Hematopoietic Stem Cell Transplantation

Reduced-Intensity Stem Cell Transplantation

“...whereof a little More than a little is by much too much.” King Henry IV, part 1, I, 2

Joseph H. Antin

Dana-Farber Cancer Institute; Brigham and Women’s Hospital; Harvard Medical School, Boston, MA

The recognition that the immune system can play a major role in the control and cure of transplantable disorders led to the development of reduced-intensity allogeneic transplantation. The notion is that a compromise can be made between the intensity of conditioning and the fostering of graft-versus-host disease/graft-versus-leukemia (GVHD/GVL), allowing the use of less intense conditioning with concomitantly less intense immediate toxicity. Reduced-intensity conditioning regimens have allowed the application of transplantation to older patients and to patients with underlying medical problems that preclude full-dose transplantation. Clearly, in some settings in which dose intensity is important, reduced-intensity regimens are less useful. However, for diseases that are either indolent, highly susceptible to GVL, or under good control before entering transplantation, this approach appears to have substantial benefits. Although the therapy appears to be valuable, concerns about delayed immune reconstitution and GVHD remain.

Introduction

The transplantation community has progressively re-evaluated our concept of how stem cell transplantation (SCT) can be used most effectively as we have learned more about the underlying mechanisms of the procedure. The original thinking provided for an escalation on the dose-response cure using the hematopoietic stem cell transfer as a cellular antidote to otherwise lethal conditioning. The need for high-dose cytoreduction has not been eliminated; however, it is now recognized that the notion that the transplantation was simply the provision of a cellular antidote to myelotoxic conditioning is simplistic. It is clear that dose intensity is very important in some diseases, less important in others, and is probably unnecessary in some diseases, where its primary role is to facilitate the graft. The basis of this change in paradigm was the recognition that in many circumstances long remissions are due less to the intensity of the therapy than to ongoing immunologic control of the malignancy by the donor immune system. This concept resulted in transplantations in which the conditioning regimen was de-escalated or attenuated, and the reduced dose is compensated for by immunologic disease control. These have been called either reduced-intensity or nonmyeloablative transplantations. Since even low-intensity regimens can ultimately result in eradication of the host lymphohematopoiesis, the least controversial and least confusing nomenclature is reduced-intensity conditioning (RIC) transplantation. One of the main limitations of transplantation had been that most people with transplantable diseases were beyond the age at which high-dose regimens are thought to be feasible. Moreover, there are both adults and children with underlying medical problems that precluded the use of high-dose regimens. The appeal of this idea and the demand for transplantation in people who are not eligible for conventional dose transplantation is demonstrated by a recent European Bone Marrow Transplantation (EBMT) analysis of transplantation usage in Europe. Between 2004 and 2005 RIC procedures increased by about 20%, and they comprised 34% of all allogeneic transplantations in 2005. Of course, it should be kept in mind that transplantations for aplastic anemia had mostly been reduced-intensity procedures, as demonstrated by the frequency of autologous recovery. The new twist was applying reduced-intensity transplantation to malignant diseases.
Background
In the 1950s, investigators observed that the leukemia relapse rate was lower in experimental allogeneic transplantation in mice than expected. In the first two decades of clinical transplantation, similar phenomena were noted in human transplantation and the effect was termed graft-versus-leukemia (GVL).\(^2\)-\(^5\) Initial efforts to take advantage of this effect were unsuccessful, because the investigators administered large numbers of T cells early after the transplant, resulting in such severe graft-versus-host disease (GVHD) that the GVL response was probably obscured.\(^6\) However, Kolb and colleagues demonstrated the first unequivocal GVL reaction in humans. They restored clinical remissions by infusing donor lymphocytes (DLI) in patients with chronic myelogenous leukemia (CML) who had relapsed after allogeneic transplantation.\(^7\) A subsequent study by Porter and colleagues demonstrated that without any cytotoxic therapy, donor lymphocytes could reduce the CML burden by at least one million-fold.\(^8\) If donor immune cells are important in allogeneic transplantation and are capable of inducing a remission without additional chemotherapy, then the intensity of the conditioning might be reduced to ameliorate its intrinsic toxicity. This would allow the application of SCT to older patients and patients with underlying medical problems who were not eligible for conventional-dose transplantsations. Porter and colleagues infused unmanipulated peripheral blood cells in the absence of conditioning and showed that a GVL response could be observed. However, it was clear that immunosuppression was necessary in most patients to prevent rejection of the graft.\(^9\) A large number of studies have been published using different conditioning strategies.\(^10\)

Two of the most prevalently used conditioning strategies are fludarabine and low-dose total body irradiation (TBI) as developed by the Seattle group and fludarabine and busulfan variants as popularized by Slavin and colleagues.\(^12\) As noted above, malignant stem cells may differ in their susceptibility to immunologic control. This may reflect cell surface presentation of molecules that can be recognized by the immune response, the expression of costimulatory molecules, or the proliferative rate of the malignancy. An allogeneic response is not immediate. The T cells must be infused, recognize antigen, become activated, proliferate to a critical mass, infiltrate the site of the cancer, and kill the malignant cells. Even in the case of CML, one of the diseases most sensitive to immunologic control, 4 to 6 weeks are required to see a response, and responses may occur as late as 10 to 12 months after the allogeneic cell infusion. Interestingly, this delay correlates with observations that chronic GVHD may have a more potent effect than acute GVHD. Moreover, it is likely that the sustained immune reactivity is an advantage compared with chemotherapy, i.e., long-term persistent antimalignant activity is the hallmark of GVL compared with time-limited cytotoxicity observed with conventional chemotherapy. The latency between the lymphocyte infusion and the development of an effective immune response is an Achilles heel of RIC transplantation. Rapidly growing diseases seem to be less susceptible to control. While the reasons for this may be multifactorial, at least one hypothesis is that they outgrow the ability of the T cells to control them.

What Are the Targets of Immunologic Attack?
One measure of the effectiveness of RIC is the establishment of full donor chimerism. In ablative, T-replete transplantation, the donor lymphohematopoiesis typically dominates immediately. However, in RIC there may be a period of mixed chimerism. The prevalence of mixed chimerism in the early stages and the ability of DLI to foster full chimerism suggest that graft-versus-hematopoiesis is a principal mechanism of this therapy. Regimens that result in high levels of chimerism often need DLI to prevent relapse.\(^13\)-\(^15\) There are a limited number of potential targets that can induce the immune system. One possibility is that there are cancer-specific proteins that are sufficiently immunogenic to allow a graft-versus-malignancy response in the absence of GVHD. However, even obvious candidates such as P210 BCR-ABL and PML-RAR\(^\alpha\) do not appear to be the targets of immunologic attack. There is some evidence that proteinase 3 may be a target in some malignancies.\(^16\) Epstein-Barr virus lymphoproliferative disorders may be quite susceptible to attack that is triggered by the viral proteins,\(^17\) and since the donor may be immune to the virus, the anticancer effect may be prompt. Under very specific conditions there do appear to be cases in which a leukemia-specific immune response can be generated.\(^18\) However, it is likely that these are the exception. Fortunately, in the context of RIC for lymphohematopoietic diseases, this distinction is not critical. Thus, antigens limited to hematopoietic precursors or mature cells that are not present on epithelia would function equally well as cancer-specific antigens. Thus, the ability of DLI or RIC to result in complete hematopoietic chimerism and the association of complete chimerism with response suggests either that an immune response to hematopoietic precursors and the malignancy are generated simultaneously, or that a common set of antigens is involved. The use of RIC in nonmalignant disorders such as sickle cell disease, other congenital disorders of hematopoiesis, and congenital disorders of metabolism are clearly not targeting a cancer-specific protein. Finally, it is possible that there is no specificity to the effect and that when GVL is observed in the absence of GVHD it simply reflects either the presence of subclinical GVHD or a difference in target-effector ratio that allows the few malignant cells to be eradicated while causing injury to the normal tissues that is promptly and subclinically repaired. Many studies show a relationship between the development of GVHD and the anticancer effect and, interestingly, evidence that unrelated donor transplantation may have a more potent GVL response than sibling donor transplantation.\(^19\)-\(^22\)
Conditioning Regimens

The emphasis on GVL in the RIC procedures should not outweigh the overall importance of dose intensity—at least in some diseases. Conventional-dose ablative transplantations have the advantage of both dose intensity and GVL but suffer from the intrinsic toxicity of the high dose regimens. It is likely that if the two approaches had similar morbidity and currently observed relapse rates, there would be little interest in RIC. A value judgment must be made on the relative importance of dose compared with regimen-related toxicity.

Commonly used reduced-intensity regimens differ significantly in their effects on the lymphohematopoietic system. The range from low-intensity regimens with little cytoreduction, such as FLAG or cyclophosphamide/fludarabine, to somewhat higher-dose regimens such as low-dose TBI (2 Gy) in combination with chemotherapy and fludarabine/busulfan, to fairly dose-intense regimens using moderately high-dose melphalan or doses of TBI up to 5.5 Gy. Moreover, one can apply therapy that is primarily lymphodepleting with little myelotoxicity. Unfortunately, there are no prospective comparisons of these regimens and importantly there are no prospective comparisons of RIC transplantation to conventional-dose conditioning regimens. Unless one is solely interested in regimen-related toxicity, such comparisons would need to be disease-specific, since there are clearly regimens that appear to be more effective in a given illness. Several retrospective comparisons of RIC with conventional transplantation have been undertaken; however, it is extremely difficult to make sensible comparisons. The RIC transplantation subjects were typically older, had co-morbid illnesses (often a high Charlson co-morbidity score), and were enriched for prior failed transplantations. In addition, at least one analysis of ablative transplantation in older people (60-68 years) has similar outcomes to RIC. Nevertheless, a fair summary of the data is that in some diseases, such as acute myeloid leukemia (AML) or intermediate-grade lymphoma, dose intensity has an important role. In less aggressive diseases such as low-grade lymphomas the role of dose intensity is far less clear. As shown in the two examples in Table 1, transplantation-related morbidity is usually lower in RIC procedures, but relapse rate and graft failure rates are typically higher.

One potential strategy to get both dose intensity and a graft-versus-malignancy effect is to follow an autologous transplantation with an allogeneic RIC. Autologous SCT can be undertaken in many patients in whom ablative allogeneic SCT is avoided, but relapses are common. The use of allogeneic SCT as a salvage therapy for relapse after autologous SCT indicates that few of these patients reject the grafts, and many appear to have long survivals. Most of these data are retrospective, but prospective data suggest that this approach warrants careful consideration.

### Table 1. Retrospective comparisons between high- and reduced-dose regimens.

<table>
<thead>
<tr>
<th>Study</th>
<th>Regimen</th>
<th>Disease</th>
<th>Age, y (range)</th>
<th>Relapse, %</th>
<th>OS, %</th>
<th>PFS, %</th>
<th>Cause of death other than relapse</th>
</tr>
</thead>
<tbody>
<tr>
<td>Scott34</td>
<td>RIC 2 Gy TBI + fludarabine</td>
<td>AML/MDS</td>
<td>38 53 (40-65)</td>
<td>40</td>
<td>28</td>
<td>27</td>
<td>TRM 8%  GVHD/Infection 36%  Graft failure 16%</td>
</tr>
<tr>
<td></td>
<td>Conventional dose  Busulfan + Cy</td>
<td>112 62 (40-70)</td>
<td>38 48</td>
<td>44</td>
<td>TRM 24%  GVHD/Infection 33%  Graft failure &lt;2%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rodriguez25</td>
<td>RIC Fludarabine + melphalan</td>
<td>NHL</td>
<td>40 51 (20-67)</td>
<td>28*</td>
<td>53</td>
<td>40</td>
<td>TRM 28%</td>
</tr>
<tr>
<td></td>
<td>Conventional dose iTBI/Cy or Bu/Cy</td>
<td>48 44 (18-54)</td>
<td>13 52</td>
<td>46</td>
<td>TRM 33%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Relapse of low-grade NHL was similar to the conventional-dose regimen but the rate in aggressive NHL was higher.

Abbreviations: OS, overall survival; PFS, progression-free survival; RIC, reduced-intensity conditioning; TBI, total-body irradiation; AML, acute myeloid leukemia; MDS, myelodysplastic syndrome; Cy, cytarabine; TRM, treatment-related mortality; GVHD, graft-vs-host disease; NHL, non-Hodgkin lymphoma; Bu, busulfan
blood mononuclear cells that have been enriched for lymphohematopoietic progenitors by administering filgrastim to the donor followed by leukapheresis. Stimulated peripheral blood products typically have ten times as many T cells as a marrow collection, thus fostering engraftment and GVL. However, a frighteningly potent GVL response is observed in umbilical cord blood transplantation, despite the small numbers of naïve T cells in the product. Since most of these transplantations are done across MHC barriers, it is possible that the limited numbers of T cells and natural killer (NK) cells provide a more potent GVL effect related to HLA mismatching. It is not clear to what degree mismatching at KIR loci contributes to this benefit.

Marrow has fewer T cells, and therefore the graft may be more susceptible to immunologic rejection by residual, unopposed host cells. Definitive trials have not been performed, but the de facto standard in RIC is a peripheral blood stem cell (PBSC) product until comparative trial can be undertaken.

If complete lymphohematopoietic chimerism is not achieved with the primary infusion or if the disease recurs, sometimes DLI is administered. Its efficacy is highly dependent on the degree of chimerism at the time of infusion. If there are fewer than 10% to 20% donor T cells, the graft is unlikely to be salvaged by adding a DLI, and an ablative transplantation may need to be considered.

Complications

The primary impetus for using RIC regimens is the expectation that conditioning-related toxicity would be less. This benefit is realistic, and the procedure can be done with little acute morbidity. Veno-occlusive disease of the liver is rare after RIC. Mucositis is generally absent or mild. Idiopathic pneumonia syndrome is much less frequent. However, early in the development of RIC transplantation it was predicted that the risk of GVHD would be less. While some studies appear to show this effect, what may actually be observed is that the overall risk of acute and chronic GVHD is very similar to conventional-dose transplantation, but the pattern of onset is different. The onset of acute GVHD may be delayed by weeks to months. One typically expects grades II-IV GVHD in approximately 50% of patients and grades III/IV GVHD in 10% to 15% of patients. This is the back edge of a two-edged sword, since GVHD is associated with the graft-versus-malignancy effect. The other significant concern is that the immunologic failure observed after RIC is identical to that seen after conventional-dose transplantation. These patients must be closely monitored for fevers and cytomegalovirus, bacterial, and fungal infection, and treated aggressively, just as if they had a myeloablative procedure. This is a particularly severe problem in umbilical cord blood transplantation.

Efficacy

RIC is not a very effective cytoreductive therapy, and most of the time the procedure needs to be performed in patients who have reasonable control of the disease. Ultimately, the value of RIC lies in its ability to eradicate malignant stem cells more effectively than can be achieved with conventional chemoradiotherapy. Critical determinants of success are disease, stage, and features intrinsic to the immune system to control. Extensive disease is probably more resistant to RIC than minimal disease. Hematologic malignancies are the primary targets of RIC. Despite early promising results, transplantation for renal carcinoma has been of limited benefit. Another immunologically sensitive solid tumor, melanoma, is largely resistant to RIC. In contrast, diseases such as chronic myelogenous leukemia (CML), chronic lymphocytic leukemia, and low-grade lymphomas appear to have excellent rates of disease control (up to 85% complete remissions) and in the short to intermediate term seem to result in disease-free periods. In these indolent illnesses, longer-term follow-up will be necessary to determine the durability of the response. These illnesses have in common a less aggressive course and a lower proliferative rate, making them more amenable to the GVL effect. The susceptibility to nonmyeloablative transplantation diminishes sharply as the disease becomes more aggressive. For instance, there are few if any responders to nonmyeloablative transplantation in blast-phase CML. At present, there are few data on the role of imatinib mesylate used as an adjunct to transplantation in either the stable phase or later phases of the disease; however, control of the disease with imatinib followed by transplantation is an appealing idea.

Attempts to cure large-cell lymphoma with allogeneic cellular therapy normally are applied after failure of au-
As noted above planned tandem transplantations for patients with high-risk disease at diagnosis is being undertaken in some centers. Hodgkin disease has not been a good target for conventional-dose transplantation, in part because of the use of prior chest irradiation complicates the application of allogeneic transplantation. Like large-cell lymphoma, recurring Hodgkin disease is usually treated with autologous transplantation, but data are accumulating that nonmyeloablative allogeneic transplantation may be an important modality. Typically, the outcome after allogeneic transplantation is better when the disease is responsive to chemoradiotherapy. It can be used either after failed autologous transplantation or as a planned procedure following autologous transplantation in relapsed disease. The tandem approach using an autologous SCT for cytoreduction and a subsequent nonmyeloablative procedure to eradicate minimal residual disease is particularly appealing.

AML and myelodysplastic syndromes have been successfully treated with nonmyeloablative transplantation. Long-term disease-free survival may be expected in as many as 30% to 50% of selected candidates. As with the aggressive lymphomas, results are best if the disease is indolent or performed in complete remission. While RIC in older patients with AML is promising, there are a number of hurdles that interfere with accomplishing the transplantation, largely reflecting donor availability and severity of the underlying disease. In children, acute lymphoblastic leukemia (ALL) is usually curable, and the role of nonmyeloablative transplantation is unknown. Moreover, some data suggest that some adults with recurring ALL will respond to this type of therapy, however, in general, ALL is much less amenable to the GVL response than other lymphoproliferative disorders, particularly if there is a Philadelphia chromosome. On the other hand, the use of tyrosine kinase inhibitors such as imatinib may control the disease long enough to establish an effective GVL response. As with AML, transplantation is best applied to patients who can achieve a second or subsequent remission.

Long-term remissions are particularly difficult to establish in multiple myeloma with conventional therapy or autologous transplantation. Conventional-dose allogeneic transplantation has resulted in excessive mortality due to transplantation-related toxicity. However, myeloma does appear to be susceptible to immunologic control. Some investigators have clearly demonstrated a measurable graft-versus-myeloma effect by monitoring the reduction in M-component following DLI. Nevertheless, several studies have shown substantial complete remission rates and long-term disease-free survival using one of several nonmyeloablative regimens. Disease response tends to correlate with extent of prior therapy. As noted above, the most promising approach reported so far is tandem autologous followed by nonmyeloablative allogeneic transplantation in which there does appear to be a flattening of the overall and disease-free survival curves. A similar intergroup Francophone du Myelome (IFM) study showed no such benefit; however, the patients were selected for high-risk characteristics. The Italian trial enrolled newly diagnosed patients without regard to stage, while the IFM trial limited enrollment to high-risk patients. Moreover, they used thymocyte globulin in the conditioning regimen, which may have attenuated the graft-versus-myeloma effect. The Blood and Marrow Transplantation Clinical Trials Network has completed enrollment in another trial of tandem autologous stem cell transplantation versus autologous followed by RIC in newly diagnosed myeloma. This is a very large study (>700 patients) and should provide convincing data on the role of allogeneic SCT in this disease.

**Future Prospects**

The promise of allogeneic transplantation has been tarnished by the associated conditioning-related toxicity as well as by the occurrence of GVHD. RIC has partially abrogated the problem of regimen-related toxicity, although at the cost of a higher relapse rate. Ongoing research into better regimens to control GVHD has resulted in a progressive reduction in GVHD risk, allowing older and higher-risk patients to undergo potentially curative therapy. The next threshold to increasing the anticancer effect of RIC will require the development of techniques to enhance the graft-versus-malignancy effect while minimizing the GVHD reaction. Cancer vaccines of various types are under active investigation. Whole cell vaccines, anti-idiotypic vaccines, and peptide vaccines are all being studied and hold substantial promise for enhancing outcomes in RIC. An important challenge is to determine why there is no graft-vs-colon cancer or graft-versus-breast cancer effect and to find ways of harnessing the allogeneic effect to the management of these more common cancers.

**Correspondence**

Joseph H. Antin, MD, Dana Farber Cancer Institute, 44 Binney St., Boston MA 02115; phone (617) 632-3667; fax: (617) 632-5175; jantin@partners.org

**References**


