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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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Abstract

During the 2006 Tandem BMT 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) prior to hematopoietic cell transplantation (HCT).

The goal of the workshop was to determine acceptance within the transplant community of available RIC definitions. The participants were surveyed during the workshop to state if they strongly agreed, agreed, disagreed or strongly disagreed with specific statements on conditioning regimen intensity. The questions included the “Champlin criteria” as well as operational definitions used in registries studies exemplified in clinical vignettes. Fifty-six participants including transplant physicians, transplant center directors and transplant nurses with a median of 12 years of experience in HCT answered the survey. Sixty-seven percent agreed with statements that a RIC regimen should cause reversible myelosuppression when administered without stem cell support; result in low non-hematologic toxicity and after transplantation results in mixed donor-recipient chimerism at the time of first assessment in the majority of patients. Likewise the majority (71%) agreed or strongly agreed that regimens with less than 500 cGy of total body irradiation as a single fraction or 800 cGy in fractionated doses, busulfan less than 9 mg/kg, melphalan less than 140 mg/m2 or thiotepa less than 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) be considered a RIC regimen. These results demonstrate that although a consensus of what constitutes a RIC regimen does not exist among HCT professionals, currently used criteria and operational definitions are accepted by a majority

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of them. These results support the continued use of current criteria for RIC regimens until a consensus statement is developed.

INTRODUCTION

Patients undergoing an allogeneic hematopoietic stem cell transplant (HCT) are prepared with chemotherapy and/or radiotherapy to reduce tumor burden and to facilitate engraftment of donor hematopoietic cells (1). Increasing the dose intensity of the conditioning regimen to improve outcomes by reducing relapse resulted in no major changes in survival due to increases in non-relapse mortality that off-set any benefits obtained from better disease control (2).

Over the last decade a major paradigm shift has occurred in the field of HCT. In an effort to explore graft versus disease effects without major regimen related toxicity, many investigators have lowered the doses of radiation or alkylating agents used in the conditioning regimen.(2–8). These regimens have been variably named non-myeloablative (NMA) or reduced intensity conditioning (RIC) regimens. This nomenclature was chosen since many of these regimens have been administered without stem cell support and the doses of agents delivered are substantially less than what is used in a traditional conditioning regimen.

Defining what constitutes a RIC regimen is an important issue that the transplant community needs to address in order to adequately perform retrospective and prospective analysis among different regimens. During the 1st International Workshop of Non-myeloablative Stem Cell Transplantation, Dr. Richard Champlin proposed a set of criteria that a so called reduced intensity regimen should fulfill (9). The “Champlin Criteria” which defines as reduced intensity any regimen that does not require stem cell support for hematopoietic recovery and that results in low non-hematologic toxicity and mixed donor recipient chimerism in a substantial proportion of patients in the early post transplant 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 “Panel of Experts” develop an operational definition of what regimens should be considered as RIC (11). These definitions were based as much as possible on available data, but still reflect the biases and opinions of the original authors and classifications are not universally accepted although similar definitions have been adopted by the European Bone Marrow Transplant Registry (EBMT) (12–14). In order to assess the acceptability of these criteria a workshop was convened during the 2006 Tandem BMT Meeting. Herein is a summary of the workshops findings.

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 transplant community, and to propose modifications if deemed appropriate. To achieve the primary goal of the workshop a survey was administered to a variety of representative groups within the transplant community including: a) workshop attendees; b) members of the Center for International Blood and Marrow Transplant Registry (CIBMTR) Regimen Related Toxicity Working Committee; c) members of the Blood and Marrow Transplant Clinical Trials

Network (BMT CTN) Steering and Toxicity Committees and d) randomly selected group of transplant program directors. The survey consisted of a series of questions some illustrated through clinical vignettes regarding currently used criteria for RIC regimen as well as operational definitions used by the CIBMTR to determine whether a specific regimen or combination of agents should be considered as a RIC regimen.

Participants were asked to state whether they strongly agreed, agreed, disagreed or strongly disagreed with a specific statement. The first assessment included questions related to the acceptability of "Champlin Criteria" in defining the general characteristics that define a RIC regimen. The criteria utilized were proposed by Champlin in the 1st International Workshop of Non Myeloablative Stem Cell Transplantation (9).

According to this criteria a RIC regimen: 1) results in reversible myelosuppression (usually within 28 days) when given without stem cell support; 2) results in mixed chimerism in a proportion of patients at the time of first assessment (usually 28–35 days post stem cell transplantation); and it is associated with low rates of non hematologic toxicity. The second assessment determined the acceptance among the transplant community of the operational definitions used by the NMDP and the CIBMTR for retrospective analysis (11). This operational definition included as RIC regimens any regimen that consisted of:

1. 500 cGy or less of total body irradiation (TBI) as a single fraction or 800 cGy or less if fractionated.
2. < 9 mg/kg busulfan oral (or intravenous equivalent).
3. <140 mg/m2 melphalan.
4. < 10 mg/kg thiotepa; or
5. BEAM regimen (carmustine, etoposide, cytarabine, and melphalan) (15).

The results were collected and summarized using descriptive statistics.

RESULTS

A total of 56 HCT professionals (representing 44 institutions from 9 different countries) answered the survey; their demographics as well as other characteristics are summarized in Table 1.

Champlin Criteria

Sixty seven percent of respondents either strongly agreed or agreed to the first statement regarding reversible myelosuppression, while 71 percent of respondents either agreed or strongly agreed to the second two criteria for what constitutes a reduced intensity regimen. These results are summarized in table 2.

NMDP/CIBMTR Operational Definitions

More than 60% of participants agreed or strongly agreed with the first four operational definitions of what constituted a reduced intensity regimen, however, only 32% agreed or strongly agreed that the BEAM combination qualified as a RIC regimen. These data are summarized in table 3.

Summary and Conclusion

Defining conditioning intensity has become an important goal for the transplant community as the use of RIC increases (16). Criteria as well as operational definitions for what constitutes a RIC regimen are essential to perform retrospective analysis between "RIC" and

"non RIC" regimens. In previous retrospective analysis of the CIBMTR and NMDP database a panel of experts provided both criteria and operational definitions for RIC regimens (9–11). A similar strategy was undertaken by the EBMT with similar but not identical results (12–14).

The results of this workshop and the survey administered to the participants suggest that the "Champlin Criteria" for defining a RIC regimen seem to be generally acceptable, likewise the operational definitions as proposed were accepted by at least 2/3 of respondents, with BEAM (carmustine, etoposide, cytarabine and melphalan combination) being the most notable exception (only 32% accepting this regimen as conforming with the RIC criteria).

Ultimately the definition of what constitutes a RIC regimen is also determined by what we define as a myeloablative regimen (conditioning regimen that can not be administered without stem cell support). Defining myeloablative conditioning regimens would allow for everything else to be considered a RIC conditioning regimen by default. A Consensus Statement is currently being pursued by the CIBMTR and the EBMT and will be helpful in clarifying nomenclature as well as providing guidelines for classifying novel regimens being investigated. Until such a statement is adopted the results of this workshop support the continued use of the proposed guidelines and operational definitions.

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Table 1

Characteristics of Persons Taking the Survey

N	**56**
Age	48 (30–60)
Sex (n male)	43
Occupation	
MD.>50% clinic	40
MD ≤ 50% clinic	14
Nurse	2
Years SCT experience	12 (0–52)*
Yearly # of SCT	140 (0–900)*

N=number; SCT: Stem cell transplant;

*One respondent was a retired transplant physician and a current stem cell transplant, he currently works for a pharmaceutical company, another respondent had just finished her residency and was planning to go to the amazons for 3 weeks.

Table 2

Acceptance Of “Champlin Criteria” For What Are The Characteristics That Define A Reduced Intensity Regimen

Criteria	N Strongly Agree	N Agree	% 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 low rates of non hematologic toxicities	18	22	71

Table 3

Acceptance of the National Marrow Donor Program Operational Criteria for Reduced Intensity Conditioning Regimens

Criteria	N Strongly Agree	N Agree	% Top 2
500 cGy or less of total body irradiation as a single fraction or 800 cGy or less if fractionated	16	19	62
9 mg/kg or less of total busulfan dose	15	27	75
140 mg/m2 or less total melphalan dose.	13	29	75
Thiotepa less than 10 mg/kg	9	28	62
BEAM	1	17	32