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REVIEW ARTICLE

Reduced intensity conditioning for hematopoietic stem cell transplantation: has it achieved all it set out to?

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Abstract

At its inception, reduced intensity conditioning (RIC) was heralded as a means to limit toxicity after hematopoietic stem cell transplantation (HSCT), especially for the older patient demographic. The aim was to promote the inherent anti-leukemic activity of the transplant whilst reducing toxicity and transplant-related mortality (TRM). More than 10 years on, much has been learnt about the role of conditioning in determining outcomes after transplantation. The use of RIC as a preparative regimen has increased the number of patients that can benefit from HSCT because the initial therapy is less toxic. However, many of the early pioneers of RIC quickly realized that the toxicity from graft-versus-host disease (GvHD) was equally as potent as that from conditioning. Furthermore, questions remain concerning the efficacy of RIC regimens in retaining anti-leukemic immunity, especially in cases of aggressive disease. The undoubted synergy between chemotherapeutic and immunologic treatment of malignancy means that reduction of conditioning intensity to minimal levels may not be entirely logical.

Key Words: *delayed-onset graft-versus-host disease, hematopoietic stem cell transplantation, myeloablative conditioning, patient outcome, reduced intensity conditioning*

Introduction

Allogeneic hematopoietic stem cell transplantation (HSCT) is increasingly being offered to older patients as a curative therapy for hematologic malignancies. The number of patients transplanted in the 51–60-year age bracket has risen from less than 5% of all transplants carried out in 1990, to 20% of HSCT in the last 15 years (1). Despite its curative potential, however, patient outcome after allogeneic HSCT remains limited by treatment failures such as disease relapse and non-relapse mortality (NRM). NRM can occur from regimen-related toxicities (RRT) as well as engraftment failure, infections, veno-occlusive disease, interstitial pneumonia and graft-versus-host disease (GvHD) (2), which are all exacerbated to some extent by the intensity of pre-transplant conditioning. This review will discuss the impact of reduced intensity conditioning (RIC) regimens on patient outcome post-transplant.

Myeloablative conditioning

HSCT traditionally relied on myeloablative conditioning (MAC) regimens to ablate underlying hematologic malignancy and control graft rejection post-transplant. However, the toxicity associated with these regimens has limited their use to younger patients in good condition (3,4). Preparative MAC regimens serve to facilitate normal hematopoietic reconstitution, with complete lymphocyte chimerism usually occurring within 30 days after MAC (5). MAC regimens initially consisted solely of total body irradiation (TBI) administered at levels that could eradicate all lymphoid and myeloid stem cells of the body. The alkylating agent cyclophosphamide (CY), which acts primarily on proliferating cells, was included to improve disease control (6). Shortly thereafter, another alkylating agent, busulphan (BU), proved to be an effective alternative to TBI (7). To reduce the incidence of relapse and graft failure

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after transplantation, the intensity of these regimens was steadily increased in the clinic. However, the desirable effects of MAC were offset by its associated toxicities and considerable transplant-related mortality (TRM). High-dose TBI in particular can cause extensive damage to the epithelial cells of the gastrointestinal tract, which in turn promotes the release of lipopolysaccarides (LPS) from the intestinal lumen into the mucosa (8,9). MAC regimens also cause prolonged immunodeficiency and damage mucosal tissues (10) such as the mouth, gastrointestinal tract and skin (11,12). This creates an ideal environment for opportunistic bacterial, fungal and viral pathogens. Furthermore, chemotherapeutics such as CY and BU have been associated with an increased incidence of hemorrhagic cystitis and hepatic veno-occlusive disease (13,14). In addition, the conditioning-induced release of pro-inflammatory cytokines, tumor necrosis factor (TNF)-α and interleukin(IL)-1β (10,15), and secondary signals such as LPS, can increase the expression of major histocompatibility complex (MHC) antigens and adhesion molecules on recipient antigen-presenting cells (APC) and enhance their recognition by donor T cells (16). T-cell proliferation, differentiation and effector cell expansion can then cause further damage to host tissues, culminating in the overt clinical symptoms of GvHD (17). While MAC may be more effective for disease eradication in patients of all ages with poor prognosis, acute myeloid leukemia (AML), acute lymphoid leukemia (ALL) or chronic myeloid leukemia (CML) in the pre-Glivec era, its associated toxicities are a major consideration for the overall survival (OS) of transplant patients. With today's increasingly aging population, MAC effectively limits the number of patients that can undergo transplantation.

RIC

Insight into the anti-leukemic effect of HSCT in the late 1990s prompted a move away from intensive pre-transplant conditioning and toward regimens that were immunosuppressive enough to promote engraftment and eradicate tumors without the toxicities associated with full myeloablation (12,18). These new RIC regimens were based on the purine analog, fludarabine (FLU), which induces lymphocyte apoptosis by acting on DNA synthesis and cell cycle progression (18–21). The success of initial attempts soon prompted many other groups to focus on preparative conditioning that could promote engraftment without the added complications of toxicity, especially in patients with contraindications for conventional therapy (22–24). Immunosuppressive conditioning regimens are now commonly used in the clinic to facilitate the engraftment of hematopoietic stem cells (HSC) and eradicate tumors (5,23–31). RIC regimens can be loosely separated into two categories: myelosuppressive RIC regimens (hereafter referred to as RIC) and non-myeloablative RIC regimens (hereafter referred to as NMC). NMC regimens combine low-dose irradiation (e.g. 2 Gy TBI) with highly immunosuppressive drugs such as FLU (3,29), whereas the RIC regimens generally consist of FLU in concert with other chemotherapeutics such as CY, BU and melphalan (MEL) (19,25,29,32). The extensive range of RIC regimens currently being used in the clinic can make meaningful comparisons, especially between different patient groups, practically impossible. This variation in conditioning intensity can result in significantly different immunologic responses in the post-transplant period, as evinced by the altered kinetics of GvHD (26,27). Several interesting features of RIC regimens have been observed in the clinic. After RIC there is a reduction in the severity and duration of neutropenia (33), important mucosal and dermal barriers remain intact (34) and, in the absence of T depletion, a higher number of antigen-specific T cells [i.e. cytomegalovirus (CMV-specific) are present (5)]. These conditions directly reduce the risk of post-transplant complications such as organ toxicity and infection. This in turn has led to a reduction in TRM and an increase in the number of older patients (with peak disease incidence) and patients with non-hematologic malignancies who can benefit from the immune effects of HSCT (3,23,28). An extensive review on the various RIC regimens has been published previously (35). The more commonly used RIC and NMC regimens are summarized in Table I.

Current status of RIC

Toxicity

Significant reductions in NRM and regimen-related toxicities have underpinned the increasing use of RIC to replace MAC as the preparative therapy prior to transplants. Significantly, more than 35% of all allogeneic transplants reported to the Centre for International Bone Marrow Transplant Registry used RIC in 2006, with up to 83% of patients aged $>$60 years receiving RIC (1). NRM and RRT have been compared in 73 NMC and 73 MAC human leukocyte antigen (HLA)-matched related HSCT recipients (36). NMC recipients in this cohort were considered to be a high-risk group because of several mitigating factors, such as increased age and co-morbidity index. Regardless of this, NRM at day 100 (NMC 3% versus MAC 23%, $P = 10^{-4}$) and at