Nonmyeloablative Allogeneic Hematopoietic Cell Transplants: Any Role for Rheumatoid Arthritis?

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ABSTRACT. Recent studies have suggested limited efficacy of high dose cyclophosphamide and autologous stem cell transplant as a treatment for severe rheumatoid arthritis. Preclinical data and anecdotal evidence from human transplants suggest that greater efficacy and possible cures might be achieved through use of allogeneic transplants. Newer less intensive methods of allogeneic transplantation have been introduced that reduce morbidity and mortality of the procedure. This article reviews the possible role of so-called nonmyeloablative transplants in the treatment of RA. (J Rheumatol 2001;28 Suppl 64:49–54)

Key Indexing Terms:
RHEUMATOID ARTHRITIS NONMYELOABLATIVE ALLOGENEIC TRANSPLANT

INTRODUCTION

Initial studies of high dose immunosuppressive therapy have recently been undertaken for severe rheumatoid arthritis (RA). Mixed results have been obtained in refractory RA, with some patients having sustained remissions but a majority relapsing early 1-4. Thus, with current approaches that mainly use high dose cyclophosphamide (CY) before autologous transplant, it seems unlikely that many cures will be achieved. Introduction of relatively effective newer agents has further restricted the investigation of dose intensive therapy. The longterm efficacy, toxicity, and cost-effectiveness of treating RA with newer tumor necrosis factor blocking drugs remain to be fully determined. Further, these agents do not cure the disease and patients require continued therapy to maintain disease control. Even with these improved treatments there will likely remain a subgroup of RA patients who will fail all available conventional therapies and pay a severe toll in life quality and ultimately survival due to disease and/or its treatment. Does allogeneic hematopoietic stem cell transplantation (HSCT) offer a potentially useful therapy for these patients through offering a possible cure of RA? This article reviews available evidence and discusses theoretical and practical issues for using allo-HSCT in RA.

ANIMAL MODELS

An important rationale for the current trials of high dose therapy and autologous SCT for autoimmune disease has come from studies in rodent models of autoimmune diseases. Allografting and to a lesser extent autologous transplants were effective in models for multiple sclerosis, systemic lupus erythematosus (SLE), RA, and diabetes mellitus among others 5,6. Allogeneic transplants were superior to autologous transplants with higher disease cure rates and protection from relapses. Two mechanisms appear to contribute to disease control in these models. First, high dose therapy with total body irradiation (TBI) or other agents can suppress disease in some models but not others. Second, establishment of donor chimerism with disease resistant strains of marrow appears to confer resistance to autoimmunity. Some experiments have suggested that mixed hematopoietic chimerism may be adequate for control of autoimmunity 7,8. Overall, these results have suggested that autoimmunity might be modulated through control of host hematopoietic and lymphoid cells, either through their regulation or through eradication by donor cells.

REPORTS FROM CONVENTIONAL ALLOGRAFTING FOR HEMATOLOGIC DISEASES

A small number of case reports have provided evidence that allogeneic HSCT may be successful in eradicating autoimmune diseases 9-13. Many of these cases involved patients with RA who developed aplastic anemia after gold therapy (Table 1). They received high dose cytotoxic therapy, usually with high dose CY, allogeneic bone marrow infusions, and temporary treatment with immune suppressing drugs to prevent or treat graft-versus-host disease (GVHD). Relative proportions of donor-host chimerism in blood and marrow were not well documented early in these transplants. A longterm followup report from Australia included 3 patients with RA who were in disease remissions at 14, 13, and 10 years after HSCT 9. In 2 patients studied, T cells were entirely of donor origin. In one patient an early recurrence of RA was of mild severity compared to previous disease and ran an attenuated course before entering a treatment-free remission of 11 years. A report from Canada documented recurrence of RA after allogeneic HSCT for aplastic anemia 14. After a posttransplant 2 year interval free of symptoms the patient developed evidence of RA, with typical joint disease and elevation of rheumatoid factor that had dropped to zero after transplant. Chimerism analyses from unfractionated peripheral blood showed full donor chimerism. This report suggests that allogeneic transplants would not be
invariably successful in controlling RA. Overall, these data suggest that a high frequency of disease control may be achieved after allogeneic HSCT for autoimmune diseases. However, it is not clear whether patients with hematologic diseases/malignancy and autoimmunity are surrogates for patients with autoimmunity but without malignancy.

At least 3 components of conventional allografting could contribute to control of RA. The first component is the intensely immunosuppressive conditioning given before the transplant. Second is the use of immune suppressing drugs such as cyclosporine, methotrexate, and prednisone given after transplant to prevent and control GVHD. Third is the establishment of a partial donor or full donor immune system. The first 2 would be expected to provide at least temporary relief from disease. Establishing donor chimerism might achieve long lasting disease control through at least 2 mechanisms. The first is through control of autoimmunity by introduction of regulatory immune cells with the graft. The second is through complete eradication of the recipient immune system through a graft-versus-host reaction similar to GVHD in which host hematolymphoid cells are targets of donor T cells through presentation of minor histocompatibility antigens or possibly other cellular targets. The establishment of donor chimerism most likely has a role given observations in allogeneic HSCT recipients with aplastic anemia. Because these patients were usually conditioned with high dose CY, similar to the regimens used in recent autografting failures with RA, the longterm control of autoimmunity seen in the allograft recipients may well relate to the allogeneic effect of donor chimerism.

When recommendations for initial transplants in autoimmune diseases were first proposed, allogeneic transplants were considered too risky for investigation in autoimmune diseases. To date, conventional allografting has been performed as the treatment of several patients with Evans’s syndrome and patients with systemic sclerosis (R. Nash, personal communication). However, newer approaches of nonmyeloablative HSCT developed in the last few years are considerably less toxic than conventional allografts and would appear to be much more appropriate for any initial studies in autoimmune disease. Thus the following sections will focus on the possible application of nonmyeloablative SCT to RA.

### INITIAL EXPERIENCES WITH NONMYELOABLATIVE SCT

The finding that fully ablative conditioning therapy could be replaced with much less intensive but still sufficiently immunosuppressive regimens that result in stable and frequently full allogeneic engraftment has set the stage for reshaping of approaches to allogeneic HSCT. Specifically, the use of reduced intensity nonmyeloablative regimens has allowed older and less medically fit patients to undergo allogeneic HSCT with acceptable toxicity. The term nonmyeloablative, while not entirely satisfactory, implies that the regimen will not ablate host hematopoiesis and that peripheral blood counts would recover within a month or so if the regimen was given without stem cell transplant. This definition, however, does not account well for differences in host hematopoietic reserve and may overestimate the safety of the regimens in this regard. The underlying concept of these transplants for malignancy is different from conventional allogeneic HSCT that relies on high dose conditioning therapy to suppress immunity and underlying disease.

Conditioning therapy for nonmyeloablative allogeneic HSCT is given to facilitate engraftment and in some cases to suppress underlying disease. In malignant disease a graft-versus-tumor reaction is required for ultimately eliminating the cancer. Different conditioning therapies of varying intensities have been used (Table 2). While some regimens, e.g., fludara-bine-busulfan, have been described as nonmyeloablative, the underlying basis for this description has not been fully substantiated. Some have involved attenuated conventional transplant regimens and some have used conventional-dose disease-directed chemotherapy. A component of many of these

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**Table 1. Results of allografting in patients with RA and severe aplastic anemia.**

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age, yrs</th>
<th>Duration of RA, yrs</th>
<th>Transplant Regimen</th>
<th>Year of Transplant</th>
<th>GVHD</th>
<th>Survival</th>
<th>Disease Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>34</td>
<td>4</td>
<td>CY 200 mg/kg</td>
<td>1974</td>
<td>Yes</td>
<td>20 yrs</td>
<td>Yes</td>
</tr>
<tr>
<td>2</td>
<td>48</td>
<td>3</td>
<td>CY 200 mg/kg</td>
<td>1974</td>
<td>Yes</td>
<td>93 days</td>
<td>Yes, short followup</td>
</tr>
<tr>
<td>3</td>
<td>34</td>
<td>15</td>
<td>CY 200 mg/kg</td>
<td>1974</td>
<td>No</td>
<td>75 days</td>
<td>Yes, short followup, graft rejection</td>
</tr>
<tr>
<td>4</td>
<td>43</td>
<td>10</td>
<td>CY 200 mg/kg</td>
<td>1975</td>
<td>No</td>
<td>58 days</td>
<td>Yes, short followup</td>
</tr>
<tr>
<td>5</td>
<td>34</td>
<td>1</td>
<td>CY 200 mg/kg</td>
<td>1982</td>
<td>Yes</td>
<td>14 yrs</td>
<td>Attenuated RA, then remission for &gt; 11 yrs</td>
</tr>
<tr>
<td>6</td>
<td>27</td>
<td>6</td>
<td>CY 200 mg/kg</td>
<td>1984</td>
<td>Yes</td>
<td>13 yrs</td>
<td>Yes</td>
</tr>
<tr>
<td>7</td>
<td>30</td>
<td>9</td>
<td>CY 200 mg/kg</td>
<td>1986</td>
<td>Yes</td>
<td>10 yrs</td>
<td>Yes</td>
</tr>
<tr>
<td>8</td>
<td>52</td>
<td>8</td>
<td>Prednisone, CY 200 mg/kg, TBI 400 cGy</td>
<td>1982</td>
<td>No</td>
<td>13 yrs</td>
<td>No, relapse after 2 year remission</td>
</tr>
</tbody>
</table>

CY: cyclophosphamide; GVHD: graft-versus-host disease; TBI: total body irradiation.
transplant regimens has been the purine analog fludarabine, which is relatively nontoxic but highly immunosuppressive. Some regimens have incorporated immunosuppressive antibodies such as antithymocyte globulin or CAMPATH-1H to reduce graft rejection risk and they may also reduce the risk of GVHD. The mortality rate for treatment of patients with malignancy has generally exceeded 10% with the use of HLA-matched sibling donors, and this remains an impediment to applying this approach to autoimmune diseases. The use of unrelated donors, mismatched family donors, or cord blood further increases the hazards from the procedure.

Conceptually important work in a large animal model has come from canine preclinical studies showing that immunosuppressive agents given after HSCT could reduce the amount of pretransplant conditioning therapy (and hence toxicity) required for achieving stable allografts. An immunosuppressive regimen of pretransplant low dose TBI (200 cGy) and posttransplant cyclosporine (CSA)/mycophenolate mofetil (MMF) allowed development of stable mixed chimerism, largely without GVHD, in dogs who received grafts from major histocompatibility complex (MHC) matched littermates. Further, TBI dose reductions were possible through the use of costimulation blockade. In human studies low dose TBI/CSA/MMF has been mildly myelosuppressive and very well tolerated when applied to older patients and younger medically compromised patients with hematologic malignancies, allowing transplants to become an outpatient procedure. In our initial report, this approach was associated with a transplant mortality of 6.7% despite the high risk patient population. While nonfatal graft rejection followed by hematopoietic recovery occurred in 20% of patients, this problem has been largely eliminated by addition of 3 doses of fludarabine to the TBI. The major limitation of this and other nonmyeloablative HSCT is the still appreciable incidence of GVHD. However, it is likely that this problem can be at least partially dealt with by modifications of the immunosuppressive regimen.

**NONMYELOABLATIVE SCT FOR RA**

Several issues need to be considered in determining whether trials of nonmyeloablative SCT should be performed in RA: (1) the underlying theoretical rationale and potential for efficacy; (2) which patients, if any, would be appropriate for allogeneic HSCT; and (3) what would be the appropriate approach to allografting given the current safety profile — what modifications, if any, from existing strategies might be indicated?

Any rationale for allogeneic HSCT needs to account for the pathogenesis of RA. Although not fully understood, evidence supports an important role for antigen activated CD4+ T cells stimulating monocytes, fibroblasts, and synovial cells through cell-surface interactions and cytokine elaboration. These cells then elaborate proinflammatory cytokines such as tumor necrosis factor, interleukin 1, and interleukin 6. The CD4+ T cells also stimulate B cells to produce autoantibodies, the role of which in RA pathogenesis remains unclear. Thus host lymphohematopoietic cells represent targets for achieving disease control and possible cure, either through their elimination or regulation. Animal studies and anecdotes from human transplant experience support the idea that allogeneic HSCT would be effective. Disappointing results from initial autografting studies temper this idea, however, since dose intensive immunosuppression was only able to produce short-lived remissions in most cases. These results contrast with those in refractory SLE, where essentially identical therapy with high dose CY was able to produce sustained responses. In considering the possible role of allogeneic HSCT, a greater under-
standing of the pathogenesis of RA, with respect to which cell populations would be targets for allografting, would greatly assist attempts to use this modality.

The choice of candidates for any initial nonmyeloablative SCT trials must take into account risks of nonmyeloablative SCT, morbidity and mortality of RA, and availability of alternative therapies. Heavily pretreated patients, those usually enrolled in trials of toxic new procedures, may be at increased risks from allografting procedures. In general, patients with RA would not have severe preexisting damage to kidneys, lungs, liver, and heart that would preclude the use of low intensity immunosuppressive regimens that have minimal related toxicities and are less intensive than high dose CY as used in initial autografting studies. Further, patients with RA rarely receive conventional therapy of the intensity frequently given to many cancer patients prior to allografting. Given the younger age profile compared to patients with malignancy who have received nonmyeloablative SCT to date, patients with RA might have lower mortality risk than reported with nonmyeloablative SCT. Thus, barring unforeseen disease-specific toxicities, no increased risk from nonmyeloablative SCT would be anticipated in patients with RA. Because the known risks of allografting would dissuade many physicians from referring patients until all other therapeutic avenues are exhausted, initial transplants would likely be performed in high risk patients. Fortunately, even prior exposure to high dose regimens does not appear to substantially increase risk of nonmyeloablative SCT using the least toxic regimens such as low dose TBI/CSA/MMF or fludarabine/CY. Thus, from the perspective of regimen related toxicities, these regimens have significant advantages. Circumstances of failed intensive prior therapy and the likelihood of needing protracted toxic immunosuppressive therapy might warrant trials of allografting. Children with severe juvenile chronic arthritis might therefore be more appropriate candidates for nonmyeloablative SCT than adults with RA. In children, nonmyeloablative SCT regimens would be unlikely to lead to regimen related growth and development problems as observed after conventional allografting.

Current approaches to nonmyeloablative SCT are aimed at inducing mixed or full donor chimerism and graft-versus-tumor reactions. A conceptual approach for using nonmyeloablative transplant is shown in Figure 1 and proposes 2 therapeutic strategies that could be used alone or sequentially. In one, the establishment of mixed chimerism per se could be tested with the idea that regulatory cells from the graft might control the autoimmunity. Stable mixed chimerism would imply that donor-host tolerance was achieved and thus a reduced risk of GVHD would be likely. However, stable mixed chimerism, while achievable in canine studies, has not been reliably established with low intensity conditioning in patients with malignancy. In a second strategy, full donor chimerism is the goal with the eradication of autoreactive cells using a graft-versus-autoimmunity (GVA) effect. This might be achieved as the initial transplant goal or by using donor lymphocyte infusion (DLI) after testing in a given patient whether mixed chimerism has achieved a therapeutic effect. GVHD and mortality risks will be higher with this strategy than with solely establishing mixed chimerism.

Most nonmyeloablative SCT have used unmodified peripheral blood stem cell (PBSC) grafts, although in vivo T cell depletion has been tested. Because the lower intensity regimens cannot be expected to cure the malignancies, some compromise in GVHD prevention is taken through shorter duration of postgrafting immunosuppression and the relatively early use of DLI for persistent or progressive disease or persistence of mixed chimerism. DLI poses a significant risk of GVHD to the recipient. PBSC have been used almost exclusively for their engraftment enhancing properties, including faster engraftment and probable lower graft rejection risk. However, PBSC grafts may increase the risk of chronic GVHD, in our experience the main cause of transplant mortality. The incidence may exceed 60%, require longterm therapy with immunosuppressive agents, and expose the recipient to protracted risks of serious infections and organ damage. Further, since followup is short and many initial patients treated on nonmyeloablative protocols have died of their underlying disease, a comprehensive picture of the risks of chronic GVHD has not yet emerged.

Because acute and chronic GVHD pose the biggest risk in these transplants, minimizing the GVHD risk might be achieved through several approaches: (1) Extend the period of postgraft immunosuppression. (2) Use marrow or T cell adjusted grafts to lower the T cell doses given. (3) Obtain more extensive T cell depletion of the grafts. While this would reduce GVHD, drawbacks include an increased risk of graft rejection and more infectious complications. More intensive regimens would be required to ensure engraftment and mixed chimerism occur more frequently. Theoretical drawbacks include the lack of a GVA effect and removal of potentially important regulatory cells from the donor graft. Overall, treatment related mortality from nonmyeloablative SCT is 10–20%; this needs to be factored into any planned trials.

**SUMMARY AND CONCLUSIONS**

While allografting as a curative strategy has appeal for treatment of patients with severe autoimmune disease including RA, the risks of such therapy require caution during investigation. Newer methods of allografting can reduce transplant risks substantially, but do not eliminate risks of GVHD and death. Patients with RA may be good candidates, in that organ dysfunction is likely to be minimal and trials could be restricted to younger patients. However, the low risk of short term mortality attributable to RA means that transplant mortalities must be very low to justify allografting. Careful selection of candidates would be necessary to include only those with severe and life threatening RA. In this regard, whether previ-
ously determined survival prognosticators for RA apply needs to be determined.

With regard to the broad concept of using allogeneic HSCT for severe autoimmune disease, it may be more appropriate to investigate life threatening disease such as severe systemic sclerosis and severe SLE before studying RA. Candidates who fail prior autologous transplants might be the most suitable candidates for any initial trials. Modifications of current approaches may soon reduce allogeneic HSCT mortalities in good risk patients to 5% or below, but this remains to be confirmed. Initial studies should be limited to the use of HLA matched sibling donors, where the risks of GVHD and mortality are lower than with lesser matched donors. Finally, it would be advisable that any initial nonmyeloablative SCT trials in autoimmune diseases use transplant procedures already established in other settings to avoid introducing new variables that might confuse analysis of results.

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