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Report

Proceedings from the National Cancer Institute's Second International Workshop on the Biology, Prevention, and Treatment of Relapse after Hematopoietic Stem Cell Transplantation: Part III. Prevention and Treatment of Relapse after Allogeneic Transplantation

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A B S T R A C T

In the Second Annual National Cancer Institute's Workshop on the Biology, Prevention, and Treatment of Relapse after Hematopoietic Stem Cell Transplantation, the Scientific/Educational Session on the Prevention and Treatment of Relapse after Allogeneic Transplantation highlighted progress in developing new therapeutic approaches since the first relapse workshop. Recent insights that might provide a basis for the development of novel, practical clinical trials were emphasized, including utilization of newer agents, optimization of donor lymphocyte infusion (DLI), and investigation of novel cellular therapies. Dr. de Lima discussed pre-emptive and maintenance strategies to prevent relapse after transplantation, for example, recent promising results suggestive of enhanced graft-versus-tumor activity with hypomethylating agents. Dr. Schmid provided an overview of adjunctive strategies to improve cell therapy for relapse, including cytoreduction before DLI, combination of targeted agents with DLI, and considerations in use of second transplantations. Dr. Porter addressed strategies to enhance T cell function, including ex vivo activated T cells and T cell engineering, and immunomodulatory approaches to enhance T cell function in vivo, including exogenous cytokines and modulation of costimulatory pathways.

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INTRODUCTION

Cancer relapse remains the major cause of treatment failure after allogeneic hematopoietic stem cell transplantation (AlloSCT). In 2009, the first National Cancer Institute–sponsored workshop on the biology, prevention, and treatment of relapse published extensive reviews of disease-specific prevention and treatment strategies [1,2]. Progress in prevention and treatment was emphasized in the second workshop as well and focused on ideas that might provide a basis for the development of novel, practical clinical trials. Use of new agents, optimal utilization of donor lymphocyte infusion (DLI) and immunomodulatory therapeutics, and investigation of targeted interventions (eg, genetically modified donor cells) and of novel cellular therapies are areas of ongoing study in the field. Promising advances reported since the first workshop are discussed here.

I. PREVENTION

Prevention is likely the most feasible and effective means of managing relapse after AlloSCT. In the case of acute leukemias, because even extraordinarily low-level minimal residual disease (MRD) is associated with a high risk of relapse, the goal of prevention should be to achieve an MRD-negative state [3]. While most clearly defined for leukemias, the goal of MRD-negative remission is also relevant to relapse prevention for indolent malignancies and after reduced-intensity AlloSCT, that is, in settings where remission is established some time after AlloSCT. Our ability to target prevention interventions at individuals whose cancers have the highest risk of relapse is improvingly rapidly, with emerging data from molecular, proteomic, and genomic tumor investigations leading to better-informed relapse risk

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stratification [4] and increasingly sensitive means of detecting residual disease [5-7]. Precise application of pre-emptive strategies that permit intervention when the burden of disease is minimal could improve our ability to eradicate malignancy before overt relapse. Indeed, many investigational treatments—even with modest efficacy in established relapse—might significantly improve AlloSCT outcomes if applied in the preventive setting. Preventive therapy decisions pose a dilemma: Withholding potentially efficacious therapy until relapse is detected compromises the patient's chance of cure, yet administering potentially toxic therapy without evidence of relapse results in overtreatment for some. Toxicity is a major concern in preventive therapy, particularly in the early months after AlloSCT, when side effects (eg, myelosuppression, rash, diarrhea) and drug interactions present significant management challenges, yet also when relapse often occurs and intervention might be most effective [8].

Strategic aims of prevention include (1) improving disease control before AlloSCT, (2) increasing graft-versus-tumor (GVT) potency of the transplant, (3) maintaining disease control while the allograft matures, and (4) detecting and pre-empting an impending relapse (Table 1). Preventing relapse in individuals whose cancers are active or demonstrate high-risk biology may require the use of multiple strategies.

Pretransplantation approaches may permit use of agents with significant hematologic toxicity but require pharmacokinetic consideration of potential effects on donor stem cell and lymphocyte populations. Use of novel agents (targeting signaling pathways, growth factors, cell surface antigens, etc.) may deepen remissions through effects on cancer cells or the tumor microenvironment and thus improve outcomes. A role for novel agents in the pretransplantation setting is suggested by observations of improved AlloSCT outcomes after their use in "bridge" therapy, such as with tyrosine kinase inhibitors in Philadelphia chromosome–positive acute lymphoblastic leukemia (ALL) [9] and brentuximab vedotin in Hodgkin's lymphoma [10]; distinct toxicity profiles and unique mechanisms of action have led to investigation of incorporating monoclonal antibodies into reduced-intensity conditioning regimens, resulting in immunomodulatory as well as direct antitumor effects [11]. New cancer drugs with novel targets and innovative methods of drug delivery are entering the clinic at a phenomenal rate; their potential to permit or augment GVT is an important research opportunity.

Transplant modifications to potentiate GVT effects may incorporate donor selection tactics, immunotherapeutic maneuvers, and tumor-specific immunotherapies. Recent advances in our understanding of natural killer (NK) immunogenetic influences on transplantation outcome, including relapse risk (particularly in acute myelogenous leukemia [AML]) may yield opportunities to prevent relapse through donor selection based on KIR genotyping in the context of HLA mismatch [12]. Early withdrawal of immune suppression, with or without prophylactic DLI, is another consideration in patients at very high risk of relapse, but randomized trial data are lacking and there is significant risk of graft-versus-host disease (GVHD) [13]. Furthermore, when used to pre-empt impending or early leukemia relapse, these immunotherapeutic maneuvers appear to have limited activity outside of chronic myelogenous leukemia and result in considerable GVHD morbidity [14]. The morbidity of prophylactic DLI may be reduced in the setting of T cell–depleted allografts or mixed chimerism [15,16]. Interestingly, preliminary results of administering ex vivo activated DLI prophylaxis suggest fairly modest GVHD toxicity after reduced-intensity conditioning AlloSCT with alemtuzumab [17]. Efforts to optimize selective subset depletion of DLI (or allograft) continue, attempting to reduce risk of GVHD while maintaining protection from relapse [18].

Table 1
Strategies for Relapse Prevention

Improved preparative therapy
• Incorporating new drugs with stronger antileukemia activity and/or less toxicity without compromising dose intensity
• Examples under investigation: monoclonal antibodies (radiolabeled or not), clofarabine, and treosulfan
Graft engineering
• Allograft enrichment with leukemia- or lineage-specific cytotoxic T lymphocytes
• Graft depletion of alloreactive T cells
• NK cell enrichment or adoptive transfer
Pre-emptive treatment
• Monitoring for MRD (cytogenetics, PCR, flow cytometry, etc.)
• Intervention based on detection of MRD
• Therapeutic approaches: pharmacologic, immunologic, and cellular therapies
Early withdrawal of immunosuppression
• High risk of GVHD may offset reduced relapse risk
Maintenance
• Relapse risk defined by pretransplantation parameters (eg, advanced disease stage, presence of high-risk karyotype or genetic mutation, or detection of MRD before and/or after AlloSCT)
• Therapeutic approaches: pharmacologic, immunomodulatory, and cellular therapy
• Approaches under investigation (AML): azacitidine, FLT3 inhibitors
Ideal maintenance agent
• Documented activity against the disease
• Acceptable nonhematologic toxicity (will be tolerated early after transplant)
• Acceptable myelotoxicity (will not interfere with engraftment)
• Minimal drug interactions
• Will not inhibit GVT
• Will not worsen GVHD
Caveats to maintenance strategies
• Dose is likely to be lower than in other scenarios
• Dose escalation trials are essential and randomized trials ultimately necessary given multiples confounding variables

There has been significant progress in developing tumor-targeted immunotherapies, including tumor vaccines, genetically modified T cells (discussed below in III. Strategies to Enhance T Cell Function), and selectively expanded antigen-specific T cells [19]. The early post-transplantation period may be an ideal time for their administration, when minimal tumor burden coincides with lymphopenia-induced homeostatic cytokine abundance and increased efficiency of antigen-specific lymphocyte proliferation[20]. The use of novel (eg, targeted) agents in maintenance therapy requires phase I evaluation of cumulative and overlapping toxicities (eg, with conditioning and immunoprophylaxis agents), with particular attention to effects on rapidly expanding progenitor and lymphocyte populations.

Maintenance therapeutics may be effective in relapse prevention, providing early tumor control and, potentially, immunomodulatory support for the development of an allogeneic immune response. Acute leukemia relapse poses a particularly great management challenge after AlloSCT due to rapid cell growth and disease progression once recurrence is detected; as such, maintenance approaches for acute leukemia may be informative in indolent malignancies as well. A phase I trial at M.D. Anderson defined a safe, low-dose azacitidine maintenance regimen (32 mg/m^2/day, days 1-5 of

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