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EDITORIAL

Transplantation Conditioning Regimens: Can We Say It Better?

H. Joachim Deeg

English is a very versatile language in which new words are readily created and accepted. For example, some 50 years ago, the *beep-beep-beep* of Sputnik I may have caught the Cold War warriors off guard, but not the scientists and linguists; in no time it seems, the satellite was said "to orbit," that is, to travel around the "orb," the globe on which we live. We have not done as well with our transplantation terminology, despite all of the Latin, Greek, and Anglo-Saxon roots on which we can draw. Although we talk about "autologous transplants," just reflect on this term for a moment: What are we *trans*planting? We actually are giving cells back to the individual from whom they were taken; if anything, the proper term should be "*auto*plantation."

The past 10 years have seen remarkable developments in the field of hematopoietic cell transplantation, including the approaches used to prepare patients for transplantation so that donor-derived cells can establish themselves in the marrow space of the patient and restore normal hematopoietic and immune functions. The language used to describe the procedures and the resulting effects has considerable room for improvement, however.

In the early years of modern hematopoietic cell transplantation for malignant disorders, the ability to provide hematopoietic stem cells was used to rescue marrow function. Patients with acute leukemia, for example, could be treated with doses of chemotherapy or radiation that otherwise would have been fatal due to treatment-induced marrow failure [1]. However, studies in rodent models showed that even the highest doses of chemotherapy or radiotherapy that could be tolerated (ie, did not result in fatal complications other than marrow failure, such as gastrointestinal toxicity or infection) were not sufficient to eradicate all leukemic blasts [2-4]. The eventual success of transplantation generally depended on the immunologic effects of (allogeneic) donor cells directed at antigens expressed on leukemic cells in the recipient, the so-called "graft-versus-leukemia" (GVL) effect. The power of such an effect was soon confirmed in clinical studies showing that patients who developed graft-versus-host disease (GVHD), particularly in its chronic form, were at lower risk for disease progression or relapse compared with allogeneic transplant recipients even without clinical evidence of GVHD [5,6] or recipients of transplants from syngeneic twin donors [7,8]. The high-dose conditioning regimens used at that time, often involving unfractionated total body irradiation (TBI) at doses of 800 to 1000 cGy (which, particularly in combination with chemotherapy, were considered "myeloablative") did not consistently eradicate the disease. Whereas further dose escalation (chemotherapy, radiation, or both) reduced the incidence of relapse, the price of that gain was a substantial increase in regimen-related mortality [9].

The impetus for the development of different, hopefully less toxic and more effective strategies came from several directions:

1. Results in patients who had received transplants from allogeneic donors but relapsed with their disease after transplantation showed that the infusion of additional donor cells (obtained from peripheral blood) after relapse was able to reinduce (lasting) remissions, with the success rate depending primarily on the patient's underlying disease [10].
2. Other studies demonstrated that preemptive donor lymphocyte infusion in patients considered at high risk for relapse could prevent relapse after transplantation [11].
3. Studies in animal models showed that TBI doses much lower than those traditionally used for transplantation conditioning provided sufficient immunosuppression in the recipient to allow for engraftment of cells from a major histocompatibility complex–matched donor [12].
4. Results from multiple clinical trials indicated that transplantation of donor cells obtained from peripheral blood after pretreatment with granulocyte

From the Fred Hutchinson Cancer Research Center and the University of Washington, Seattle, Washington.
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Correspondence and reprint requests: H. Joachim Deeg, MD, Fred Hutchinson Cancer Research Center, 1100 Fairview Avenue N, D1-100, PO Box 19024, Seattle, WA 98109-1024 (email: jdeeg@fhcrc.org).
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colony-stimulating factor to "mobilize" stem cells from the marrow (peripheral blood progenitor cells [PBPCs]) was associated with more rapid engraftment and lower frequency of relapse compared with cells harvested directly from the marrow. These mobilized cells contain larger proportions of T lymphocytes and carry an increased risk of (chronic) GVHD, but also are associated with an enhanced GVL effect [13,14]. Thus, a substantial body of information exists suggesting the possibility of carrying out successful transplantation using conditioning regimens of lower intensity and thus lower toxicity, particularly when PBPCs are the hematopoietic stem cell source.

It is not surprising that this goal can be achieved with more than one conditioning regimen, and by now a large body of literature supports this concept [15-20]. The descriptions of the various regimens are confusing, however; for example, investigators have reported on "conventional" compared with "mini" transplantations, on "high-intensity" versus "reduced-intensity" or "dose-reduced" conditioning regimens, and on "myeloablative" versus "nonmyeloablative" transplantations, with the recent addition of a "submyeloablative" regimen [21]. This creativeness is fascinating and entertaining, but is it useful?

In principle, all transplantations performed in patients with malignant disorders are intended to be myeloablative, in the sense that the goal is disease eradication. What differs among the various approaches may be the strategy used to achieve this goal. If this (ie, myeloablation) is not what we mean when we say myeloablative, then we should find a more appropriate and specific term. It is clear that the lower the intensity of a conditioning regimen, the more we need to rely on the immune effects mediated by donor cells; as noted earlier, the requirement for such an effect was already apparent in studies reported 3 decades ago [5]. Furthermore, a mini-transplantation is "mini" only in the sense that the conditioning regimen is of lower intensity than regimens used historically; it is still a full transplantation, intended to replace the patient's marrow with donor-derived marrow cells, and as such is accompanied by the risk of GVHD. Admittedly, the frequency and severity of GVHD may be somewhat lower than that seen in higher-dose regimens, but GVHD remains a problem even with low-intensity conditioning [15,22,23]. Moreover, *all* efforts in clinical hematopoietic cell transplantation are directed, as they should be, at improving relapse-free survival in patients. As a part of these efforts, higher-dose conditioning regimens have been continuously modified with the aim of reducing transplantation-related toxicity and improving outcome. As a result, a very broad spectrum of conditioning regimens has emerged, ranging from low-dose TBI or antibody plus chemotherapy to multidrug regimens combined with high-dose TBI. It follows that it is simply not possible to contrast myeloablative with nonmyeloablative conditioning—how myeloablative or nonmyeloablative is a given regimen? Our goal is always to eradicate the patient's disease and replace the patient's marrow (and thereby immune function) with donor-derived cells. Unfortunately, however, the goal of consistently achieving a state of mixed chimerism associated with tolerance and disease eradication has not yet been achieved.

Our responsibility is to provide patients and colleagues with clear information on procedures and to offer the best available therapy, regardless of whether the term that we use to describe the proposed strategy was coined by our group or by someone else. I propose that we avoid vague, confusing, and potentially misleading terminology. I suggest that regimens be described by their composition, for example, a low-dose TBI (eg, 200 cGy, 2 × 200 cGy) plus fludarabine (eg, 3 × 30 mg/m^2, 5 × 50 mg/m^2) regimen, a fludarabine (eg, 3 ×30 mg/m^2, 5 × 50 mg/m^2) plus melphalan (eg, 140 mg/m^2) regimen, and so on. The physician reader must know (and the patient is entitled to know) the composition of each regimen and the possible side effects, both acute and delayed. Journal editors should enforce a policy of accurately conveying to the reader what the report describes.

I would not be surprised if someone were to suggest a nomenclature committee to sort things out and provide guidance. That would be fine, but probably would be unnecessary if we could agree to clearly state what we mean.

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