



Nonmyeloablative Bone Marrow Transplants

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Question: For years, I have heard about bone marrow and stem cell transplants in which ablation of the bone marrow is a necessary step in the transplant. Now I am hearing about nonmyeloablative bone marrow transplantation. How does this work, and what is the reason for these types of transplants?

Answer: Allogeneic bone marrow transplantation, in which a donor is used, was developed as a curative therapy for a wide range of hematologic malignancies. Standard preparative regimens have been designed to deliver ablative doses of radiation and chemotherapy to immunosuppress the host so that it will accept the donor graft and eradicate the patient's underlying disease (Kelemen, Masszi, Reményi, Barta, & Pálóczi, 1998; Popplewell & Forman, 2002). Bone marrow transplantation may include a human leukocyte antigen (HLA) matched sibling donor, a matched unrelated donor (MUD), or, in some cases, an HLA mismatched donor. HLA has been recognized as the primary factor responsible for rejection of tissue grafts between unmatched individuals. In humans, this major histocompatibility complex region lies on the short arm of chromosome six and is called the HLA region (Waldmann, 2001).

The beneficial effects of these ablative preparative regimens often are offset by the increased incidence of acute and long-term side effects, which are responsible for considerable transplant-related mortality (Carella, Champlin, Slavin, McSweeney, & Storb, 2000). During the past several years, researchers have determined that high-dose therapy does not entirely eradicate the disease in many patients. One of the major benefits of allogeneic transplantation is the development of an associated immune-mediated graft-versus-tumor (GVT) effect (Popplewell & Forman, 2002; Waldmann,

2001). Nonmyeloablative preparative regimens rely on this GVT effect to eradicate the underlying disease. In some academic institutions, these transplants are termed "mini" allogeneic bone marrow transplants. However, this is misleading because it suggests that patients undergo a procedure that is benign in nature. Transplant-related morbidity and mortality still exist despite the nonmyeloablative conditioning regimens and, therefore, cannot be underestimated.

Evidence of an immune-mediated effect has been derived mostly from allogeneic transplantation for leukemia, giving rise to the term GVT (Waldmann, 2001). Differences exist among malignancies in their susceptibility to the GVT effect. Chronic myeloid leukemia is the most sensitive to this effect, acute myeloid leukemia is moderately sensitive, and acute lymphoblastic leukemia is the least affected by the GVT effect. Indolent lymphoid malignancies, such as chronic lymphocytic leukemia, low-grade lymphoma, and multiple myeloma, also appear to have a GVT effect (Carella et al., 2000; Vindelov, 2001).

The GVT effect against solid tumors is not as well understood. Metastatic renal cell carcinoma is a solid tumor that has been studied in recent years using nonmyeloablative-conditioning regimens (Childs et al., 2000). Because renal cell carcinoma does not respond to most high-dose chemotherapies, a nonmyeloablative regimen has been found to provide sufficient immunosuppression to allow engraftment to occur (Childs et al., 2000). Purine analogs, which are common agents given in nonmyeloablative conditioning regimens, have a dramatic effect on the immune system. These agents likely can be used in treating other autoimmune disorders, such as multiple sclerosis, systemic lupus erythematosus, rheumatoid arthritis, and scleroderma (Margolis, Miller, & Weiss, 2002). Further clinical studies are needed to accurately determine whether a meaningful GVT effect occurs, thereby justifying the added morbidities associated with allogeneic transplantation.

With the recognition that the GVT effect is responsible for many of the observed cures following allogeneic transplantation,

preparative regimens have been developed that aim to establish hematopoietic chimerism. Chimerism is a state where donor and host cells coexist with one another. During nonmyeloablative allogeneic bone marrow transplantation, patients may remain in what is called a mixed chimerism. Nonmyeloablative regimens lessen the ablative effect on the host but are able to preserve the GVT effect. In general, these regimens do not completely eradicate the underlying disease because they rely on the immune response of the patient (i.e., GVT) to eradicate the underlying disease to achieve full donor chimerism. During mixed chimerism, the signs of graft-versus-host disease (GVHD) or a GVT effect seldom are seen, perhaps because of a diminished cytokine release (Childs, Clave, & Contentin, 1999). If full donor chimerism does not develop, donor lymphocyte infusion may be offered to achieve this goal (see Figure 1). Donor lymphocytes are collected from the donor during an outpatient visit and given to the host patient to stimulate a prolonged GVT effect.

GVHD occurs when donor T cells recognize the change in antigens on host tissue cells. These T cells activate and proliferate in response to the foreign antigens of the recipient cells. GVHD can present on host organ tissues such as the skin, liver, and gastrointestinal system. It can present as a body rash, diarrhea, or elevations in liver function tests. The cytokine storm that develops can be difficult to manage and actively treat in the acute and chronic phases (Chan, Gorgun, Miller, & Foss, 2003).

The nonmyeloablative regimens are associated with less toxicity and, therefore, can be offered to patients who are poor candidates for standard allogeneic transplants.

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