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DEFINING THE INTENSITY OF CONDITIONING REGIMENS : working definitions

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SUMMARY

Defining conditioning regimen intensity has become a critical issue for the hemopoietic stem cell transplant community. In the present report we propose to define conditioning regimens in three categories: (a) myeloablative conditioning (MA) , (b) reduced intensity conditioning (RIC) and (c) non myeloablative conditioning (NMA). Assignment to these categories is based on the duration of cytopenia and on the requirement for stem cell (SC) support: MA regimens cause irreversible cytopenia and SC support is mandatory. NMA regimens cause minimal cytopenia and can be given also without SC support. RIC regimens do not fit criteria for MA or NMA regimens : they cause cytopenia of variable duration and should be given with stem cell support, although cytopenia may not be irreversible. This report also assigns commonly used regimens to one of these categories. based upon the agents, dose or combinations. Standardized classification of conditioning regimen intensities will allow comparison across studies and interpretation of study results.

INTRODUCTION

Patients undergoing an allogeneic hemopoietic stem cell transplant (HSCT), are prepared with chemotherapy alone or chemotherapy combined with radiotherapy , the so called conditioning regimen, with two aims: reduce the tumor burden -when the disease is neoplastic- and suppress the recipient's immune system, in order to allow engraftment of stem cells (1). Exceptions to this rule are infants with combined immune deficiency (SCID) (2) and patients with severe aplastic anemia (SAA) with an identical twin donor, who may be grafted without conditioning.

The intensity of the conditioning regimen can vary significantly. The conventional conditioning for most young patients with leukemia/lymphoma is either cyclophosphamide (CY) 120 mg/kg and total body irradiation (TBI) (10–15 Gy) (referred to as CY-TBI) (3) or busulfan (BU) 16 mg/kg p.o. and CY 120 mg/kg, (referred to as BU-CY) (4). Several attempts have been made in the past 30 years to limit early transplant toxicity, by reducing the intensity of the conditioning regimen: John Hobbs used half the dose of BU (8 mg/kg) in children with inborn errors (5); Peter Tutchka reduced the dose of CY from 200 to 120 in the classic BU-CY regimen (6), and Guido Lucarelli reduced the dose of busulfan from 16 mg/kg to 14 mg/kg for his thalassemia conditioning regimen (7). In contrast some regimens were intensified with the aim of reducing leukemia relapse: the Seattle team delivered 15.75 Gy rather than 12 Gy in patients with leukemia (8). Other investigators introduced the use of etoposide in combination with TBI (9). Very few regimens have been prospectively compared head to head, with the exception of the Seattle TBI regimens (8), and we have no evidence that intensified conditioning improves survival: the reason being that any decrease of leukemia recurrence with a higher dose of TBI is achieved at the expense of increased toxicity (8).

Within the past 15 years two changes have occurred in the conditioning regimens: the introduction of fludarabine (10–13) and further dose reduction of the alkylating agents (14–16) or TBI (17). These regimens, were specifically designed for patients ineligible for conventional conditioning, either because of age (usually above 50 years) or because of the presence of co-morbidities (18). By reducing the intensity of the conditioning regimen, the benefit of allogeneic transplantation would come from a graft-versus-malignancy effect, rather than from the upfront cyto-reductive effect of the conditioning regimen (12). These modified regimens have rapidly become popular, such that by 2001 almost 30% of transplants were performed with reduced intensity regimens (19) .

Regimens using fludarabine and/or reduced doses of chemo/radiotherapy have been referred to as non myeloablative stem cell transplants (NMA), reduced intensity conditioning transplants (RIC) or mini transplants. Several workshops have been convened on this issue: a panel of transplant physicians on behalf of the European Group for Blood and Marrow Transplantation (EBMT) considered the term mini-transplant inappropriate , because it was misleading for patients , care providers, physicians and insurance companies (18). A workshop convened by the CIBMTR addressed the dose spectrum which defines a reduced intensity conditioning regimen (20) . The interest on defining conditioning regimens, is justified by the need of a common language in the scientific community, and also pertains transplant registration and documentation requirements , which are now mandatory in several national and international regulatory agencies.

In the present report we will discuss three categories of conditioning regimens: myeloablative, reduced intensity and non myeloablative. The terminology reflects the early regimen related toxicity towards host marrow cells , and not the biologic effect of the transplant. The latter component is complex, involving engraftment of donor lymphohematopoietic cells, followed by "displacement" of host lympho-hematopoietic cells , through an immune-mediated myeloablation (1).