Reduced-Intensity Regimens in Allogeneic Hematopoietic Stem Cell Transplantation for Hemoglobinopathies

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The only well-established curative therapy for patients with hemoglobinopathies is allogeneic hematopoietic stem cell transplantation (HSCT), which, in the last 20 years, has been mainly performed from an HLA-matched, related donor, using bone marrow as source of hematopoietic progenitors. More recent studies indicate that HSCT from unrelated donors may offer results comparable to those obtained with HLA-identical family donors, provided that stringent criteria of compatibility are employed for selecting the donor. Cord blood transplantation was also suggested to be an equally effective, but safer, procedure than bone marrow transplantation, due to the lower incidence and severity of both acute and chronic graft-versus-host disease. In view of the early, as well as late, morbidity and mortality associated with conventional myeloablative transplantation in patients with hemoglobinopathies, it is not surprising that great interest and relevant expectations for patients with hemoglobinopathies have been raised by the introduction in the clinical practice of reduced-intensity preparative regimens. However, few reports have demonstrated the feasibility of using reduced-intensity preparative regimens for successfully treating these patients and many treatment failures, mainly due to the lack of sustained donor engraftment, have been reported. Despite these limitations, some of the concepts obtained from the use of reduced intensity regimens, such as the substitution of fludarabine for cyclophosphamide, may be important to further improve the outcome of patients with hemoglobinopathies, especially of those with poor prognostic characteristics, given HSCT.

Almost 25 years have elapsed since the first successful allogeneic transplant of hematopoietic stem cells (HSCT), performed in a patient with thalassemia major.1 Since then, several hundred patients with this disease, as well as with sickle cell disease (SCD), have been cured of their original disorder through HSCT, the majority of cases performed using an HLA-identical sibling as the donor.2-5 More recently, many reports have shown that unrelated donor HSCT can successfully cure a proportion of patients with thalassemia major comparable to that cured using an HLA-identical sibling, provided that the unrelated volunteer be selected according to stringent criteria of compatibility with the recipient and using high-resolution molecular typing for both HLA class I and II loci.6-10 Preliminary, although encouraging, results have been reported on the use of cord blood-derived hematopoietic progenitors from either a relative or an unrelated donor.11,12 The large number of patients with hemoglobinopathy transplanted worldwide has allowed the identification of clinical parameters influencing post-transplant outcome, thus permitting more refined prognostic counseling for patients considering the option of HSCT and their parents.2,5,8,10,13 In particular, in patients with thalassemia, the risk of death due to transplant-related complications has been shown to be mainly dependent on advanced patient age, iron overload and liver viral infections. In fact, adults, especially when affected by chronic active hepatitis, have an inferior outcome as compared to children.14 Among pediatric patients with thalassemia, three classes of risk have been identified on the basis of regularity of previous iron chelation, liver enlargement and presence of portal fibrosis.7,3,13 Patients belonging to the first two classes of risk, namely class 1 and 2, have a better probability of benefiting from transplantation than patients who have low compliance with iron chelation and show signs of severe liver damage (i.e., class 3 patients). In the most recent update of the largest single-institution experience, the probability of thalassemia-free survival in patients younger than 17 years at time of transplantation, who received the allograft from an HLA-identical relative, and belonged to class 1 and 2 was 87% and 84%, respectively;15 it was reported to be lower, in the order of 50-60%, in patients assigned to class 3.16 Both transplant-related mortality (TRM) and lack of sustained donor engraftment contribute to treatment failure in patients with hemoglobinopathies. In particular, TRM has been reported to range between 5% and 35% in different reports on patients with either thalassemia or SCD, and up to 10% of patients have been reported to experience either early or late graft failure.2,5,8,10,13-16 It is noteworthy that cord blood transplantation from an HLA-iden-
the vast majority of patients given a cytotoxic sibling has been suggested to be safer, in terms of risk of experiencing fatal transplant-related complications, than bone marrow transplantation.11

The mortality and morbidity associated with conventional myeloablative transplantation curtail the number of patients who accept HSCT, especially considering that for thalassemia patients living in developed countries the optimization of blood transfusion support and iron chelation therapy have dramatically improved both survival and quality of life over the last two decades, changing a previously fatal disease associated with early death to a chronic, although progressive, disease compatible with prolonged survival.17 The risk/benefit balance related to the use of HSCT has to be differently weighed in developing countries, where most children with thalassemia or SCD succumb before the age of 20 years due to the unavailability of safe blood products in adequate amounts and/or reduced access to expensive iron-chelating drugs or other effective supportive therapies.13

The most significant long-term complications of HSCT in patients with hemoglobinopathies include infertility and gonadal failure, especially among females, chronic graft-versus-host disease (GVHD), and a potential for secondary malignancies.18 Effects on fertility are particularly worrying as, despite anecdotal reports of successful pregnancy after transplantation,19 the vast majority of patients given a standard preparative regimen before HSCT lose fertility,18 thus raising concerns among families and clinicians that justifiably curb their willingness to consider transplantation more broadly.

In view of all these considerations on the risk of early life-threatening toxicity and long-term complications associated with conventional allogeneic HSCT in patients with nonmalignant disorders, such as hemoglobinopathies, it is not surprising that great interest and relevant expectations have been raised by the introduction in the clinical practice of reduced-intensity preparative regimens. This approach may represent an effective strategy to reduce the toxicity of transplantation, as shown in canine transplantation models20 and in older debilitated patients with hematologic malignancies,21-24 and may also help reduce the incidence of late effects, in particular those concerning growth and fertility, resulting from high-dose chemotherapy used for conventional HSCT. This novel approach to transplantation, extensively investigated for the treatment of patients with malignancies who are not eligible for standard allograft either because of age or poor medical conditions, is based on immune suppression (mainly achieved with the use of purine analogues like fludarabine) with minimal or limited host myeloablation, but sufficient to achieve donor chimerism, with engraftment of donor T and NK cells. Once T and NK cells of the donor have engrafted, they can either completely eliminate residual host cells, thus leading to a state of complete chimerism, or favor the induction of mixed chimerism sustained over time. Post-transplantation donor lymphocyte infusion (DLI) may also help eradicate residual host hematopoiesis, thus promoting the achievement of either complete or mixed chimerism.22

Support for the concept that reduced-intensity regimens may play an important role in the transplantation strategy of patients with inherited disorders is provided by the observation that stable mixed chimerism (i.e., coexistence of hematopoietic cells of host and donor origin sustained over time) is not uncommon among patients successfully transplanted for hemoglobinopathies from an HLA compatible sibling.4,11,25 Patients with hemoglobinopathies developing stable chimerism, even with a low percentage of donor marrow progenitors (20-30%), have been reported to experience marked enrichment of donor cells in the mature red blood cell compartment, which makes them clinically asymptomatic and transfusion-independent.26 Moreover, studies in the mouse model, aimed at evaluating the effect of mixed chimerism on SCD pathophysiology, have shown that a significant enrichment of erythrocyte over leukocyte chimerism occurred in these mice because of the dramatic survival advantage of donor over sickle red blood cells (RBCs) in the peripheral blood.26 Increasing degrees of erythrocyte chimerism provided progressive correction of hematological and pathologic abnormalities in the mouse model, although sickle bone marrow and splenic hematopoiesis was not corrected until peripheral blood sickle RBCs were fully replaced with donor erythrocytes, indicating that 100% peripheral blood RBC chimerism is the most rigorous benchmark for cure after non-myeloablative allograft.26 The presence of residual host cells may also offer the advantage of reducing the incidence and severity of GVHD, as, in animal models, mixed chimerism is associated with reduced susceptibility to GVHD, probably thanks to mechanisms of central tolerance, with negative selection of host-alloreactive donor T cells.27,28

Having said that the rationale for using reduced-intensity preparative regimens in patients with thalassemia or SCD exists, so far few reports have demonstrated the feasibility of using reduced-intensity preparative regimens for successfully treating patients with hemoglobinopathies,29-33 and results of well-controlled, clinical trials of less toxic conditioning regimens by centers experienced in HSCT are not available. Moreover, unfavorable outcomes in patients given reduced-intensity preparative regimens have been frequently reported, being mainly attributable to the lack of sustained donor engraftment.29,34 In particular, the largest cohort of subjects with hemoglobinopathies (6 with SCD and 1 with thalassemia), reported by Iannone et al, included 7 patients, 6 transplanted with bone marrow cells and 1 with mobilized peripheral blood stem cells, who were prepared for the allograft with nonmyeloablative regimens, which produced minimal toxicity, but resulted in only transient donor engraftment in 6 of them, in any case always followed by late graft failure.34 Graft failure is not a negligible problem even when a conventional preparative regimen is administered.2,6,8,11,25,35 and reduction of the dose of cyclophosphamide in the preparative regimen has been as-
sociated with an increase in rejection (particularly in patients who had received less than 100 RBC transfusions before transplantation). Several factors may explain the high incidence of graft failure after an allograft in patients with hemoglobinopathies, including previous sensitization to alloantigens through repeated transfusions, no chemotherapy treatment before HSCT and, in patients with thalassemia, expanded erythropoietic marrow together with splenomegaly. It is reasonable to hypothesize that reduced-intensity preparative regimens could further increase this risk and that, for successful transplantation, stem cell doses higher than those attainable with marrow harvesting would be needed. This means a preferential use of donor mobilized peripheral blood hematopoietic stem cells, a practice that raises concerns when the donor is a minor and because of the increased risk of chronic GVHD suggested by some studies. Moreover, the use of DLI for obtaining a stable chimerism may promote the development of severe, life-threatening or invalidating GVHD.

The available evidence indicates that the barrier to stable full or partial donor engraftment after minimally toxic regimens employed for HSCT in patients with hemoglobinopathies seems more difficult to overcome than in adults with hematological malignancies. The use of intermediate-intensity regimens displaying both immune suppression and myelosuppression to prevent host-versus-graft reaction and promote engraftment, although more effective in inducing full donor chimerism, was in some cases associated with an increased risk of regimen-related toxicity and severe GVHD, occasionally facilitated by recourse to DLI.

Therefore, we may ask, should we abandon this approach in patients with hemoglobinopathies for the future years and is there room for ameliorating the preparation of these patients to the allograft? An affirmative answer to the first question is probably premature. In fact, reduced intensity preparative regimens may find their appropriate application in older patients or in those with poor performance status and/or organ dysfunction, predicting a high risk of life-threatening complications if a fully myeloablative regimen is employed.

The second question deserves a more structured answer. Certainly, an evolution of the approach used for conventional myeloablative regimens is desirable, and some recent reports prove that pretransplant therapy can be optimized in terms of reduction of the risk of both graft failure and TRM. In fact, a more recent survey, reporting on a limited number of class 3 thalassemia patients, has suggested that the adoption, during the 2 months preceding HSCT, of a hypertransfusion regimen, intended to reduce the expansion pressure on the erythron, together with the use of azathioprine and hydroxyurea to suppress hematopoiesis and fludarabine for reducing the risk of rejection, may lower the probability of treatment failure and improve post-transplant outcome in this subgroup of patients; the reported probability of survival with transfusion independence was 85%. The addition of thiotepa to the preparative regimen and the substitution of cyclophosphamide with fludarabine, a drug displaying comparable immune suppression with lower extra-medullary toxicity, were also shown to improve the outcome of patients with thalassemia transplanted from an unrelated volunteer or with cord blood progenitors. Use of intravenous busulfan should also reduce the risk of either inappropriately low (in some reports demonstrated to predict the occurrence of graft failure) or excessive systemic exposure to the drug, especially in younger children in whom a marked interpatient variability in plasmatic level of busulfan has been reported after oral administration, due to accelerated clearance, wider distribution volume and unpredictable intestinal absorption. Likewise, new opportunities could be offered by the new alkylating agent treosulfan, which in the future could represent a valid alternative to busulfan in terms of efficacy and safety.

References

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