BRIEF ARTICLES

Defining the Intensity of Conditioning Regimens: Working Definitions

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Defining conditioning regimen intensity has become a critical issue for the hemopoietic stem cell transplant (HSCT) community. In the present report we propose to define conditioning regimens in 3 categories: (1) myeloablative (MA) conditioning, (2) reduced-intensity conditioning (RIC), and (3) nonmyeloablative (NMA) conditioning. 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.

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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 2 aims: reduce the tumor burden—when the disease is neoplastic—and suppress the recipient's immune system, to allow engraftment of stem cells (SCs) [1]. Exceptions to this rule are infants with combined severe 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 orally 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 and colleagues used half the dose of BU (8 mg/kg) in children with inborn errors [5]; Peter Tutchka and his coworkers [6] reduced the dose of Cy from 200 to 120 in the classic Bu-Cy regimen, and Lucarelli et al. [7] reduced the dose of Bu from 16 mg/kg to 14 mg/kg for his thalassemia conditioning regimen. 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

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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, 2 changes have occurred in the conditioning regimens: the introduction of fludarabine (Flu) [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 comorbidities [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 conditioning (RIC) regimens [19].

Regimens using Flu and/or reduced doses of chemo/radiotherapy have been referred to as nonmyeloablative (NMA) SC transplants, RIC transplants, or minitransplants. 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 minitransplant inappropriate, because it was misleading for patients, care providers, physicians, and insurance companies [18]. A workshop convened by the Center for International Blood and Marrow Transplant Research (CIBMTR) addressed the dose spectrum, which defines an RIC 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 3 categories of conditioning regimens: myeloablative (MA), RIC, and NMA. The terminology reflects the early regimen-related toxicity toward 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 lymphohematopoietic cells, through an immune-mediated myeloablation [1].

MYELOABLATIVE CONDITIONING (MA)

The term myeloablation refers to the administration of TBI and/or alkylating agents, at doses that will not allow autologous hematologic recovery. Over 50 years ago Lorenz and coworkers [21] showed that mice exposed to 10 Gy of TBI would succumb to pancytopenia. Work of Lorenz and other outstanding investigators confirmed that animals could be rescued by intravenous administration of a bone marrow (BM) cell suspension [21,22]: BM transplantation (BMT) was born and human studies were initiated [23]. Initial attempts to apply BMT in humans were hampered by the lack of appropriate donor-recipient matching procedures: the discovery of the human leukocyte antigen system (HLA) initiated the widespread clinical use of allogeneic transplants [3,4]. The agents chosen to prepare humans for BMT were TBI, Cy, and Bu, at the dose used in animals: TBI 10 Gy, Cy 200 mg/kg [3] and BU 16 mg/kg [4]. The combinations of Bu-Cy or Cy-TBI are considered to be an MA conditioning regimen. Other agents have been introduced in the conditioning regimen at high doses, and in different combinations with Cy or TBI, usually with the intention of further intensification: these include melphalan (MEL) [24], thiotepa (THIO) [10], etoposide (VP16) [25], and dimethylbusulfan [26].

MA regimens usually produce rapid engraftment of donor cells, which may be followed in a proportion of patients, by graft-versus-host disease (GVHD). MA regimens are associated with toxicity and mortality—referred to as treatment-related mortality (TRM)—depending on variables such as patient age, donor age, donor/recipient HLA matching, sex matching, phase of the underlying disease (early or advanced), and year of transplant. The risk of TRM after a MA regimen has decreased over time, although the exact reason for improvement is not entirely clear [27]. It most probably relates to improved HLA-matching technology, in the unrelated donor setting, and better supportive care. Patients with early leukemia seem to have most benefited of this improvement [27].

Cure of the underlying disease depends in part on the intensity of the MA regimen [1]: this was proved in a prospective randomized trial showing that TBI 15.75 Gy was associated with a lower risk of relapse compared to TBI 12 Gy [8]. However, patients receiving the higher dose of TBI also had a higher incidence of GVHD ,thus, making unclear the relative contribution of the TBI to the lower risk of relapse. Other retrospective studies have confirmed the impact of conditioning intensity on relapse [9]. Unfortunately, the higher TBI dose was also associated with a higher risk of TRM, so that survival was comparable in the 2 groups [8]. The antileukemia effect of MA regimens can be further enhanced with the use of targeted radioimmunoconjugates [28], which would, in theory, not increase regimen-related toxicity. However, because the use of these agents in the context of conditioning regimens remains investigational, their exact place in the intensity spectrum is unknown.

It should be noted that it is probably impossible to "myeloablate" completely an animal or an individual

[29], and indeed, cases of autologous reconstitution have been reported after high-dose chemotherapy or accidental exposure to radiation [30,31]. Therefore, the term MA should be considered an operational definition, indicating a regimen causing irreversible pancytopenia in almost all patients: autologous recovery (at best following prolonged life-threatening cytopenia) would be the exception.

Definition of MA regimen: a combination of agents expected to produce profound pancytopenia and myeloablation within 1-3 weeks from administration; pancytopenia is long lasting, usually irreversible, and in most instances fatal, unless hematopoiesis is restored by hemopoietic stem cell infusion

Examples of MA regimens are shown in Table 1.

A workshop was convened at a CIBMTR/ASBMT meeting to assess whether expert transplanters would agree on what is considered an MA regimen [20]. The regimens listed in Table 1 obtained a general consensus.

NMA CONDITIONING REGIMENS

TRM after MA regimens increases with increasing patient age, and 50 years used to be considered an upper age limit [25]. With the aim of reducing toxicity, thus making transplantation available in the older patient population, so-called NMA conditioning regimens were developed. Examples of NMA regimens include: Flu-Cy [32], TBI 2 Gy [17], TBI 1 Gy [33], total lymphoid radiation (TLI), and antithymocyte globulin (ATG) [34]. NMA typically cause minimal cytopenia, and little early toxicity, but are immunosuppressive to the extent that, when followed by granulocyte-colony stimulating factor (G-CSF) mobilized peripheral blood stem cells (PBSCs), they usually result in full engraftment of donor lymphohemopoietic SCs. A good example is the Flu-Cy combination developed in Houston for the treatment of chronic lymphocytic leukemia (CLL): the same regimen followed by mobilized allogeneic PBSC, results in donor engraftment [30]. In addition to *myeloablation*, we introduce here the concept of *immunoablation*. NMA are immunoablative regimens, and this is why donor cells engraft. However, NMA also require a large number of donor T lymphocytes and donor $CD34^+$ cells, to facilitate donor engraftment. It is therefore the combination of *immunoablation* and large numbers of donor cells that constitute the essence of NMA programs [33]. These transplants are followed by low early toxicity, despite older patient age and greater number of patients with comorbidity [35]. TRM is lower after NMA compared to MA regimens [35].

Acute GVHD (aGVHD) after NMA is delayed, and may develop after day 100, at a time when chronic GVHD (cGVHD) is usually diagnosed after an MA regimen [36]. GVHD remains a significant cause of morbidity and mortality also after NMA [36]. NMA have been explored in patients with leukemia [37] lymphoma [32], myeloma [38], and solid tumors [39].

Definition of NMA regimen: a regimen that will cause minimal cytopenia and does not require stem cell support.

This is an operational definition: indeed, only some of the regimens classified as NMA are truly nonablative, such as the Flu-Cy or TLI-ATG. On the other hand, TBI also at low doses causes some degree of ablation of the SC reservoir. But because TBI 1 or 2 Gy do not cause cytopenia and can be given without SC support, they can be defined as NMA. In addition, NMA refers only to the conditioning regimen: in fact, the transplant, as a procedure, is MA, because engrafted donor T cells will eventually eliminate host hemopoietic cells, allowing the establishment of donor hematopoiesis.

Examples of NMA regimens are shown in Table 1.

Table 1. Example of Myeloablative and Nonmyeloablative Regimens According to Commonly Used Agents and Combinations

Myeloablative (MA)*
TBI ≥5 Gy single dose or ≥8 Gy fractionated
Bu >8 mg/kg orally or intravenous equivalent
Nonmyeloablative (NMA)†
TBI ≤2 Gy± purine analog
Flu + Cy ± ATG
Flu +AraC + Ida
Cladribine + AraC
Total Lymphoid Irradiation + ATG

AraC indicates cytarabine; ATG, antithymocyte globulin; Bu, busulfan; Gy, grays; Cy, cyclophosphamide; Flu, fludarabine; Ida, idarubicin; TBI, total body irradiation.
Reduced-intensity regimens (RIC) are regimens that do not fit these two categories; examples of these regimens in the text.
*See [1].
†See [12,17,32-34].

RIC REGIMENS

RIC regimens is an intermediate category of regimens that do not fit the definition for MA or NMA. *RIC regimens differ from NMA*: they cause cytopenia, which may be prolonged, and do require stem cell support. It is possible that autologous recovery would eventually occur, although pancytopenia would be of such duration to cause significant morbidity and mortality.

RIC regimens differ from MA conditioning, because the dose of alkylating agents or TBI is reduced by at least 30%. Most often these regimens combine Flu with an alkylating agent, melphalan (Mel) [40], Bu [14], thiotepa [15] in reduced doses, or Flu with reduced-dose TBI [41]. TRM is reduced after RIC

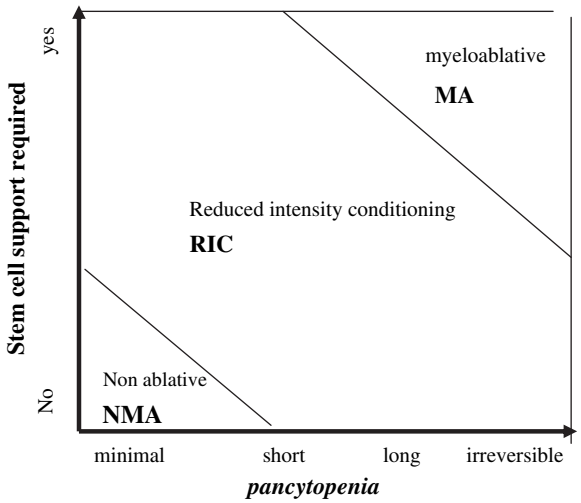

Figure 1. Classification of conditioning regimens in 3 categories, based on duration of pancytopenia and requirement for stem cell support. Myeloablative fregimens (MA) produce irreversible pancytopenia and require stem cell support. Non myeloablative regimens (NMA) produce minimal cytopenia and does not require stem cell support. Reduced intensity regimens (RIC) are regimens which can not be classified as MA nor NMA.

regimens, as shown by several registry-based studies comparing RIC and MA regimens [42-45]. *RIC programs require SCl support* to be practical in the clinic: RIC regimens have used a wide selection of agents, given at a wide range of doses RIC regimens have been explored in patients with acute and chronic leukemia, lymphoma, myeloma, and patients with myelodysplastic syndromes (MDS), as shown by large Registry-based studies [42,46].

For some conditioning regimens, classification may be not straightforward. One example is Cy 200 mg/kg, with or without thymic radiation [47,48]. This is a truly nonablative regimen, because it does not kill SCs, but it does cause profound cytopenia, especially when given over 4 days (50 mg/kg/day $\times$4) in patients with SAA, and is followed by allogeneic hemopoietic SC. Some of these patients may recover an autologous hematopoies, and Cy 200 mg/kg has also been given in aplastic anemia, without SC support [49], although the rate of lethal infections, because of prolonged cytopenia, was very high [50]. Therefore, Cy 200 mg/kg does not fit our working definition of a MA conditioning nor of a NMA conditioning, and falls in the category of RIC conditioning.

Definition of a RIC regimen: a regimen that cannot be classified as NMA or MA.

CONCLUSION

We propose to define the intensity of the conditioning regimen on the basis of the duration of pancytopenia induced and on the requirement for SC support, as shown in Figure 1.

An MA conditioning regimen will cause irreversible (or close to irreversible) pancytopenia. SC support is required to rescue marrow function, and prevent aplasia-related death.

An NMA *regimen (NMA)* is a regimen that will produce minimal cytopenia, and there is no need for SC support.

A conditioning regimen that does not fulfill MA or NMA is defined as an *RIC regimen.*

These definitions should be regarded as a starting point, which may be rediscussed in the near future. The notion of the 2 conventional MA regimens (Cy-TBI and Bu-Cy) is well established. The concept of NMA regimens, is also clear, and based on agents, or combination of agents, producing minimal cytopenia. All other regimens should be called RIC, not because they are Flu based, but rather because they do not fit criteria for MA or NMA regimens.

Adoption of a classification for preparative regimens in 3 different categories would be important for crossreferencing in the scientific literature. The inclusion of new agents in conditioning regimens, such as disease specific drugs or targeted therapies with monoclonal antibodies, will need to be incorporated in the intensity spectrum. This classification and terminology, if adopted by the transplant community, will serve as a starting point to standardize these transplant modalities, and facilitate interpretation of retrospective studies and development of prospective trials.

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