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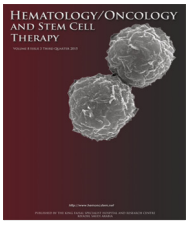

Reduced-intensity versus myeloablative allogeneic transplantation

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Abstract
Allotransplantation cures patients by cytoreduction and the graft-versus-tumor (leukemia; graft-versus-leukemia [GVL]) alloresponse; both eliminate residual disease. The spectrum of conditioning intensity influences toxicities and non-relapse mortality. The spectrum of tumor sensitivity to the GVL response influences relapse. Balancing tolerable toxicities (influenced by patients' performance status and comorbidities) is also influenced by the graft. Intense immunosuppression (for engraftment and graft-versus-host disease prevention) may constrain the immunologic potency of the graft and limit the antineoplastic capacity of the transplant, thus requiring more intense or more effective conditioning regimens to limit the risks of relapse and permit satisfactory disease-free survival.
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Introduction

Allotransplantation cures patients by cytoreduction of their residual tumor and by allowing the antineoplastic effects of the graft-versus-tumor (leukemia; graft-versus-leukemia [GVL]) alloresponse to eliminate residual disease. While conditioning intensity has a spectrum which influences transplant toxicities and non-relapse mortality (NRM), there is also a spectrum of tumor sensitivity to the GVL response. Some diseases (chronic myelogenous leukemia, follicular lymphoma, chronic lymphocytic leukemia) are highly GVL responsive and in those situations, a lesser intensity, better tolerated conditioning regimen may suffice. However, other more resistant diseases (advanced acute leukemia, high-risk cytogenetic or molecular phenotype leukemia or even remission leukemias with detectable minimal residual disease) may escape control with even more intense regimens. They may be particularly vulnerable to relapse following reduced-intensity conditioning (RIC) transplantation.

This clinical dilemma balancing tolerable toxicities (influenced by patients' performance status and associated comorbidities) and influenced by the graft source may

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require lesser intensity regimens to ensure safety. However, intensive immunosuppression may be required to facilitate engraftment, particularly using umbilical cord blood or mismatched donor grafts. More intense immunosuppression for graft-versus-host disease (GVHD) prophylaxis, including graft T-cell depletion, use of anti-thymocyte globulin or alemtuzumab, may constrain the immunologic potency of the graft, thereby limiting the antineoplastic capacity of the transplant procedure. Particularly in these circumstances, more intense or more effective conditioning regimens must be employed to limit the risks of relapse and yield satisfactory disease-free survival [1].

Myeloablative versus reduced-intensity versus non-myeloablative regimens

Consensus discussions reported from the Center for International Blood and Marrow Transplant Research (CIBMTR) have defined myeloablative or high-dose regimens, most often including single or multiple alkylators and sometimes including total body irradiation (TBI) [2]. These high-dose regimens are called myeloablative because they preclude hematologic recovery in the setting of graft rejection. Additionally, they are profoundly myelosuppressive and thus, induce pancytopenia promptly after transplantation. Non-myeloablative regimens are less myelosuppressive, although potently immunosuppressive, to facilitate engraftment of matched donor cell infusions, but offer little in antineoplastic potency [3]. Majority of transplants, particularly in older people, are now performed using intermediate intensity or RIC, which generally use lower dose alkylator or even intermediate to low dose TBI. They occasionally are called reduced-toxicity regimens.

Myeloablative regimens

Cyclophosphamide and TBI or busulfan plus cyclophosphamide have been the long standing and most commonly

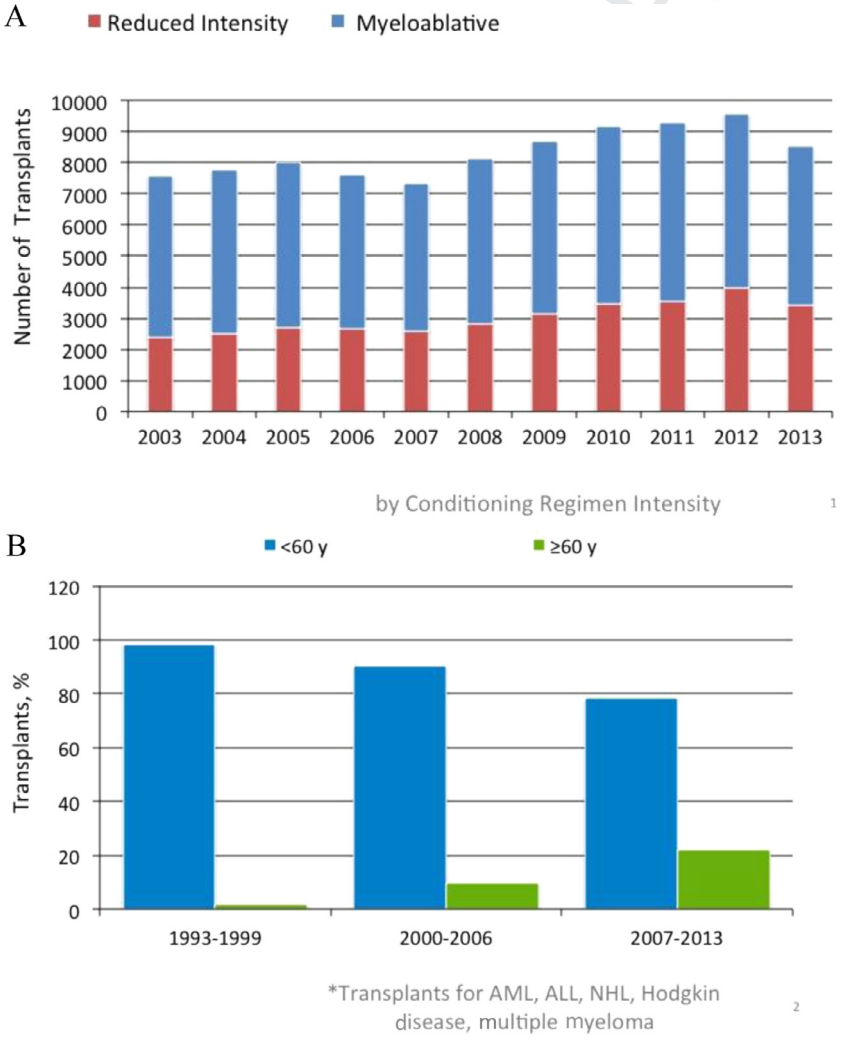

Fig. 1 Increasing utilization of RIC transplantation (CIBMTR); adapted from CIBMTR Summary slides (2015). (A) Allogeneic transplants registered with the CIBMTR. (B) Increasing allogeneic transplant recipients >60 years-of-age. ALL = acute lymphoblastic leukemia; AML = acute myeloid leukemia; CIBMTR = Center for International Blood and Marrow Transplant Research; NHL = non-Hodgkin lymphoma; RIC = reduced-intensity conditioning.

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