Considerations in the Selection of an Appropriate Conditioning Regimen for the Treatment of Rheumatoid Arthritis by Autologous Peripheral Blood Stem Cell Transplantation

ASHWIN KASHYAP and JOHN SNOWDEN

***ABSTRACT*.** Autologous hematopoietic stem cell transplantation (HSCT) is becoming more widely accepted as an investigational therapeutic modality for selected patients with severe autoimmune diseases such as rheumatoid arthritis. However, many aspects of the procedure remain controversial — not the least of these is the choice of conditioning regimen. This article briefly reviews the potential advantages and disadvantages of the conditioning regimens commonly employed for the treatment of severe autoimmune diseases in order to facilitate the development of future clinical trials of HSCT for rheumatoid arthritis. (J Rheumatol 2001;28 Suppl 64:39–41)

Key Indexing Terms:
HEMATOPOIETIC STEM CELL TRANSPLANTATION
AUTOIMMUNE DISEASES
RHEUMATOID ARTHRITIS
CONDITIONING REGIMENS

INTRODUCTION

Autologous hematopoietic stem cell transplantation (PBSCT) has emerged as an investigational therapy for the treatment of rheumatoid arthritis (RA) and other severe autoimmune diseases[1]. However, many aspects of the procedure remain controversial. Not the least of these is the choice of the conditioning regimen (the drugs or radiation employed just before reinfusion of stem cells to suppress the recipient's hematopoietic and immune system). The choice of regimen needs to take into account not only the usual short and longterm risks associated with transplant regimens in general, but also specific risks as they apply to protean manifestations of patients with RA. Further, these conditioning regimen toxicities have to be weighed carefully against their potential efficacy. Few data are currently available to help guide the choice(s) of conditioning regimen for the treatment of patients with severe autoimmune diseases in general and RA in particular. We review theoretical advantages and disadvantages of the various commonly employed conditioning regimens in conjunction with the limited preliminary data available in order to facilitate the development of future clinical trials (Table 1).

RADIATION BASED REGIMENS

Fractionated total body irradiation is usually administered in combination with chemotherapeutic agents such as cyclophosphamide and VP-16. This approach is attractive principally because of the potential efficacy of radiation as initially suggested by animal data from Van Bekkum, *et al* and indirectly supported by human data[2]. Radiation is known to be highly immunosuppressive in humans as shown by the relatively low graft rejection rate after allogeneic or matched unrelated donor transplantation even with some degree of histo-incompatibility[3]. The main concern with the use of radiation based regimens is their potential toxicities. These can be considered in 2 main groups: short and longterm. There are many short term toxicities that are well known to bone marrow transplant physicians: severe mucositis, interstitial pneumonitis, hepatic venoocclusive disease, pancytopenia with associated neutropenic fever, etc. Some of these are of heightened importance in patients with RA because of the unique nature of this disease. Preliminary experience from another autoimmune disease — systemic sclerosis — suggests that in patients that have significant underlying organ system damage (either from disease or prior therapy), the use of radiation may accentuate the risk of toxicity (McSweeney P, personal communication). Serious longterm toxicities of radiation are also a significant cause for concern. These include cataract development, sterility, permanent renal impairment, and most notably, the increased risk of developing secondary malignancies such as myelodysplastic syndrome and solid tumors[4]. For these reasons, this approach is unlikely to be widely employed in the treatment of patients with RA.

From the City of Hope National Medical Center, Duarte, California, USA; and Leicester Royal Infirmary, Leicester, United Kingdom.

Supported by NCI PPG CA 30206 and NCI CA 33572.

A. Kashyap, MD, City of Hope National Medical Center; J. Snowden, BSc (Hons), MD, MRCP, MRCPath, Consultant.

Address reprint requests to Dr. A. Kashyap, City of Hope National Medical Center, Department of Hematology and Bone Marrow Transplantation, 1500 E. Duarte Road, Duarte, CA 91010.
E-mail: akashyap@coh.org

Table 1. The most common preparative regimens for autologous hematopoietic stem cell transplantation.

Regimen	Dose	Common Toxicities
FTBI	12.0 Gy fractionated irradiation	GI, hepatic, pneumonitis, renal,
CY	120 mg/kg CY	secondary malignancy, cataracts, sterility
VP-16	60 mg/kg VP-16	
BEAM	BCNU 300–600 mg/m^2	Seizures, pneumonitis, GI,
	VP16 400–800 mg/m^2	cerebellar
	Cytarabine 800–1600 mg/m^2	
	Melphalan 140 mg/m^2	
CY	CY 200 mg/m^2	Cardiac, bladder
Bu/CY (oral)	Oral Bu 1 mg/kg × 16 doses	Seizures, hepatic, GI, alopecia, sterility
	CY 120 mg/kg	
Bu/CY (IV)	IV Bu 0.8 mg/kg × 16 doses	Seizures, alopecia, sterility
	CY 120 mg/kg	

FTBI: total body irradition, CY: cyclophosphamide, Bu: busulfan.

CYCLOPHOSPHAMIDE BASED REGIMENS

Cyclophosphamide has relatively low toxicity, even in the dose-escalated setting, and therefore has been a popular choice as a conditioning modality for autologous hematopoietic stem cell transplantation (HSCT) in patients with RA. It has also been used, in a dose-escalated manner without stem cell support, in a small number of highly selected patients with aplastic anemia, lupus, and RA[5]. However, the degree of efficacy is of some concern. Initial experiences with patients with aplastic anemia undergoing allogeneic transplantation using cyclophosphamide alone as compared to cyclophosphamide with radiation showed a high graft rejection rate, suggesting a relative lack of immunosuppression[6]. Also, the initial experience of patients with RA treated with cyclophosphamide based regimens by autologous transplantation has been somewhat disappointing because of a relatively high relapse rate. It may be theorized that this is due to the lack of a myeloablative effect of this drug[7]. The cardiotoxicity associated with this drug could be of concern. Therefore, although cyclophosphamide is well tolerated, it may be suboptimal for conditioning by itself[7].

BEAM

This conditioning regimen (carmustine (BCNU), etoposide, cytarabine, and melphalan) has been extensively used, particularly in Europe, for autologous transplantation of patients with hematologic malignancies (principally lymphoma) and more recently severe autoimmune diseases. Indeed it is the most commonly used regimen in Europe for transplantation for multiple sclerosis[8]. It is generally well tolerated. The BCNU component is of concern as it can cause significant late lung toxicity, which may be additive to other underlying lung problems in patients with severe autoimmune disease, such as RA or systemic sclerosis[9].

ORAL AND INTRAVENOUS (IV) BUSULFAN BASED REGIMENS

Oral busulfan has long been used as an allogeneic transplant conditioning regimen agent because of its profound myeloablative properties[3]. This agent is also very immunosuppressive. It has been used extensively to overcome immunologic barriers to facilitate standard allogeneic and matched unrelated donor transplants with low graft rejection rates[10]. The main disadvantage of this agent is that it has very variable bioavailability[11]. This may be a contributing factor to both the relatively high incidence of venoocclusive disease of the liver associated with this drug and the increased incidence of graft rejection, as compared to radiation based regimens, when plasma levels are either too high or too low, respectively[10,12]. This drug also has longer term side effects that are noteworthy, such as sterility and permanent alopecia, in a small percentage of patients.

Because of the limitations of oral busulfan, IV busulfan has recently been developed and used in conjunction with cyclophosphamide and antithymocyte globulin for the treatment of patients with severe autoimmune diseases. The principal attractions are still largely theoretical. IV busulfan has significantly lower toxicity — especially venoocclusive disease — compared to oral busulfan. This may be due to the lack of a liver first-pass effect seen with this agent[13]. IV administration of this drug also ensures high bioavailability, maximizing the known immunosuppressive effect of busulfan[14]. However, this agent has only become widely available recently and longterm effects, such as permanent alopecia, remain to be quantified. Therefore it can only be regarded currently as a relatively novel choice, both for use as a conditioning agent for transplant of severe autoimmune disease in general and RA in particular.

MONOCLONAL ANTIBODIES

The application of recombinant DNA technology has ushered in a new era in cancer therapy, which may be very applicable in the development of new conditioning regimens for RA transplantation. We are moving from the use of nonspecific antibodies (e.g., antithymocyte globulin) to highly specific monoclonal antibodies such as Rituximab (anti-CD20) or Campath 1-H (anti-CD52). This advance will undoubtedly be applied to conditioning regimens in general and probably to those used in the treatment of severe autoimmune diseases such as RA.

FLUDARABINE BASED REGIMENS

Fludarabine is in some respects an attractive, if somewhat novel, choice. It is relatively nontoxic in low doses, such as those in therapy for treatment of hematologic malignancies (e.g., low grade non-Hodgkin's lymphoma) in the nontransplant setting. It is also clearly immunosuppressive — being a key component of many "mini" allogeneic transplant regimens[15]. Unfortunately, the efficacy of this agent in the treatment of autoimmune diseases in standard doses has undergone very limited testing. There is very little experience with the use of this agent as part of an *autologous* (vs allogeneic) HSCT conditioning agent for the suppression of hematologic malignancies. Initial experience with fludarabine at higher doses (e.g., treatment of acute myelogenous leukemia) suggested that it was relatively toxic — leading to very prolonged neutropenia[16]. The cause of this prolonged neutropenia is unclear; it is also unclear whether this can be overcome by performing autologous HSCT. Further, in a dose-escalated manner, this agent does have other serious toxicity — especially neuropathy[16].

REFERENCES

1. Passweg J, Gratwohl A, Tyndall A. Hematopoietic stem cell transplantation for autoimmune disorders. Curr Opin Hematol 1999;6:400-5.
2. Van Bekkum DW. BMT in experimental autoimmune disease. Bone Marrow Transplant 1993;11:183-7.
3. Bensinger W, Buckner CD. Preparative regimens. In: Thomas ED, Blume K, Forman SJ, editors. Hematopoietic cell transplantation. Oxford: Blackwell Science; 1999:123-34.
4. Armitage J. Myelodysplasia and acute leukemia after autologous bone marrow transplantation. J Clin Oncol 2000;18:945-6.
5. Brodsky RA, Petri M, Smith BD, et al. Immunoablative high dose cyclophosphamide without stem cell rescue for refractory, severe autoimmune disease. Ann Intern Med 1998;12:1031-5.
6. Storb R. Transplantation for nonmalignant disease, allogeneic marrow transplantation in patients with aplastic anemia. In: Marrow transplantation reviews. Kluge-Carden-Jennings 1993:61-6.
7. McSweeney PA, Furst DE, West SG. High-dose immunosuppressive therapy for rheumatoid arthritis: Some answers, more questions. Arthritis Rheum 1999;42:2269-74.
8. Fassas A, Anagnostopoulos A, Kazis A, et al. Autologous stem cell transplantation in progressive multiple sclerosis — an interim analysis of efficacy. J Clin Immunol 2000;20:24-30.
9. Phillips GL, Fay JW, Herzig GP, et al. Intensive 1,3-bis (2-chloroethyl)-1-nitrosourea (BCNU), NSC #4366650 and cryopreserved autologous marrow transplantation for refractory cancer. A phase I-II study. Cancer 1983;10:1792-802.
10. Slattery JT, Sanders JE, Buckner CD, et al. Graft-rejection and toxicity following bone marrow transplantation in relation to busulfan pharmacokinetics. Bone Marrow Transplant 1995; 16:31-42.
11. Grochow I. Busulfan disposition: The role of therapeutic monitoring in bone marrow transplantation induction regimens. Semin Oncol 1993;20:18-25.
12. McDonald GB, Hinds Ms, Fisher LD, et al. Veno-occlusive disease of the liver and multiorgan failure after bone marrow transplantation: A cohort study of 355 patients. Ann Intern Med 1993;118:255-67.
13. Intravenous vs oral busulfan as part of a Bu/Cy (cyclophosphamide) preparative regimen for allogeneic hematopoietic stem cell transplantation: decreased incidence of hepatic veno-occlusive disease (VOD), VOD related mortality and overall 100-day mortality [abstract]. Bone Marrow Transplant 2000;25:81.
14. Vaughan WP, Cagnoni P, Fernandez H, et al. Pharmacokinetics of intravenous busulfan in hematopoietic stem cell transplantation [abstract]. Presented at ASBMT Meeting, March 1999, Keystone, Colorado.
15. Slavin S. New strategies for bone marrow transplantation. Curr Opin Immunol 2000;12:542-51.
16. Von Hoff DD. Phase I clinical trials with fludarabine phosphate. Semin Oncol 1990;17 Suppl 8:3-8.