

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

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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
RHEUMATOID ARTHRITIS

AUTOIMMUNE DISEASES
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 diseases¹. 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 data². 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-incompatibility³. 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 tumors⁴. For these reasons, this approach is unlikely to be widely employed in the treatment of patients with RA.

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

FTBI: total body irradiation, 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 RA⁵. 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 immunosuppression⁶. 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 drug⁷. The cardiotoxicity associated with this drug could be of concern. Therefore, although cyclophosphamide is well tolerated, it may be suboptimal for conditioning by itself⁷.

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 sclerosis⁸. 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 sclerosis⁹.

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 properties³. 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 rates¹⁰. The main disadvantage of this agent is that it has very variable bioavailability¹¹. 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 agent¹³. IV administration of this drug also ensures high bioavailability, maximizing the known immunosuppressive effect of busulfan¹⁴. 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 regimens¹⁵. 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 neutropenia¹⁶. 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 neuropathy¹⁶.

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