RISK FACTORS FOR ACUTE GRAFT-VERSUS-HOST DISEASE ASSOCIATED WITH CYCLOSPORINE AND METHOTREXATE PROPHYLAXIS

To the Editor:

We were interested in the recent report by Nash et al1 of their analysis of risk factors for acute graft-versus-host disease (GVHD) in a large series of patients undergoing allogeneic bone marrow transplantation (BMT) from an HLA-identical sibling. One of their conclusions was that patients who received reduced doses of cyclosporine A (CSP) or methotrexate (MTX) were at higher risk of developing moderate to severe (grade II through IV) GVHD. We have recently reported a low incidence of GVHD in a group of patients receiving MTX and CSP prophylaxis in whom the dose of CSP was controlled by monitoring of CSP levels to maintain the trough whole blood level within a relatively low therapeutic range.2 We have now re-analyzed our current experience of 38 patients undergoing allogeneic BMT from an HLA-identical sibling for a variety of conditions (Table 1). Conditioning was administered with fractionated total body irradiation to a total dose of 12 Gy in 6 fractions given twice daily for 3 days and either intravenous (IV) cyclophosphamide (60 mg/kg) for two successive days for patients with leukemia or IV melphalan (110 mg/m²) for patients with multiple myeloma. Three patients with myelodysplastic syndromes were conditioned with busulphan (16 mg/kg) and cyclophosphamide (120 mg/kg).3 The one patient with aplastic anemia received cyclophosphamide 50 mg/kg on each of 4 successive days. All patients received GVHD prophylaxis using MTX and CSP. Analysis of the amount of GVHD prophylaxis actually given showed that all patients received full dosage with IV MTX according to the Seattle protocol (15 mg/m² on day +1, 10 mg/m² on days +3, +6, +11) and IV CSP at a dose of 3 mg/kg/d from day −1 to a median of day +13 before switching to oral CSP. In contrast, we found that because we maintained trough serum CSP levels within the range of 95 to 205 pg/mL (assayed twice weekly with a monoclonal radioimmunassay (Cyclotrac: Incstar Corp, Stillwater, MN), the dose of oral CSP administered was only 40% of the predicted Seattle dose from the start of oral therapy to day +50 posttransplantation.4 The incidence of GVHD in our series of patients was 31%, but no patient developed greater than grade 1 disease, contrasting with an incidence of grade II through IV GVHD of 35% reported by Nash et al. This absence of moderate to severe acute GVHD in our series of patients does not appear to be explained by a low incidence of other risk factors identified by Nash et al. In particular, the median patient age in our series was 35.9 years (range 15 to 55 years), and 47% were over 40 years old at transplant (Table 1).

Thus, our data does not support the conclusion that dosage reduction of CSP is a risk factor for developing moderate to severe GVHD because our patients all received low-dose CSP after the first 2 weeks posttransplant. In contrast, we administered full-dose MTX prophylaxis to all our patients whereas a significant number of patients in the Seattle series had dose reduction or omission. Our data would suggest that CSP dosage reduction can be achieved without increasing the risk of GVHD if full-dose MTX is administered. The use of low-dose CSP has potential advantages. High doses of CSP have been associated with an increased risk of relapse posttransplantation;4 therefore, it is possible that, as we have previously suggested,2 low-dose CSP prophylaxis may be associated with a lower risk of relapse than conventional dose CSP/MTX regimens.

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REFERENCES
2. Hunter AE, Bessell E, Russell NH: Effective prevention of acute GVHD following allogeneic BMT with low leukaemic relapse using methotrexate and therapeutically monitored levels of cyclosporin A. Bone Marrow Transplant 10:431, 1992

Table 1. Patient Characteristics

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>No. of Patients</th>
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</thead>
<tbody>
<tr>
<td>AML/ALL remission</td>
<td>22</td>
<td>Patients age (yr)</td>
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<tr>
<td>AML-advanced</td>
<td>2</td>
<td>&lt;20</td>
</tr>
<tr>
<td>CML-chronic phase</td>
<td>6</td>
<td>20–39</td>
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<tr>
<td>Myeloma</td>
<td>4</td>
<td>&gt;60</td>
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<td>Myelodysplasia</td>
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<td>Donor-patient sex match</td>
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<tr>
<td>Aplastic anemia</td>
<td>1</td>
<td>Match</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Mismatch</td>
</tr>
</tbody>
</table>

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RESPONSE

In the letter from Russell et al., in which a follow-up of their previous experience is reported, there were 31% of a total of 38 patients who developed acute graft-versus-host disease (GVHD), none of which were considered to be greater than grade I. The incidence as reported was low in comparison with the observations in Seattle, even though the dose of oral cyclosporine (CSP) administered was only 40% of the intended dose (as prescribed by the Seattle regimen) from the start of oral therapy to day +50 after transplantation as a result of targeting serum CSP levels between 95 and 205 ng/mL.

Several explanations may account for the apparent difference between the reports. It can be difficult to compare the diagnoses and grading of GVHD in different marrow transplant centers. Also, 36 of the 38 patients reported by Russell et al. were "good-risk" patients (without advanced malignant disease) who received preparative regimens of standard intensity. This is in contrast to our report, where many patients had advanced malignant disease and/or received a preparative regimen with higher doses of total body irradiation (TBI). Both advanced malignant disease and higher doses of TBI (>1200 cGy) were associated with a higher incidence of acute GVHD.2,5,6 Russell et al. also did not note an increase in acute GVHD associated with reductions of the CSP dose to maintain CSP levels at a targeted range. Dose reductions secondary to toxicity may be associated with a higher incidence of acute GVHD as compared with dose reductions based on blood levels. This may occur because dose reductions secondary to toxicity can be large and precipitous, whereas the dose adjustments to maintain a specific range of serum CSP levels may be in smaller increments. Moreover, Russell et al. did not describe how dose adjustments were done, except that they occurred between day +14 and +50 after marrow transplantation. Specifically, they did not state the percent of the intended CSP dose administered between day +14 and +33, when their dose adjustments were made, which was also within the period of time that we studied. Therefore, it is unclear whether most of the dose reduction in their study occurred before or after day +33.

Our study showed that a reduction of CSP dose was a risk factor for GVHD, illustrating a relationship between dose and immunosuppression. A relationship between a reduction of CSP and risk of acute GVHD has also been observed after marrow grafting from unrelated donors (Claudio Anasetti, personal observations, December 1992). Moreover, the relationship between CSP dose and risk of GVHD has also been observed after marrow transplantation in a randomized study where those patients receiving a higher dose of CSP had a lower incidence of acute GVHD, although the same group had a higher relapse rate and more organ toxicity.5 Although higher doses of CSP can be associated with increased morbidity and a higher relapse rate, some patients may benefit from increased levels of immunosuppression if the drug is tolerated without severe toxicity.8,9

The importance of serum CSP levels in the management of patients remains controversial. CSP concentrations have demonstrated only weak ability to predict acute GVHD after marrow transplantation or graft rejection after solid organ transplantation.19 In a recent retrospective study, we were unable to find any relationship between serum cyclosporine levels and GVHD in patients receiving marrow grafts from HLA-matched siblings. One of the several possible explanations for our inability to show an association is that an already weak relationship between CSP levels and acute GVHD observed in some studies in which CSP is used as a single agent could be made weaker with the use of the second immunosuppressive drug, methotrexate. Therefore, cyclosporine levels in this setting can assure the clinician that the oral form of the drug is being absorbed adequately and that metabolism is not unexpectedly too rapid or slow. Cyclosporine levels also help to determine whether organ dysfunction in certain situations after marrow transplantation could be related to the toxic effects of the drug.

Finally, our recent study confirms the importance of full-dose methotrexate (MTX), which Russell et al. were able to administer to all patients despite significant mucositis.

Clinical studies showing the effectiveness of the combination of MTX and CSP were first reported in 1986,11,12 A relationship between dose of drug and risk of GVHD can be demonstrated. Modifications to this regimen as Russell et al. and others have described are interesting, and may lessen toxicity while maintaining adequate immunosuppression for prevention of acute GVHD.13,14 Full evaluation of the modifications would require prospective randomized trials.

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1. Hunter AE, Bessell EM, Russell NH: Effective prevention of acute GVHD following allogeneic BMT with low leukaemic relapse using methotrexate and therapeutically monitored levels of cyclosporin A. Bone Marrow Transplant 10:431, 1992


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Risk factors for acute graft-versus-host disease associated with cyclosporine and methotrexate prophylaxis [letter; comment]

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