References


Response:

Increased incidence of cytomegalovirus infection and disease after autologous CD34-selected PBSC transplantation

Unlike the work of Peggs et al, our paper reported on the incidence of cytomegalovirus (CMV) disease and infection in CMV seropositive patients with a number of different diseases who received a transplant with autologous CD34-selected peripheral blood stem cells (PBSCs). Overall, 7 out of 31 (22.6%) CD34-selected patients developed CMV disease within 100 days after transplantation. In a univariate analysis, CD34 selection alone was significant for the development of CMV disease, with an odds ratio (OR) of 6.62 (confidence interval [CI], 2.3-19; P < .001). By evaluating combinations of factors together in a multivariate logistic regression model, the inclusion of conditioning with a TBI-based regimen and the dose of CD34 cells infused amplified the effect of CD34 selection. With respect to the development of CMV infection, CD34 selection and steroid use were highly significant in a univariate analysis: OR was equal to 3.0 and 2.69, respectively. Because all patients in our CD34-selected group and 3 out of 10 patients in the unselected group who received CMV disease had received a transplant for multiple myeloma or lymphoma, an additional subset univariate analysis was performed. In this analysis, CD34-selected patients had a significant chance of developing disease, with an OR of 17, (CI, 3.8-76.7; P < .001).

We are not the only group to report an increased incidence of CMV disease associated with CD34 selection. Recently, Stockerl-Goldstein et al presented their results. In 40 multiple myeloma patients who received CD34-selected cells, there were 4 (10%) patients who developed CMV disease.

In our cohort of patients, there were 6 patients with multiple myeloma who received CD34-selected cells and 26 who did not. Four of the 6 CD34-selected patients developed CMV disease, as compared to 1 of the 26 unselected.

As mentioned in the discussion section of our paper, we believe that differences in the reported incidence of CMV disease are due to differences not only in the evaluation of patients but in the immunologic function of the patients at risk. In our 6 multiple myeloma patients who received CD34-selected PBSC, all were mobilized with intermediate dose chemotherapy for stem cell collection. The number of regimens the patients received prior to their mobilization chemotherapy were 1, 2, 2, 2, and 3, thus making our multiple myeloma patients probably more heavily treated than the group treated by Peggs et al, which received a median of 1 chemotherapy regimen. In addition, 3 of our 6 CD34-selected multiple myeloma patients received steroid therapy after transplantation. In general, we have found the following differences in the median number of immune cells infused in the CD34-selected and unselected stem cells product: CD3, 8.8 vs 1273; CD4, 4.2 vs 518; CD8, 6 vs 246; CD3+/CD56+, 10.8 vs 865; CD3-/CD56+, 0.79 vs 123; and CD3-/CD56+, 2.55 vs 158 x 10^6. Patients who developed CMV disease after the infusion of CD34-selected cells had the lowest number of immune cells infused, with a median of 2.5 CD3, 3.1 CD4, 4.6 CD8, 7.6 CD3+/CD56+, 0.49 CD3-/CD56+, and 2.2 x 10^7 CD3-/CD56+. At present, we are in the process of retrospectively determining the number of specific T cells that recognize CMV that were infused in the different patient populations.

We agree with Peggs et al that CMV antigenemia is not helpful, because 2 of 3 of our patients who developed CMV disease had no evidence of CMV antigenemia. In addition, the median day to developing disease among our CD34-selected patients was 26 days (range, 16-76 days). Thus the early onset of CMV disease may make it hard to follow patients by CMV antigenemia testing because their white blood cell count may be too low. We also agree with Peggs et al that PCR by itself may not be the best monitoring for risk for CMV infection and disease and that quantitative PCR may be more informative. To date, because there are no published studies using quantitative PCR in the setting of CD34 selection, we have adopted a policy at our institution of screening all patients prior to initiation of transplant conditioning with a quantitative PCR. All patients who have at least 100 copies of CMV in their blood are treated with prophylactic antiviral therapy during conditioning. Weekly after the infusion of CD34-selected PBSC, all patients are screened also by CMV PCR. A level of at least 100 copies of CMV results in the initiation of antiviral therapy.

Leona A. Holmberg and William I. Bensinger
Fred Hutchinson Cancer Research Center
University of Washington School of Medicine
Seattle, WA

References


To the editor:

Myocardial ischemia following allogeneic bone marrow transplantation: possible implication of tacrolimus overdose

It has been reported that clinically significant heart involvement affected 5% to 10% of patients undergoing bone marrow transplantation (BMT) after pretreatment with CY and TBI and that life-threatening or fatal cardiac toxicity occurred in about 1%-5%

VOLUME 96, NUMBER 1
BLOOD, 1 JULY 2000
of patients receiving CY-containing preparative regimens. But ischemic heart disease has not been a common event in the setting of BMT. Tacrolimus, developed by Fujisawa Pharmaceutical Company, has a potent immunosuppressive activity in vitro and in vivo. Nowadays, tacrolimus is widely used for prophylaxis and treatment of graft versus host disease (GVHD) after BMT, but some adverse effects have been reported: renal impairment, hyperlipidemia, hyperglycemia, hypertension, and cardiac event. Concerning cardiac event, sinus arrest, bradycardia, Q-T prolongation, and hypertrophic cardiomyopathy have been reported. Reports from kidney transplantation showed cardiac symptoms suggesting ischemic heart disease, but there is no report of myocardial ischemia related to tacrolimus in the BMT setting. Here we report a case of myocardial ischemia after BMT, which we suspect was caused by tacrolimus overdose.

A 20-year-old patient was found to have chronic myelocytic leukemia in the first chronic phase when she presented with leukocytosis. Her bone marrow cells were all Ph1 positive. She was treated only with hydroxycarbamide until conditioning was started for BMT. She underwent an allogeneic BMT from a human lymphocyte antigen (HLA) genotypically matched and ABO minor mismatched unrelated donor, with hyperfractionated total body irradiation and a cyclophosphamide preparative regimen. Tacrolimus was used for GVHD prophylaxis started on day 1a sa continuous intravenous infusion at a dose of 0.05 mg/kg per day. The initial posttransplantation course was uneventful, and hematopoietic recovery was smooth with granulocyte colony stimulating factor administration from day 9 to day 17, and the granulocyte count exceeded 500/µL on day 17 (Figure 1). The patient began having diarrhea on day 17 and on day 21 presented with a rash that spread over 25% of her body surface area by day 24. Diagnosis of acute GVHD grade II was made, and she was treated with methylprednisolone. At the same time, the blood concentration of tacrolimus was gradually increased, and the serum creatinine level rose to 2.0 mg/dL. We discontinued tacrolimus on day 25, when its concentration rose to 45.4 ng/mL, and on that day the patient manifested severe chest pain and dyspnea (Figure 1). Electrocardiography (ECG) showed ST depression in the chest leads from V2 to V6 (Figure 2). We started nitroglycerin and diltiazem immediately after the attack of pain, and it soon disappeared. Troponin T rose to 0.5 ng/mL on the next day. Coagulation studies showed no remarkable abnormality except a low antithrombin III (ATIII) activity (59.3%). The serum thrombomodulin was elevated to 6.0 ng/mL, which suggested endothelial damage. Thallium scintigraphy showed no definite perfusion defect on day 30, and the patient’s ECG reverted to normal by day 32. For GVHD we treated the patient only with methylprednisolone from day 25 to day 31, and we carefully readministered tacrolimus by oral intake on day 32. Her rash and diarrhea were successfully controlled whereas the concentration of tacrolimus never exceeded 15 ng/mL. We performed coronary angiography on day 47. It revealed spastic coronary arteries without any significant organic lesions, which widened more than twice the width of controls shortly after intracoronary injection of isosorbide dinitrate.

Figure 2. Ischemic changes on electrocardiography and on diameter of coronary artery. (A) Ischemic changes on electrocardiography before and during angina attack. During the attack, ST level was depressed significantly in the chest leads from V2 to V6. (B) Changes of diameter of coronary artery before and after intracoronary injection (IC) of isosorbide dinitrate (NTG). Coronary arteries were spastic without any significant organic lesions and widened more than twice the width of controls shortly after intracoronary injection of isosorbide dinitrate.
concentrations tended to be higher in patients with cardiac symptoms as shown in this case,\(^1\) we propose that tacrolimus could be the causative agent of this patient’s myocardial ischemia, and clinicians should be aware of this potential toxic manifestation. The patient’s ATIII activity was decreased below normal when the attack occurred. There are reports that the ATIII level decreases during BMT, which could cause a hypercoagulable state and result in a wide spectrum of thrombotic complications.\(^1\) But in this case, because coronary angiography revealed no organic stenosis, microthrombi formation due to low ATIII activity would be unlikely as the cause of this event.

Naoyuki Uchida, Shuichi Taniguchi, Naoki Harada, and Tsunefumi Shibuya
Department of Hematology
Hamamomachi General Hospital
Fukuoka, Japan

References

To the editor:

Differences between refractory anemia with excess blasts in transformation and acute myeloid leukemia

The recently proposed World Health Organization (WHO) classification of hematologic malignancies attempted to integrate morphologic, clinical, immunophenotypic, and genetic features in defining disease entities. One of the major changes proposed by this classification is to lower the blast count for acute myeloid leukemia (AML) from 30% to 20%, thereby eliminating the previously recognized entity of refractory anemia with excess blasts in transformation (RAEB-T). WHO indicated that the reason for eliminating the RAEB-T entity is the fact that the survival of these patients is not significantly different from those with AML.

While we were among the first to point out that response to chemotherapy was independent of the distinction between AML, RAEB-T, and refractory anemia with excess blasts (RAEB),\(^2\) after accounting for features such as poor prognosis cytogenetics and older age which are more frequent in MDS and while we recognize that the 30% (or 20%) cutoff is arbitrary, we believe that consideration should be given to retaining RAEB-T as a specific entity. In particular, we believe that while response to therapy is a highly important criterion in a classification system, biologic features also need to be included. Therapies may change, but “biology” is invariant. Here we present data suggesting that the biology of RAEB-T more resembles that of refractory anemia (RA), refractory anemia with ringed sideroblasts (RARS), and RAEB (“other MDS”) than that of AML. Some of this has been previously noted, such as the frequency of particular cytogenetic abnormalities and duration of abnormal blood accounts in RAEB-T versus AML.\(^2\)

In order to investigate other biologic features, we compared patients in our database who were enrolled on clinical protocols at

Table 1. Comparison of RAEB-T with AML

<table>
<thead>
<tr>
<th></th>
<th>RAEB-T (median, range)</th>
<th>AML (median, range)</th>
<th>(P)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Caspase 3 activity*</td>
<td>7.87 (0-26)</td>
<td>1.94 (0-26)</td>
<td>.0001</td>
</tr>
<tr>
<td>PCNA*</td>
<td>3.35 (98-7.88)</td>
<td>1.92 (74-17.28)</td>
<td>.008</td>
</tr>
<tr>
<td>Age</td>
<td>61.5 (19-84)</td>
<td>59.5 (16-87)</td>
<td>NS</td>
</tr>
<tr>
<td>AHD</td>
<td>1 (0-1000)</td>
<td>0 (0-168)</td>
<td>NS</td>
</tr>
<tr>
<td>B2M</td>
<td>2.4 (1-8.10)</td>
<td>2.6 (0-31)</td>
<td>NS</td>
</tr>
<tr>
<td>PLT</td>
<td>38.5 (1-471)</td>
<td>49 (3-2292)</td>
<td>.017</td>
</tr>
<tr>
<td>HGB</td>
<td>7.7 (3.6-15.1)</td>
<td>7.8 (2.8-15)</td>
<td>NS</td>
</tr>
<tr>
<td>VEGF*</td>
<td>4 (1-15)</td>
<td>3 (5-15)</td>
<td>.04</td>
</tr>
<tr>
<td>BM cellularity</td>
<td>65 (5-100)</td>
<td>75 (5-100)</td>
<td>.05</td>
</tr>
<tr>
<td>Poor cytogenetics</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>((8), (-7),7q21, -8)</td>
<td>50%</td>
<td>35%</td>
<td>.01</td>
</tr>
<tr>
<td>Therapy-related</td>
<td>27%</td>
<td>15%</td>
<td>.011</td>
</tr>
</tbody>
</table>

*The values of caspase 3 activity, PCNA, and VEGF represent folds of the mean level observed in 12 normal control bone marrows, which is assigned a value of 1.