blood advances

Second chances for secondary AML

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Comment on Nagler et al, page 4223

In this issue of *Blood Advances*, Nagler et al[1] report that outcomes are similar for patients with secondary acute myeloid leukemia (sAML) compared with those with de novo AML following transplantation for active disease using haplo-identical donors and posttransplant cyclophosphamide. Specifically, in a large European Society for Blood and Marrow Transplantation registry study of 719 patients with primary induction failure (PIF) or relapsed disease, ~30% were alive and disease-free 2 years after transplantation with no discernable difference between those with de novo AML or sAML. These results are somewhat surprising given the generally acknowledged worse prognosis with sAML after standard chemotherapy or transplant in first remission using matched related or matched unrelated donors.

Does this mean that patients with PIF or recurrent sAML should be considered for transplantation? The answer is a tentative "yes." In general, the outcomes with nontransplant salvage therapy for both of these groups are very poor. Among patients refractory to high dose cytarabine regimens, a 20% response to salvage therapy has been observed, with <10% surviving without transplant.[2,3] Intensification of salvage chemotherapy does not seem to improve outcomes[4]; survival after standard salvage therapies such as mitoxantrone, etoposide, and cytarabine (MEC; 5.4 months[5]) or fludarabine, cytarabine, and granulocyte colony stimulating factor (FLAG; 3.4 months[6]) are similar to the survival durations of ~4 months observed after use of venetoclax in combination with low dose cytarabine or hypomethylating agents by the Programa Español de Tratamientos en Hematología group.[7] In patients who did not undergo transplant, survival of 6 months was observed after venetoclax in combination with FLAG-Idarubicin.[8] Although transplantation is associated with considerable morbidity and mortality, a leukemia-free survival probability of 30% at 2 years, as described by Nagler et al, makes transplantation a reasonable option to consider and discuss with patients.

Admittedly, in this retrospective registry study, there is no way to know how restrictive centers were in selecting patients for transplant. It would have been helpful if the authors had provided a more precise definition of PIF, specifically to make clear whether the definition included patients whose only induction attempt was a brief exposure to hypomethylating agents or other low-intensity regimens. In this study, the average age was 61 years, 50% had a performance status of <90, and 40% had an HCT comorbidity index score of ≥3, so it does seem likely these results should be reasonably generalizable.

When considering transplant candidates, their individual characteristics inform risk/benefit judgments. Nagler et al help us by demonstrating that the usual factors (age, performance status, cytomegalovirus status, and cytogenetics) help predict outcome. Surprisingly, a multivariate analysis for survival, relapse, nonrelapse mortality (NRM), and composite end points found no other baseline covariates predictive of outcomes. In particular, neither the use of reduced intensity (vs myeloablative conditioning) nor disease status (primary refractory vs first relapse), nor HCT comorbidity index ≥3 was associated with any outcome measure. Although some centers would decline to consider HCT for patients with sAML and active disease, these data indicate a strong rationale to consider allogeneic hematopoietic cell transplant for the difficult-to-treat population of patients with AML (both de novo and sAML) with active disease.

Nagler et al's present report, focused on haplo-identical donors and posttransplant cyclophosphamide, raises questions about best management of such patients moving forward if matched donors are available. Should haplo-identical donors become the first choice in this setting? Randomized prospective comparative data are not available, but outcomes using matched sibling and haplo-identical donors appear similar among older adults who received transplantation for disease in remission.[9]

However, haplo-identical family members offer the possibility of quicker donor acquisition and potentially improved graft-versus-leukemia (GVL) effect than unrelated donors. Turning to haplo-identical family members when a matched sibling is not available seems reasonable.

An additional question is whether patients with PIF or relapsed AML benefit from efforts at remission reinduction before HCT. This is a question that has existed for decades.[10,11] Consistent with results from 40 years ago, 2 more recent studies suggest blast reduction before initiating the transplant regimen is unlikely to be beneficial. First, retrospective analyses found similar posttransplant outcomes among patients with morphologic vs measurable residual disease at the time of transplant.[12] Second, in a recently published study, patients with AML with PIF or untreated first relapse were randomized to either an attempt at reinduction or immediate transplant. Overall survival 4 years after randomization was similar: 49% in the reinduction cohort vs 46% for those going immediately to transplant. Patients in the immediate transplant group were all treated using a regimen of combination chemotherapy (fludarabine, amsacrine, cytarabine), followed within a week with reduced intensity alkylator-based conditioning,[13] so perhaps the question is more one of timing rather than the actual treatment received.

Despite the potential for cure, transplantation for patients with PIF or recurrent AML, particularly those with sAML, is not widely applied. Timely identification of a suitable donor can be challenging, and simultaneous attempts to "debulk" refractory leukemia before initiating the transplant procedure may impair patient fitness, while adding to financial and logistical challenges. Therefore, data from Nagler et al's study supporting the use of haplo-identical donors in patients with sAML with active disease are particularly welcome and may encourage physicians and motivated patients to reach for a treatment option that provides a substantial chance for long-term survival.

These data once again emphasize the impressive power of the GVL effect and its distinct activity from cytotoxic chemotherapy. Further progress may be made both by reevaluating which patients are likely to benefit from transplant and improving the balance of GVL vs graft-versus-host disease. Multimodal evaluation of patient fitness (eg, by the Composite Health Risk Model[14]) may better identify patients at low risk of NRM, but molecular AML features that sensitize leukemic stem cells to GVL remain an area of active research. Novel cell type manipulation (such as naïve T-cell depletion[15]) or immune augmentation (such as application of decoy-resistant-IL-18[16]) holds promise. Patients and physicians may be ready to throw in the towel when AML is not chemotherapy-sensitive, but Nagler et al show that haplo-identical transplant can be a viable salvage. In life, as in sports, when you are given a second chance, put in your best player.

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