BLOOD RESEARCH
Volume 50 · Number 2 · June 2015
http://dx.doi.org/10.5045/br.2015.50.2.69

Perspective

Reduced-intensity conditioning hematopoietic stem cell transplantation: looking forward to an international consensus

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The treatment for hematological malignancies has excelled over the past decade. A vast number of hematological malignancies are now amenable to cure with hematopoietic stem cell transplants (HSCTs) [1]. Older patients with comorbidities are poor candidates for standard myeloablative conditioning (MAC). While myeloablative therapy remains the standard curative conditioning regimen in the treatment of malignant disorders such as acute myeloid leukemia, its use is limited to patients in the younger age group, and to those in good physical health. Therefore, the older population is generally unsuited to this form of treatment, even though most hematological malignancies are often diagnosed at the age of 70–80 years. The advent of reduced-intensity conditioning (RIC) has provided these patients with a viable treatment option.

Prior to undergoing HSCT, patients are treated with a conditioning regimen. This not only decreases the tumor burden, but also maximizes the capability of the donor cells to engraft successfully by suppressing the patient's immune system. Conditioning regimens vary in the amount of agent used. These compounds are often used at highly toxic dosage levels that are required to induce an immunocompromised state through a cytoreductive effect [2]. Over the past decade, conditioning regimens have considerably evolved with the development of RIC. These regimens are composed of reduced doses of cytotoxic agents in addition to a T-cell depleting agent [3]. The most commonly used regimens include fludarabine in combination with low-dose total body irradiation, or an alkylating agent such as busulfan, cyclophosphamide, or melphalan [3]. This treatment modality relies on a graft-versus-leukemia effect and has minimal associated toxicity.

It is difficult to define RIC as it falls into an intermediate category between the MAC and the non-myeloablative regimens, since it does result in prolonged pancytopenia. Sources of donor cells include peripheral blood stem cells, bone marrow, and umbilical cord blood. Peripheral blood stem cells are more commonly used owing to the decreased engraftment time associated with their use [4]. Umbilical cord blood stem cells are a promising alternative source of stem cells with an associated 1-year survival rate of up to 40%, and a 9% incidence of grade III-IV acute graft-versus-host disease (GVHD). However, studies have also reported a transplant-related mortality (TRM) rate of 39–48% associated with use of umbilical cord blood stem cells [5, 6].

Studies assessing the influence of age on the outcomes of RIC treatment have not shown any significant association between the two. Patients in the age group >65 years have a reported non-relapse mortality (NRM) rate of 30% and 34% at 1 and 2 years respectively; whereas in the younger age group (40–54 years), the reported corresponding rates are 21% and 50% respectively [7].

A meta-analysis of results from 13 studies conducted by Zeng *et al.* [8] found no significant difference between MAC and RIC in terms of overall survival rate, event-free survival, and NRM. Furthermore, the incidence of GVHD was significantly lower with RIC. GVHD is an important cause

of mortality associated with the MAC regimen due to the highly toxic doses of agents that are often necessary to eradicate diseased host cells from the bone marrow. The leading causes of death in patients treated with a MAC regimen are GVHD and toxicity. Thus, these findings call for extensive research on RIC regimens. The reported risk of TRM associated with MAC is 20%–60%, whereas RIC is known to be associated with higher overall survival and lower TRM at the same time [9]. A retrospective study on patients with MDS and AML treated with different conditioning regimens revealed a lower NRM in patients treated with RIC; however, there was also an increased risk of relapse in the first 12 months in these patients [10].

Although disease relapse continues to be a complication associated with both treatment regimens, RIC has a relatively higher incidence of relapse. This may be attributable to the additional host factors including, but not limited to, cytogenetics and disease status at the time of allogeneic HSCT.

The use of RIC has opened up new channels to treat malignant hematological disorders in the elderly and patients with multiple comorbidities. With reduction in GVHD, in conjunction with decreased TRM, RIC provides a treatment option for patients who were previously unsuited for standard conditioning regimens. However, the RIC regimens may vary from one center to another and therefore it is conceivable that the differences in outcomes may be related to different procedures and/or different criteria used for decision making by individual physicians. This indicates the need for further studies, particularly in developing countries, so that an international consensus on protocols and guidelines for RIC may be reached.

Authors' Disclosures of Potential Conflicts of Interest

No potential conflicts of interest relevant to this article were reported.

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