Seminars in Immunology 23 (2011) 273–281

Contents lists available at ScienceDirect

Seminars in Immunology

journal homepage: www.elsevier.com/locate/ysmim

Review

Translational studies in hematopoietic cell transplantation: Treatment of hematologic malignancies as a stepping stone to tolerance induction

Samuel Strober[a], Thomas R. Spitzer[b], Robert Lowsky[c], Megan Sykes[d,*]

[a] Division of Immunology and Rheumatology, Department of Medicine, Stanford University School of Medicine, Stanford, CA, United States
[b] Division of Bone Marrow Transplantation, Department of Medicine, Massachusetts General Hospital, Harvard Medical School, Boston, MA, United States
[c] Division of Blood and Marrow Transplantation, Department of Medicine, Stanford University School of Medicine, Stanford, CA, United States
[d] Columbia Center for Translational Immunology, Department of Medicine, Surgery and Microbiology/Immunology, College of Physicians and Surgeons, Columbia University, New York, NY, United States

ARTICLE INFO

Keywords:
Transplantation
Tolerance
Graft-vs-host disease
Graft-vs-leukemia
Rejection
Kidney transplantation

ABSTRACT

Allogeneic hematopoietic cell transplantation (HCT) has most commonly been used to treat hematologic malignancies, where it is often the only potentially curative option available. The success of HCT has been limited by transplant-associated toxicities related to the conditioning regimens used and to the common immunologic consequence of donor T cell recognition of recipient alloantigens, graft-vs-host disease (GVHD). The frequency and severity of GVHD observed when extensive HLA barriers are transgressed has essentially precluded the routine use of extensively HLA-mismatched HCT. Allogeneic HCT also has potential as an approach to organ allograft tolerance induction, but this potential has not been previously realized because of the toxicity associated with traditional conditioning. In this paper we review two approaches to HCT involving reduced intensity conditioning regimens that have been associated with improvements in safety in patients with hematologic malignancies, even in the HLA-mismatched transplant setting. These strategies have been applied in the first successful pilot studies for the induction of organ allograft tolerance in humans. Thus, we summarize an example of vertical translational research between animal models and humans and horizontal translation between two separate goals that culminated in the use of HCT to achieve allograft tolerance in humans.

1. Introduction

Allogeneic hematopoietic cell transplantation (HCT) has most commonly been used to treat hematologic malignancies, where it is often the only potentially curative option available. While it has revolutionized the therapy of many of these diseases, the success of HCT has been limited by transplant-associated toxicities related to the conditioning regimens used and to the common immunologic consequence of donor T cell recognition of recipient alloantigens, graft-vs-host disease (GVHD). While GVHD can be effectively prevented by removing mature T cells from the donor graft, this maneuver is associated increased relapsed rates, demonstrating the beneficial graft-vs-leukemia/lymphoma (GVL) effect of the GVH alloresponse, as well as high rates of infectious complications due to poor immune reconstitution, and increased rates of graft rejection. A mild to moderate level of GVHD is considered acceptable when hematologic malignancies are treated, as GVHD is associated with enhanced anti-tumor effects [1]. However, the frequency and severity of GVHD observed when extensive HLA barriers are transgressed has essentially precluded the routine use of extensively HLA-mismatched HCT. In this review, we discuss two different approaches to HCT for the treatment of hematologic malignancies that, based on data on rodent models, aim to reduce the toxicity and GVHD rates associated with HCT and to thereby extend its availability to extensively HLA-mismatched donor-recipient pairs. We also describe how iterative translational studies between animals and humans have resulted in the extension of one of these strategies to a third, novel approach, in which hematopoietic cell engraftment is followed by intentionally induced marrow rejection in order to achieve anti-tumor effects without GVHD.

HCT also has potential as an approach to organ allograft tolerance induction. Immune tolerance denotes a state in which the immune system accepts donor organs or tissues but is capable of

Abbreviations: APC, antigen-presenting cell; ATG, anti-thymocyte globulin; ATS, anti-thymocyte serum; BMT, bone marrow transplantation; DLI, donor leukocyte infusion; GVHD, graft-versus-host disease; GVL, graft-versus-leukemia/lymphoma; GVT, graft-versus-tumor; HCT, hematopoietic cell transplantation; HLA, human leukocyte antigen; NKT, natural killer T; TLI, total lymphoid irradiation; TBI, total body irradiation.

* Corresponding author at: Columbia Center for Translational Immunology, Columbia University Medical Center, 650 West 168th Street, BB1512, New York, NY 10032, United States. Tel.: +1 212 304 5696; fax: +1 646 429 0019.
E-mail address: megan.sykes@columbia.edu (M. Sykes).

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doi:10.1016/j.smim.2011.05.001

responding normally to foreign antigens. While recent improvements in immunosuppressive drugs have enhanced early organ allograft survival rates, they have had little impact on late graft loss due to chronic rejection. Moreover, malignancies, opportunistic infections and metabolic and organ-specific toxicities severely limit the tolerability of long-term chronic immunosuppressive therapy. The induction of donor-specific immune tolerance would avoid these toxicities while preventing chronic rejection. The association of mixed chimerism, a state in which donor and recipient hematopoietic elements coexist, with a state of donor-specific tolerance, was first demonstrated in the pioneering studies of Owen on bovine mixed chimerism generated in utero due to sharing of a placental circulation [2]. However, achievement of chimerism in adult recipients with pre-existing immune systems is far more challenging, largely due to the immune resistance imposed by recipient T cells [3,4]. The potential of tolerance induction via allogeneic HCT has not been realized because of the considerable toxicity that has been associated with conditioning traditionally used to achieve hematopoietic cell engraftment in recipients with established immune systems.

In recent years, however, a variety of clinical HCT protocols have been developed for the treatment of hematologic malignancies that utilize reduced intensity conditioning. The two approaches to HCT discussed in this article involve reduced intensity conditioning regimens that have been associated with improvements in safety in patients with hematologic malignancies, even in the HLA-mismatched transplant setting. Efficacy data for the induction of transplantation tolerance were obtained initially in rodent models, followed by non-human primate studies. Critical safety data permitting the radical departure from the standard of care for organ transplantation entailed by removal from immunosuppression was obtained in the development of these regimens as less toxic approaches to HCT in the treatment of hematologic malignancies. Thus, our review describes how vertical translational research between animal models and humans and horizontal translation between the two separate goals of organ allograft tolerance induction and optimization of HCT for the treatment of malignancies has culminated in the first successful pilot studies of intentional allograft tolerance induction in humans.

2. Approach I: hematopoietic cell transplantation (HCT) for organ allograft tolerance induction and treatment of hematologic malignancies using conditioning with total lymphoid irradiation (TLI) and anti-thymocyte globulin (ATG) to prevent graft-versus-host disease (GVHD)

2.1. Studies in preclinical models of tolerance induction

The use of TLI in humans as a curative and safe treatment of Hodgkin's disease has been reported extensively in clinical trials in the United States and Europe based on the initial development of this radiotherapy procedure by Henry Kaplan and his colleagues at the Stanford University School of Medicine more than 50 years ago [5–7]. The TLI procedure was adapted to laboratory animal studies by Stanford investigators as a conditioning regimen for bone marrow transplantation to achieve mixed chimerism without the major side effect of GVHD in MHC mismatched strains of mice and rats [8–12]. The recipients were found to be tolerant to skin and heart allografts that were transplanted at the same time as the donor bone marrow cells after pretransplant conditioning that targeted the spleen, thymus, and peripheral lymph nodes with multiple small fractions of radiotherapy over a period of 2–3 weeks [8–12]. Radiotherapy was non-myeloablative and all recipients survived without marrow transplants [8–12]. However, marrow transplantation was required to achieve tolerance to organ grafts [8–12].

In order to model clinical bone marrow transplantation in which the marrow cells are heavily contaminated with blood T cells that are potent inducers of acute GVHD, spleen or peripheral blood mononuclear cells from donors were added to the marrow cells in the animal model [13–16]. When myeloablative or non-myeloablative total body irradiation (TBI) was used to condition recipients with combined marrow and spleen or blood cells, all recipients given MHC mismatched transplants developed lethal GVHD [13–17]. Although conditioning with TLI significantly reduced the severity of GVHD, a proportion of murine recipients still died of this complication [13]. However, the addition of injections of ATG (or anti-thymocyte serum; ATS) during the first week of TLI conditioning prevented the development of GVHD, and resulted in the survival of all recipients [13,16]. The number of donor T cells added to the bone marrow cells determined whether the TLI and ATS conditioned recipients became mixed or complete chimeras after transplantation [16]. When high numbers of splenic T cells were added (contained within 60×10^6 spleen cells), then recipients became complete chimeras, whereas when marrow cells alone were used then all recipients became mixed chimeras [16]. Protection against GVHD was observed regardless of whether the recipients became mixed or complete chimeras.

Since mixed chimerism is desirable for the development of tolerance to organ transplants, and complete chimerism increases the risk of GVHD, the protocols used for tolerance were designed to induce mixed chimerism, and the hematopoietic cell grafts were manipulated to contain restricted numbers of donor T cells [17]. On the other hand, complete chimerism is desirable for the development of graft anti-leukemia/lymphoma (GVL) activity for the treatment of hematologic malignancies, and protocols were designed to contain high numbers of donor T cells in the hematopoietic cell grafts [16]. Accordingly, the studies of tolerance and treatment of malignancies were performed along parallel but different paths due to the different goals.

In the case of tolerance to organ transplants, the conditioning regimen was changed to perform the TLI and ATG administration after the organ transplant was in place [18–21], in order to accommodate to the clinical situation of deceased donor organ transplantation. The timing of the availability of the latter organs is not predictable, and a posttransplant conditioning regimen is desirable. Accordingly, the laboratory animal models started the ATG on the day of organ transplantation, and the TLI 1 day later. After 2 weeks of posttransplant conditioning, the donor bone marrow cells were injected [18–21]. The delayed injection still resulted in uniform mixed chimerism in murine recipients, and tolerance to the organ grafts [18–21].

The mechanisms of tolerance using the posttransplant conditioning regimen have been studied in detail [22,23]. Both clonal deletion and immune regulation play required roles [22,23]. Clonal deletion in the mixed chimeras was demonstrated by examining the Vβ repertoire of T cells as compared to non-chimeric mice [22]. The requirement for regulatory NKT cells of host origin was shown by the abrogation of tolerance in NKT cell deficient $CD1d^{-/-}$ or $J\alpha18^{-/-}$ recipients [22,23]. An additional requirement for host Treg cells was shown by abrogation of tolerance after depletion of the Treg cells with an anti-CD25 monoclonal antibody [23]. Both types of regulatory T cells become favored subsets among surviving T cells due to resistance to apoptosis induced by the radiation and ATS [23,24].

2.2. Studies in preclinical models of treatment of lymphoma

The TLI and ATS conditioning regimen was adapted to treat the BCL1 B cell lymphoma in murine studies [16]. These recipients were given the tumor cells along with a combination of MHC mismatched marrow and spleen cells in order to induce complete chimerism