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CLINICAL TRIALS AND OBSERVATIONS

Comment on DeZern et al, page 3031

Reward from half a match

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In this issue of *Blood*, DeZern et al show impressive results with transplantation from HLA-haploidentical family members in patients with aplastic anemia not previously exposed to immunosuppressive therapy (IST).[1] A conditioning regimen combining cyclophosphamide (Cy), fludarabine, rabbit antithymocyte globulin (ATG), and 4 Gy total body irradiation (TBI) allowed for consistent engraftment, and with the inclusion of posttransplant Cy, the incidence of clinically relevant acute and chronic graft-versus-host disease (GVHD) was <10%.

Severe aplastic anemia is a life-threatening disease with 2 age peaks, one in young adults and one in the sixth decade of life. In most patients, the disease is acquired and autoimmune mediated; in some, it is genetically determined. The 2 most widely used treatment modalities are IST and bone marrow transplantation (BMT), both of which were developed in the 1970s. Initially upfront BMT was restricted to younger patients who had HLA-identical siblings. All others received IST because of concerns about toxicity and graft failure, related to allosensitization or histoincompatibility.

As outcomes with HLA-identical sibling transplants improved, transplants from "alternative" donors, HLA-matched unrelated volunteers, were used with increasing frequency. However, those patients had generally first received IST but failed to achieve a sustained response. Often no HLA-matched donor could be identified. This was true particularly for patients from ethnic minorities, related to the heterogeneity of HLA types and the low representation of donors from similar backgrounds in the national and international donor registries. Results with HLA-mismatched family members or unrelated volunteers were disappointing. Yet, Henslee-Downey et al had suggested early on that at least in patients with malignant disorders the use of family donors who were matched for 1 of the 2 HLA haplotypes inherited from the parents was feasible, with promising results.[2]

The team at Johns Hopkins then systematically developed transplant strategies with HLA-haploidentical donors (typically children, parents, or siblings) for malignant diseases and aplastic anemia. For patients with aplastic anemia who had failed IST, they used a conditioning regimen comprised of a combination of rabbit ATG, fludarabine, Cy, and TBI before the donor cell infusion (day 0) and additional Cy, 50 mg/kg per day, on days 3 and 4 after donor cell infusion, followed by daily mycophenolate mofetil and tacrolimus as GVHD prophylaxis.[3] Results in 37 patients, most of whom had received IST, were gratifying, with an overall survival of 94% at 1 and 2 years and an incidence of acute GVHD grades II to IV of 11% and chronic GVHD of 8%. An important observation was that 3 of 17 treatment-naive patients, that is, patients who had not received IST, experienced graft failure (compared with 1 among 20 who had received IST first). An increase of the TBI dose in the conditioning regimen from 2 Gy to 4 Gy in 10 additional patients prevented graft failure. These results suggested that the level of immuno(in) competence pretransplant was a major determinant of outcome, and this hurdle could be overcome by increasing the dose of TBI. At the same time, the incidence of GVHD, which is affected by conditioning intensity, was very low.[3,4]

The current article by DeZern et al is a systematic extension of their previous reports, restricting the analysis to treatment-naive patients and confirming that with a TBI dose of 4 Gy, sustained engraftment of HLA-haploidentical donor cells is achieved consistently even in patients who had not first received IST. Furthermore, the incidence of GVHD remained very low. With an overall survival of 92%, an incidence of acute GVHD of 7%, chronic GVHD of 4% (most likely related to the induction of regulatory T cells mediated by posttransplant administration of CY[5]), and no rejection, these results are quite striking. Since more than 90% of patients have an HLA-haploidentical family member, the transplant strategy described here would be applicable to the vast majority of patients.

Will these results be practice changing? A major problem in all patients with marrow failure is infections. The authors argue that overall outcome can be improved with early BMT by circumventing the often long period required for hematological recovery following IST. This strategy might also reduce the frequency of allosensitization related to transfusions required during that interval.[6] The concern that the absence of prior IST would jeopardize engraftment was addressed by increasing the dose of TBI. Although there is a slightly higher risk of acute toxicity, apparently, this did not negatively impact GVHD. However, further follow-up is needed to identify potential effects on growth and development (in young patients) and fertility (in older patients), although data in a canine model suggest that the doses of TBI employed here would not impact fertility.[5] Another concern is the development of new malignancies, be it in the hematopoietic system or solid tumors.

Assuringly, recent data suggest that the incidence after low-dose TBI is not higher than in patients conditioned with chemotherapy-only regimens.[7]

What else is required? We need data on larger numbers of patients, preferentially treated in a multicenter setting and followed for longer. Such a study should include more older patients who have a worse prognosis of aplastic anemia. Also, we do not have results from prospective randomized trials comparing upfront BMT from HLA-haploidentical donors with results of IST, possibly combined with eltrombopag,[8] particularly in children (effect of TBI on growth?). On the other hand, IST still comes with the risk of clonal evolution.[9] A multicenter study in pediatric patients comparing BMT (from unrelated donors) with IST is currently ongoing (NCT05600426). Although the trial does not enroll haploidentical donors, additional data relevant for BMT decision-making should emerge. Finally, should a regimen as used for HLA-haploidentical transplants in patients with aplastic anemia also be used for patients receiving HLA-identical transplants? Preliminary data suggest that the incorporation of posttransplant Cy is of similar benefit.[10]

Conflicts-of-interest: The author declares no competing financial interests. ■

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LYMPHOID NEOPLASIA

Comment on Eertink et al, page 3055

A man's best friend is his PET

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In this issue of *Blood*, Eertink et al[1] validate that a new radiomics-based prognostic classification outperforms the traditional International Prognostic Index (IPI) in identifying patients with diffuse large B-cell lymphoma (DLBCL) who are at high risk for treatment failure.

DLBCL is the most common lymphoma histology. Although this disorder is an aggressive one, 50% to 70% of patients are cured with initial standard chemoimmunotherapy. However, currently no method is routinely available to identify, prior to therapy, those patients who are unlikely to benefit and should therefore be considered for an alternative treatment. The unfortunate consequence is that all patients with DLBCL are currently treated the same, regardless of differences in their predictable prognosis. At presentation, patients with DLBCL are given an anatomic stage, per the 4-stage Ann Arbor (AA) system that dates back to 1971. Next, they are assigned to a prognostic group according to the somewhat archaic, 30-year-old IPI, which uses simple clinical and laboratory features, including age, performance status, serum lactate dehydrogenase, number of extranodal sites, and AA stage. Unfortunately, neither AA stage nor IPI provides adequate information for therapeutic guidance. Thus, the range of treatment results has remained relatively stagnant.

Over the past 2 decades, the precision of staging and restaging has improved greatly, owing largely to the availability of 2′-fluorodeoxyglucose positron emission tomography–computed tomography (FDG-PET-CT) scanning. PET-CT is more sensitive and specific than simple CT scans, and it helps distinguish viable tumor from fibrous tissue.[2] In several histologies, PET-CT has eliminated the need for subjecting patients to the dreaded bone marrow biopsy. Improvements in equipment and better standardization of interpretation with the 5-point Deauville score have further enhanced the usefulness of PET-CT. Such advances justified, in part, the revised staging and response criteria used to classify nodal lymphomas—the widely used Lugano classification of 2014.[3]

Recent enhancements in metabolic imaging have further improved the ability to predict, pretreatment, which patients are likely to benefit from therapy. Numerous studies have demonstrated that the quantification of metabolic tumor volume (MTV) derived from the PET-CT scan is highly correlated with patient outcome in DLBCL[4] as well as other lymphoma histologies. Radiomics, or quantitative FDG-PET features, examines other characteristics of the lymphoma phenotype, including the peak standardized uptake value, the