

by Jaime Sanz, University Hospital La Fe, Valencia, Spain

The conditioning regimen, also so-called preparative regimen, is a critical element in the hematopoietic stem cell transplant (HSCT) procedure. This is usually a combination of chemotherapy agents, with or without radiation therapy. The purpose of the preparative regimen is dual and varies according to the type of HSCT: i) to provide adequate immunosuppression to facilitate the patient's body to accept the donor's bone marrow cells and prevent rejection; and ii) to eradicate the disease for which the transplant is being performed.. The former goal is needed only in patients undergoing allogeneic stem cell transplantation, but not in those receiving autologous transplants. Fortunately, today most preparative regimens achieve high efficiency in this regard, with graft rejection being an uncommon complication. Nevertheless, when this complication occurs it is associated with a dismal outcome. It is well known that the risk of graft rejection increases with the degree of HLA mismatch between donor and recipient. Regarding the latter objective, conditioning regimens are usually designed to kill tumor cells resistant to conventional chemotherapy by giving maximally tolerated doses of multiple chemotherapeutic agents without causing fatal nonhematologic organ toxicity. Nevertheless, several novel approaches have been designed in an attempt to minimize toxicity. As an example, RIC and nonmyeloablative conditioning regimens have been developed to treat older patients or those with concurrent comorbidities.

Types of preparative regimens

Myeloablative regimens

A myeloablative regimen usually consists of a combination of agents given at maximally tolerated doses expected to eradicate the hematopoietic cells in the bone marrow and results in profound pancytopenia within one to three weeks from the time of administration. The resulting pancytopenia is long-lasting, usually irreversible, and in most instances fatal, unless hematopoiesis is restored by infusion of hematopoietic stem cells.

Nonmyeloablative regimens

A nonmyeloablative regimen results in minimal cytopenia, significant lymphopenia, and does not require stem cell support. In this respect, fludarabine, cyclophosphamide, antithymocyte globulin and total body irradiation (TBI) ≤ 2 Gy are the most common agents used with this purpose.

Reduced intensity regimens

Reduced intensity regimens (RIC) are an intermediate category of regimens that do not fit the definition of myeloablative or nonmyeloablative. Such regimens cause cytopenias, which may be prolonged and result in significant morbidity and mortality, and require hematopoietic stem cell support.

Toxicity of preparative regimens

Apart from the aforementioned myelotoxicity, the most common side effects that some of them can be life-threatening include:

- Mucositis
- Nausea and vomiting
- Alopecia

- Diarrhea
- Rash
- Peripheral neuropathies
- Infertility. Sperm cryopreservation for male and oocyte cryopreservation in female patients can be attempted to overcome this complication, which is almost universal when using myeloablative regimens..
- Pulmonary toxicity: interstitial lung disease
- Hepatic toxicity: hepatic venoocclusive disease or sinusoidal obstructive syndrome.

Long-term complications following TBI used as part of a preparative regimen are relatively common:

- Asymptomatic alterations in pulmonary function (20%)
- Cataracts (15%)
- Sicca syndrome (13%)
- Hypothyroidism (6%)

- Thyroiditis (3%)

Myeloablative preparative regimens

All myeloablative regimens are associated with a high degree of myelotoxicity. There are only a few well designed trials comparing the efficacy of different myeloablative regimens. Therefore, it is difficult to make direct statements about the suitability of a given preparative regimen in a particular disease setting. Cyclophosphamide plus TBI or busulfan are typical approaches for fully myeloablative regimens, but combining busulfan with fludarabine is being increasingly used. According to the use of radiation or not, conditioning regimens can be classified as follows

Radiation-containing regimens

TBI has been the mainstay of preparative regimens since the beginning of the activity of HSCT. Initial preparative regimens included TBI administered as a single dose using opposing Cobalt-60 sources. At present, TBI-based regimens typically fractionate the radiation and administer the total dose over several days, typically four, which helps decrease toxicity and increase tolerability. Partial lung shielding is included in an effort to reduce the potential for irreversible lung injury.

The most common radiation-containing regimen used for patients receiving allogeneic HSCT has been TBI with cyclophosphamide. The maximally tolerated dose of TBI is approximately 15 Gy. Higher doses produce excessive nonhematologic toxicity, primarily to the lungs, but also to other organs including the heart. Cyclophosphamide is usually given at a dose of 60 mg/kg of adjusted ideal body weight on each of two successive days.

[Etoposide](#)

(VP16) or high dose

[cytarabine](#)

also have been given with TBI, with and without

[cyclophosphamide](#)

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Chemotherapy-based conditioning regimens (without radiation)

A number of non-radiation-containing regimens in which TBI is replaced with additional chemotherapy have been developed. These approaches were initially developed for autologous transplantation, but they have also been used widely in the allogeneic setting. The most widely used chemotherapy-based regimen is the combination of [busulfan](#) and [cyclophosphamide](#) (BuCy) with their variants BuCy2 and BuCy4 (2 or 4 days of cyclophosphamide). A variety of other combinations that have been successful used include:

- [Busulfan](#) and [etoposide](#) (in AML)
- BCNU, [cyclophosphamide](#) , cytosine arabinoside and [melphalan](#) (BEAM)
- [Cyclophosphamide](#) , [carmustine](#) (BCNU), and etoposide (Hodgkin and non-Hodgkin lymphomas)
- Busulfan, [melphalan](#) , and [thiotepa](#) (aggressive or relapsed lymphoma).

Nonmyeloablative and reduced intensity preparative regimens

Less intense conditioning regimens are being used more frequently today to retain the desirable effects of standard high-dose conditioning regimens, but with significantly lower toxicity and, therefore, lower transplant-related mortality. The general principle in which the use of both nonmyeloablative and RIC preparative regimen is based is the so-called graft-versus-tumor (GVT) effect, which is mediated by donor immunocompetent cells in allogeneic HSCT. It is well known that the engraftment of donor type immunocompetent cells does not necessarily require

a myeloablative preparative regimen, and can be achieved by using nonmyeloablative or RIC regimens.

RICy regimens are an intermediate category of regimens that do not fit the definition of myeloablative or nonmyeloablative. Such regimens cause cytopenia, which may be prolonged and result in significant morbidity and mortality, and require stem cell support. Regimens generally considered as RIC include ≤ 9 mg/kg of oral [busulfan](#), or ≤ 140 mg/m² of [melphalan](#). The adoption of these less toxic conditioning regimens has expanded the number of patients eligible to receive transplants -- patients who may have previously been excluded due to older age or existing co-morbidities. It should be noted, however, that not all diseases are equally susceptible to GVT effect. It is generally accepted that chronic myeloid leukemia, chronic lymphocytic leukemia, and low-grade indolent lymphomas (follicular lymphoma and mantle cell lymphoma) appear particularly responsive to GVT effect.

RIC regimens typically use combinations of chemotherapy drugs such as fludarabine, busulfan, and melphalan, with or without low-dose radiation.