associated with an acceptable safety profile and was effective in delaying or even preventing hematological relapse.

Conclusion

Treatment with hypomethylating agents, either azacitabine or decitabine, has been established as standard of care for MDS, particularly in patients with high-risk MDS, while the question has remained controversial in patients with low-risk disease. The role of hypomethylating agents in patients who are candidates for or are undergoing HCT is not well defined. As these drugs are well tolerated and appear to be altering the natural course of MDS (patients may be gaining on average 9 months of life), it is likely that they will also continue to be used in patients who are candidates for HCT.

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Key Points

- The available data strongly suggest that transplant candidates being treated with hypomethylating agents should not delay HCT until disease progression occurs, but, rather, should proceed to HCT when “best response” is achieved.
- This may be particularly important for older patients who are likely to undergo HCT with reduced-intensity conditioning regimens, which carry a higher probability of disease recurrence than observed in patients conditioned with high-intensity regimens.
- Data on the use of hypomethylating agents *after* HCT are limited, and this strategy should continue to be studied in controlled clinical trials.
- As additional agents, such as FLT-3 inhibitors and other small molecules are coming into use, the question as to which would be the optimum post-HCT approach, be it preemptive or prophylactic, will require further investigation.
- Patients who are considered candidates for HCT should have a consultation with a physician experienced in the overall management of patients, including HCT, early in their disease course to develop the optimum treatment plan.