ASBMT American Society for Blood and Marrow Transplantation

WORKSHOP REPORT

Reduced-Intensity Conditioning Regimen Workshop: Defining the Dose Spectrum. Report of a Workshop Convened by the Center for International Blood and Marrow Transplant Research

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During the 2006 BMT Tandem Meetings, a workshop was convened by the Center for International Blood and Marrow Transplant Research (CIBMTR) to discuss conditioning regimen intensity and define boundaries of reduced-intensity conditioning (RIC) before hematopoietic cell transplantation (HCT). The goal of the workshop was to determine the acceptance of available RIC definitions in the transplant community. Participants were surveyed regarding their opinions on specific statements on conditioning regimen intensity. Questions covered the "Champlin criteria," as well as operational definitions used in registry studies, exemplified in clinical vignettes. A total of 56 participants, including transplantation physicians, transplant center directors, and transplantation nurses, with a median of 12 years of experience in HCT, answered the survey. Of these, 67% agreed that a RIC regimen should cause reversible myelosuppression when administered without stem cell support, result in low nonhematologic toxicity, and, after transplantation, result in mixed donor–recipient chimerism at the time of first assessment in most patients. Likewise, the majority (71%) agreed or strongly agreed that regimens including $<$ 500 cGy of total body irradiation as a single fraction or 800 cGy in fractionated doses, busulfan dose $<$ 9 mg/kg, melphalan dose $<$140 mg/m^2, or thiotepa dose $<$ 10 mg/kg should be considered RIC regimens. However, only 32% agreed or strongly agreed that the combination of carmustine, etoposide, cytarabine, and melphalan (BEAM) should be considered a RIC regimen. These results demonstrate that although HCT professionals have not reached a consensus on what constitutes a RIC regimen, most accept currently used criteria and operational definitions. These results support the continued use of current criteria for RIC regimens until a consensus statement can be developed.

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INTRODUCTION

Patients undergoing allogeneic hematopoietic stem cell transplantation (HCT) are prepared with chemotherapy and/or radiotherapy to reduce the tumor burden and facilitate engraftment of donor hematopoietic cells [1]. Increasing the dose intensity of the conditioning regimen to improve outcomes by reducing the risk of relapse has produced no major changes in survival, because of increases in nonrelapse mortality (NRM) that offset any benefits obtained from better disease control [2].

The past decade has seen a major paradigm shift in the field of HCT. In an effort to explore graft-versus-disease effects without major regimen-related toxicity, many investigators have lowered the dose of radiation or alkylating agents used in the conditioning regimen [2-8]. These regimens are known as nonmyeloablative (NMA) or reduced-intensity conditioning (RIC) regimens. This nomenclature was chosen because many of these regimens are administered without stem cell support, and the doses of agents delivered are substantially lower than those used in a traditional conditioning regimen.

Defining what constitutes a RIC regimen is an important issue that the transplantation community

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needs to address to perform adequate retrospective and prospective analyses of different regimens. At the First International Workshop of Nonmyeloablative Stem Cell Transplantation, Dr Richard Champlin proposed a set of criteria that an RIC regimen should fulfill [9]. These so-called "Champlin criteria" define as reduced intensity any regimen that does not require stem cell support for hematopoietic recovery and that results in low nonhematologic toxicity and mixed donor–recipient chimerism in a substantial proportion of patients in the early posttransplantation period (around day +30) [9,10].

As part of the initial retrospective analysis of the outcomes of RIC regimens in recipients of unrelated donor hematopoietic stem cells, the National Marrow Donor Program (NMDP) and the Center for International Blood and Marrow Transplant Research (CIBMTR) had a Expert Panel develop an operational definition of what regimens should be considered RIC [11]. Even though these definitions were based as much as possible on available data, they still reflect the Panel members' biases and opinions, and they are not universally accepted, although similar definitions have been adopted by the European Bone Marrow Transplant Registry (EBMT) [12-14]. To assess the acceptability of these criteria, a workshop was convened during the 2006 BMT Tandem Meeting. Here we summarize the findings of this workshop.

METHODS

During the 2006 BMT Tandem meeting, the Organizing Committee assigned Drs Sergio Giralt and Brenda Sandmaier to chair a workshop addressing the issue of defining regimen intensity. The chairs agreed that they would use the workshop to demonstrate the acceptability of current available criteria for RIC regimens among the transplantation community, and propose modifications as deemed appropriate. To achieve the workshop's primary goal, a survey was administered to persons representing various groups in the transplantation community, including workshop attendees, members of the CIBMTR's Regimen-Related Toxicity Working Committee, members of the Blood and Marrow Transplant Clinical Trials Network (BMT CTN) Steering and Toxicity Committees, and randomly selected transplantation program directors. The survey comprised a series of questions, some illustrated through clinical vignettes, regarding currently used criteria for RIC regimens, as well as operational definitions used by the CIBMTR to determine whether a specific regimen or combination of agents should be considered an RIC regimen.

Participants were instructed to state whether they strongly agreed, agreed, disagreed, or strongly disagreed with specific statements. The first assessment included questions related to the acceptability of the Champlin criteria in defining the general characteristics of an RIC regimen (9). According to these criteria, an RIC regimen results in reversible myelosuppression (usually within 28 days) when given without stem cell support, results in mixed chimerism in a proportion of patients at the time of first assessment (usually 28 to 35 days after stem cell transplantation), and has a low rate of nonhematologic toxicity. The second assessment evaluated the transplantation community's acceptance of the operational definitions used by the NMDP and the CIBMTR for retrospective analysis (11). This operational definition identifies as an RIC regimen any regimen that includes (a) total body irradiation (TBI) of $\leq$ 500 cGy as a single fraction or $\leq$ 800 cGy if fractionated, (b) $<$ 9 mg/kg of oral busulfan (or intravenous equivalent), (c) $<$ 140 mg/m^2 of melphalan, (d) $<$ 10 mg/kg of thiotepa, (e) the BEAM regimen (carmustine, etoposide, cytarabine, and melphalan) (15). The results were collected and summarized using descriptive statistical methods.

RESULTS

A total of 56 HCT professionals, representing 44 institutions from 9 different countries, answered the survey. Their demographic information, as well as other characteristics, are summarized in Table 1.

Champlin Criteria

Of the 56 respondents, 67% either strongly agreed or agreed to the first criterion regarding reversible myelosuppression, and 71% either agreed or strongly agreed with the next 2 criteria for what constitutes an RIC regimen. These results are summarized in Table 2.

NMDP/CIBMTR Operational Definitions

More than 60% of the respondents agreed or strongly agreed with the first 4 operational definitions of what constituted an RIC regimen, however, only 32% agreed or strongly agreed that the BEAM combination qualified as an RIC regimen. These data are summarized in Table 3.

Table 1. Characteristics of Survey Respondents

Number of respondents	56
Age, years, median (range)	48 (30 to 60)
Male sex, n	43
Occupation, n	
MD > 50% clinic	40
MD ≤ 50% clinic	14
Nurse	2
Years of SCT experience, median (range)	12 (0 to 52)*
Annual number of SCTs, median (range)	140 (0 to 900)*

*One respondent was a retired transplantation physician and a current transplant recipient who currently works for a pharmaceutical company. Another respondent had just finished her residency and was planning to travel to the Amazon region for 3 weeks.

Table 2. Acceptance of the Champlin Criteria as the Characteristics Defining an RIC Regimen

Criteria	Strongly Agree, n	Agree, n	% that Strongly Agree or Agree
Results in reversible myelosuppression (usually within 28 days) when given without stem cell support	26	12	67
Results in mixed chimerism in a proportion of patients at the time of first assessment	18	22	71
Associated with a low rate of nonhematologic toxicity	18	22	71

SUMMARY AND CONCLUSION

Defining conditioning intensity has become an important goal for the transplantation community as the use of RIC continues to increase [15]. Criteria as well as operational definitions for what constitutes a RIC regimen are essential for performing retrospective analyses comparing RIC and non-RIC regimens. In a previous retrospective analysis of the CIBMTR and NMDP database, an Expert Panel provided both criteria and operational definitions for RIC regimens [9-11]. Similar work was done by the EBMT, with similar, although not identical, results [12-14].

The findings of our survey suggest that the Champlin criteria for defining an RIC regimen seem to be widely acceptable. Likewise, 4 of the 5 proposed operational definitions were deemed acceptable by at least 2/3 of the respondents. Only the inclusion of the BEAM regimen was not generally accepted; only 32% of the respondents agreed that BEAM conforms with the criteria for an RIC.

Ultimately, the definition of what constitutes a RIC regimen is also determined by what we define as a myeloablative regimen (ie, a conditioning regimen that cannot be administered without stem cell support). Defining myeloablative conditioning regimens would allow for everything else to be considered an RIC conditioning regimen by default. The CIBMTR and the EBMT are currently working on a consensus statement regarding this issue, which should help clarify nomenclature as well as provide guidelines for classifying novel regimens under investigation. Until such a statement is adopted, the findings from this workshop support continued use of the proposed guidelines and operational definitions.

Table 3. Acceptance of the NMDP Operational Criteria for RIC Regimens

Criteria	Strongly Agree, n	Agree, n	% in Top 2
TBI $\leq$ 500 cGy as a single fraction or $\leq$ 800 cGy if fractionated	16	19	62
Total busulfan $\leq$ 9 mg/kg	15	27	75
Total melphalan $\leq$ 140 mg/m^2	13	29	75
Thiotepa < 10 mg/kg	9	28	62
BEAM	1	17	32

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