Available online at www.sciencedirect.com

SCIENCE DIRECT®

Transplant Immunology 14 (2005) 207 – 219

Transplant Immunology

www.elsevier.com/locate/trim

# Nonmyeloablative stem cell transplantation and cell therapy for malignant and non-malignant diseases

I.B. Resnick*, M.Y. Shapira, S. Slavin

*Department of Bone Marrow Transplantation and Cancer Immunotherapy, Cell Therapy and Transplantation Research Laboratory, Hadassah University Hospital, PO Box 12000, Jerusalem, 91120, Israel*

Accepted 14 March 2005

**Abstract**

The conditioning prior to allogeneic stem cell transplantation was originally designed as a myeloablative conditioning, designed to eliminate malignant or genetically abnormal cells and then use the transplant procedure for rescue of the patients or to replace missing bone marrow products. However, allografts can induce effective graft vs. malignancy effects and can also eliminate undesirable hematopoietic stem cells in patients with genetic disorders and autoimmune diseases, thus documenting that alloreactive effects mediated by donor lymphocytes post-grafting can play a major role in eliminating hematopoietic cell of host origin, as well as provide effective immunotherapy for the treatment of disease recurrence. The efficacy of donor lymphocyte infusion (DLI) could be improved by activation with rIL-2 or by donor immunization. The cumulative experience over the years suggesting that alloreactive donor lymphocytes were most effective in eliminating tumor cells of host origin resulted in an attempt to reduce the intensity of the conditioning in preparation for the transplant procedure used for the treatment of hematological and other malignancies as well as life-threatening non-malignant disorders for which allogeneic stem cell transplantation may be indicated. Our working hypothesis proposed that the myeloablative conditioning which is hazardous and may be associated with early and late side effects, may not be required for treatment of patients with any indication for allogeneic stem cell transplantation. Instead, nonmyeloablative conditioning based on the use of reduced intensive preparatory regimen, also known as nonmyeloablative stem cell transplantation (NST), may be sufficient for engraftment of donor stem cells while avoiding procedure-related toxicity and mortality, followed by elimination of undesirable cells of host origin by post-transplant effects mediated by alloreactive donor lymphocytes infused along with donor stem cells or administered subsequently as DLI. Improvement of the immediate outcome of stem cell transplantation using NST due to a significant decrease in transplant related mortality has broadened the spectrum of patients eligible for allogeneic stem cell transplantation, including elderly patients and other patients with less than optimal performance status. Likewise, the safer use of stem cell transplantation prompted expanding the scope of potential indications for allogeneic stem cell transplantation, such as metastatic solid tumors and autoimmune disorders, which now are slowly becoming much more acceptable. Current strategies focus on the need to improve the capacity of donor lymphocytes to eliminate undesirable malignant and non-malignant hematopoietic cells of host origin, replacing abnormal or malignant stem cells or their products with normal hematopoietic stem cells of donor origin, while minimizing procedure-related toxicity and mortality and improving the quality of life by reducing the incidence and severity of hazardous acute and chronic GVHD.


*Keywords:* SCT, stem cell transplantation; Nonmyeloablative stem cell transplantation (NST); Reduced intensity conditioning (RIC); Hematological malignancies

*Abbreviations:* ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; ATG, anti-thymocyte globulin; BMT, bone marrow transplantation; CGD, chronic granulomatous disease; CML, chronic myeloid leukemia; CTL, cytotoxic T lymphocytes; CSA, cyclosporine A; DLI, donor lymphocytes infusion; EAE, experimental allergic encephalomyelitis; FASL, Fas ligand; GVHD, graft-versus-host disease; GVL, graft-versus-leukemia/lymphoma; GVT, graft-versus-tumor; HSC, hematopoietic stem cells; HSCT, hematopoietic stem cells transplantation; MHC, major histo-compatibility complex; NST, nonmyeloablative stem cell transplantation; PID, primary immunodeficiency; RA, rheumatoid arthritis; RIC, reduced intensity conditioning; SLE, systemic lupus erythematosus; TBI, total body irradiation; VLCFA, very long chain fatty acids.

* Corresponding author. Tel.: +972 2 6778353; fax: +972 2 6422731.
*E-mail address:* gashka@hadassah.org.il (I.B. Resnick).

0966-3274/$ - see front matter © 2005 Elsevier B.V. All rights reserved.
doi:10.1016/j.trim.2005.03.009

## 1. Introduction

The first successful allogeneic bone marrow transplants (BMT) were done using HLA identical siblings in 1968, by the team of Robert Good in Minneapolis, and by Fritz Bach and colleagues of UW Madison, and were reported in the same issue of Lancet [1,2]. Despite the fact the BMT course of the first patient was complicated the patient is still alive and doing well [3].

Since that time, the range of diseases treatable by BMT or mobilized peripheral blood hematopoietic stem cell transplantation (HSCT) has been constantly growing, and in addition to severe combined immune deficiency to include other diseases caused by marrow stem cell deficiencies (such as aplastic anemias), genetically abnormal stem cells (such as beta thalassemia major; osteopetrosis; chronic granulomatous disease; Wiscott-Aldrich syndrome), or enzyme deficiencies (such as Gaucher's disease and Hurler syndrome, to mention just a few), and, of course, hematological malignancies. Acute leukemia, which is one of the most common hematological malignancies in children, is a highly lethal disease that frequently responds initially to conventional doses of chemotherapy. Later, however, the disease becomes resistant to subsequent chemotherapy, which is the main cause of disease recurrence and mortality.

Past experience has shown that more aggressive chemo-radiotherapy tends to cause increased toxicity with minimal or no improved disease-free survival. A certain proportion of patients with relapsing or primary resistant leukemia or other hematological malignancies may respond to more intensive, myeloablative chemotherapy followed by "rescue" with autologous bone marrow or blood stem cells. However, bone marrow or blood stem cells obtained from a genetically matched family member or matched unrelated donor (MUD) are likely to be much more effective due to the graft-versus-leukemia (GVL) effects mediated by alloreactive donor lymphocytes, usually but not exclusively, in association with anti-host responses causing graft-versus-host disease (GVHD) [4–6]. Taken together, myeloablative conditioning with the goal in mind of eliminating or minimizing the number of resistant tumor cells or otherwise abnormal host cells, followed by allogeneic stem cell transplantation was until recently considered the most powerful treatment available for patients with blood cancer not expected to be cured by any alternative therapy. A similar approach was considered the treatment of choice for a large number of non-malignant diseases correctable by stem cell transplantation. The intensity of the conditioning regimens used for BMT/HSCT escalated with time, and procedure-related toxicity and mortality rose accordingly [7,8]. The increased incidence and severity of late complications also became an important issue in evaluating the quality of life of long-term survivors. For this reason, in the 1990s it became clear that newer modalities must be developed to improve the cure rate of patients with hematological malignancies, as well as to improve their quality of life. In parallel, from the early 1970s more and more data were published concerning the effect of allogeneic lymphocytes on host, specifically malignant, cells and the clear association between GVHD and GVT (graft versus tumor) effect in the clinical setting.

## 2. Reduced intensity conditioning, or nonmyeloablative stem cell transplantation

### 2.1. Rationale, principles and history

This novel approach to transplantation was based on the following philosophy and premises:

1. Given that in cases of relapsed or resistant disease any new combination or escalation of cytotoxic chemo-radiotherapy, including supralethal toxicity rescued with autologous transplantation, is usually not enough to eradicate the disease and there are at present no alternative therapies based on medication to restore many deficiencies in hematopoiesis and the immune system, or to cure numerous other "non-malignant" diseases with poor prognosis especially in the case of compromised performance status, and
2. Since allogeneic transplantation and donor cell therapy at present are the only known tools which can kill *the last* tumor cell using natural immune mechanisms, and
3. Since traditional allogeneic transplantation in combination with myeloablative conditioning causes severe life-threatening complications,

the reduction of conditioning intensity to a point that would still be enough to forge a new immune system for a patient, with the help of subsequent immune manipulations, sounded like the Holy Grail of transplantology. This approach was named "nonmyeloablative stem cell transplantation" (NST) or "reduced intensity conditioning" (RIC).

The success of NST depends on the initial engraftment of donor stem cells for induction of transplantation tolerance in the host to the graft to prevent rejection of donor cells and permit durable engraftment of donor lymphocytes. Fludarabine-based protocols initially introduced in MD Anderson in Houston and Hadassah Hospital in Jerusalem [9–11] were found to constitute the optimal conditioning regimens for recipients of HLA matched sibling or matched unrelated donor (MUD) allografts, a finding that has since been confirmed by many transplant centers worldwide [12–14]. Fludarabine is usually used in combination with low-dose busulfan or cytoxan with or without ATG. Recently, we have carried out successful trials on novel conditioning protocols with even less cytotoxicity of conditioning than the initially reported conditioning for the "classical NST" and achieved a good engraftment rate. We named this