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Reduced-Intensity Allogeneic Stem Cell Transplantation in Adults and Children with Malignant and Nonmalignant Diseases: End of the Beginning and Future Challenges

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ABSTRACT

During the last 10 years, multiple studies using reduced-intensity (RI) conditioning followed by allogeneic stem cell transplantation (AlloSCT) have been reported in adult and, less so, pediatric recipients. RI AlloSCT allegedly eradicates malignant cells through a graft-versus-leukemia/graft-versus-tumor effect provided by alloreactive donor T lymphocytes, natural killer cells, or both. Various studies have clearly demonstrated a graft-versus-leukemia/graft-versus-tumor effect in hematologic malignancies and solid tumors. Acute short-term toxicity, including infection and organ decompensation after myeloablative conditioning therapy, can result in a significant incidence of early transplant-related mortality. More importantly, long-term late effects—including growth retardation, infertility, and secondary malignancies—are major complications after myeloablative conditioning therapy, especially in vulnerable children, who are more susceptible to these complications. Recent results comparing RI conditioning with myeloablative conditioning followed by HLA-matched sibling AlloSCT have demonstrated a significant reduction in use of blood products, risk of infections, transplant-related mortality, length of hospitalization, and feasibility of conditioning therapy in outpatient settings. Despite the success of RI AlloSCT, large prospective randomized multicenter studies are necessary to define the appropriate patient population, optimal conditioning regimens and pretransplantation immunosuppression, role of donor lymphocyte infusions, duration of hospitalization, overall survival, cost-benefit ratio, and differences in long-term effects to evaluate the role of RI AlloSCT more fully. We review the recent experience of RI AlloSCT in adults and children with both malignant and nonmalignant diseases and discuss the challenges for the future.

KEY WORDS

Reduced-intensity stem cell transplantation • Nonmyeloablative transplantation • GVL • GVHD

INTRODUCTION

Allogeneic hematopoietic stem cell transplant (AlloSCT) from related or unrelated histocompatible donors has been well established as potentially curative therapy for children and adults with selected hematologic malignancies [1]. The concept of AlloSCT as a treatment option for hematologic malignancies has long been based on the assumption that myeloablative doses of cytotoxic therapy were required for both disease eradication and host immunosuppression. Several observations, however, have challenged the dogma that high-dose cytotoxic therapy was a sine qua non for disease eradication with AlloSCT. These observations include (1) decreased relapse rates in recipients of AlloSCT compared with autologous or syngeneic stem cell transplants (SCT) [2]; (2) increased risk of relapse after T cell–depleted compared with unmodified allografts [3]; (3) decreased risk of relapse in patients who develop acute or chronic graft-versus-host disease (GVHD) after allografting [4-10]; and (4)

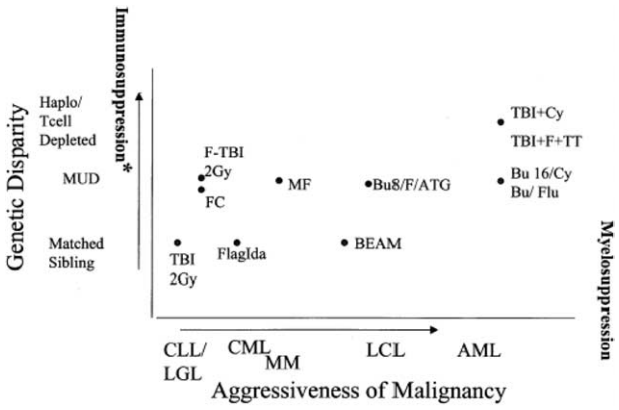

Figure 1. The most widely used preparative regimens in nonmyeloablative stem cell transplantation and conventional transplantations. The aggressiveness of the underlying malignancy and the donor-recipient genetic disparity, the recipient's immunocompetence, and sensitization are important in the decision-making process for each clinical situation. MUD indicates matched unrelated donor; CLL/LGL, chronic lymphocytic leukemia/low-grade lymphoma; CML, chronic myelogenous leukemia; LCL, large-cell lymphoma; AML, acute myelogenous leukemia; MM, multiple myeloma; F-TBI 2 Gy, fludarabine and total body irradiation (TBI) 2 Gy; FlagIda, fludarabine, cytosine arabinoside, and idarubicin; MF, melphalan and fludarabine; BEAM, carmustine, etoposide, cytosine arabinoside, and melphalan; Bu8/F/ATG, busulfan 8 mg/m^2, fludarabine, and antithymocyte globulin; TBI+Cy, TBI and cyclophosphamide; TBI+F+TT, TBI, fludarabine, and thiotepa; Bu 16/Cy, busulfan 16 mg/m^2 and cyclophosphamide; Bu/Flu, busulfan (escalated doses) and fludarabine. *The immunosuppression required depends on the genetic disparity, immunocompetence, and sensitization of the recipient. Reprinted with permission from Elsevier Ireland Ltd [17].

remission induction after donor lymphocyte infusion (DLI) in some patients whose disease had relapsed after SCT [11-16]. Taken together, these observations suggested that immune cell genetic disparities between donors and recipients also included graft-versus-tumor (GVT) effects capable of eradicating the underlying host malignancy. These observations, in addition to better ways of controlling both host and donor immune reactions, led to reassessment of strategies for AlloSCT. Specifically, instead of eradicating tumors through intensive and, thereby, toxic chemoradiation, the SCT donor's immune cells might be used for that purpose, relying on allogeneic GVT effects. Elimination of high-dose cytotoxic therapy would then allow elderly or medically infirm patients to be treated with SCT.

There is a substantial heterogeneity between various reduced-intensity (RI) conditioning regimens in terms of dose of chemotherapy and radiotherapy and degree of immunosuppression [17] (Figure 1). As a working definition, a truly nonmyeloablative regimen should not eradicate host hematopoiesis and should allow relatively prompt hematopoietic recovery (<28 days) without a transplantation [18]. Upon engraftment, mixed chimerism should be present. If the graft is rejected, prompt autologous recovery should occur. Conversely, an ablative regimen requires hematopoietic transplantation for recovery, and complete chimerism occurs upon engraftment. Many of the reduced-toxicity regimens referred to as nonmyeloablative have not been documented to meet these criteria [19]. These regimens require a transplantation for hematologic recovery, and if the graft is rejected, prolonged aplasia typically occurs. These should be referred to as "reduced-toxicity" ablative regimens [20]. This distinction in intensity of regimens is crucial to differentiate the graft-versus-leukemia (GVL) effects of donor engraftment from the antitumor effect of the conditioning regimen.

The theoretical reduction in incidence of acute GVHD after RI AlloSCT may be due to limited tissue damage in the recipient. This may translate into decreased cytokine storm, which has been described after myeloablative conditioning therapy to provide a proinflammatory milieu for the development of acute GVHD [21,22]. Also, studies in animals have demonstrated that the development of transient mixed donor-host chimerism may facilitate establishment of mutual tolerance, which, in turn, may downregulate graft-versus-host (GVH) activity [23,24]. Several years ago, Storb et al. [25] and Georges et al. [26] originally demonstrated the ability to achieve mixed and, ultimately, complete donor chimerism after RI conditioning (200 cGy) in dog leukocyte antigen–identical canine allogeneic transplant recipients and subsequently demonstrated the successful ability to administer DLI as potential adoptive cellular immunotherapy after RI conditioning in a similar animal model. Subsequently, the group from Israel [27] demonstrated the initial early results of this approach in humans with refractory hematologic malignancies with comorbid features. In this article, we review the recent experience of RI AlloSCT in adults and children with both malignant and nonmalignant diseases and discuss the challenges for the future.

RI AlloSCT FOR ADULT ACUTE MYELOID LEUKEMIA AND MYELODYSPLASTIC SYNDROME

The median age of presentation in acute myeloid leukemia (AML) is more than 60 years, and the adequate management of AML in older patients remains the major challenge. Because of an increase in comorbidities such as infections and impaired organ function, the arbitrary age limit for intensive conditioning therapy before allogeneic transplantation in patients with AML is between 50 and 55 years. RI AlloSCT might be one way to reduce the substantial treatment-related mortality of older patients and thus provide the curative potential of allogeneic cell therapy. How-