Correspondence

To the editor:

Cytomegalovirus infection following transplantation of autologous CD34-selected progenitor cells

In their report of autologous CD34-selected peripheral blood stem cell transplantation, Holmberg et al reported a very high incidence (22.6%) of cytomegalovirus (CMV) disease with 4 of the 7 patients who developed disease dying of CMV infection.¹ This high incidence of infection after autologous transplantation is unusual, leading the authors to suggest that the process of CD34 selection, which results in 2- to 3-log T-cell depletion, may be responsible for susceptibility to CMV infection. Based on extensive experience with depletion technology, however, we think alternative explanations should be considered.

We recently completed a phase III trial that compared autologous CD34-selected and -unselected peripheral blood progenitor cell transplantation in 193 patients with chemotherapy-sensitive intermediate-to-advanced-stage multiple myeloma.²³ Both groups underwent stem cell mobilization with cyclophosphamide/prednisone/G-CSF and a preparative regimen consisting of busulfan/cyclophosphamide; patients did not routinely receive prophylactic immunoglobulin therapy. Although CD34 selection achieved the same degree of T-cell depletion as described by Holmberg et al,¹ we were unable to detect an increased susceptibility to infection. The incidence of overall infection was equivalent in patients receiving CD34-selected and -unselected transplants; specifically, CMV infection was documented in 2 patients and 1 patient, respectively. Interstitial pneumonitis occurred in 3 and 2 patients, respectively.

The results of this randomized study suggest to us that, although the process of CD34 selection does produce significant T-cell depletion, immune reconstitution is apparently sufficient to prevent life-threatening infection in a population of treated patients with multiple myeloma undergoing autologous transplantation.⁴ Alternative explanations for the relatively high incidence of CMV infection in Holmberg et al’s study should focus on pretreatment characteristics. Their study used a population of more heavily pretreated patients, especially patients who may have received long-term glucocorticoid immunosuppression (autoimmune disease patients) or multiple cycles of pretransplant chemotherapy (oncology patients). A more intensive preparative regimen, including a greater percentage of patients in the CD34-selection arm receiving total body irradiation (TBI), may also have contributed to the high incidence of CMV-related complications and the poor outcome in their study.

Gary John Schiller, Robert Vescio, and James Berenson
Transplantation Biology Program
Division of Hematology/Oncology
University of California Los Angeles
Los Angeles, CA

References

To the editor:

Cyclosporine (CSP) or CSP plus methylprednisolone for graft-versus-host-disease prophylaxis in patients with high-risk lymphohemopoietic malignancies: long-term follow-up of a randomized trial

Several randomized trials of graft-versus-host-disease (GVHD) prophylaxis have included methylprednisolone (MP)¹⁻⁴ but in those studies MP was administered in both study arms in combination with other agents. A trial reported from this institution compared the effect of a combination of methotrexate (MTX) plus cyclosporine (CSP) with the 3-drug combination MTX plus CSP plus MP and failed to show an overall advantage of the addition of MP.⁵ The effects of the addition of MP to a standard regimen of CSP had never been studied in a randomized trial. In the early 1990s we conducted such a trial comparing CSP as a single agent to CSP plus MP as GVHD prophylaxis. The hypothesis was that the incidence of GVHD would be lower with the drug combination, but there was also concern that the addition of MP might increase the risk of infections⁶ and other posttransplantation complications. Because of continued interest in the role of MP for GVHD prophylaxis, we thought it would be important to provide long-term follow-up on our study.

The study involved 122 patients with advanced lymphohemopoietic malignancies who were considered to be at high risk for

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CML = chronic myelogenous leukemia; MDS = myelodysplastic syndrome; TBI = total body irradiation.

*Patients were not in remission (resistant disease or relapse) or, with lymphoid malignancies, were in third or subsequent remission or, with myeloid malignancies, in second or subsequent remission.
posttransplantation complications and relapse. All patients received marrow from HLA-identical sibling donors. Patient and transplantation characteristics are summarized in Table 1. Daily CSP was started on day −1 (5 mg/kg/d IV) and given at gradually reduced doses until day 180. MP was started on day +7 at 0.5 mg/kg/d, increased to 1 mg/kg/d on day 15, started on a taper schedule on day 29, and discontinued on day 72. In the initial publication, we reported incidence rates of acute GVHD grades II-IV of 73% and 60% for patients given CSP and CSP plus MP, respectively (P = .01). Chronic GVHD, however, was more frequent among patients who received CSP plus MP (44% vs 21%; P = .02). The conditional probabilities of developing chronic GVHD were 94% and 51% for patients receiving CSP plus MP or CSP, respectively (P = .03). There was a suggestion that the risk of relapse was lower in patients who received CSP plus MP (P = .10). While early overall survival did not differ between the 2 groups (P = .44), there was a trend toward better relapse-free survival in patients on CSP plus MP (P = .07). There was no significant difference in the incidence of early posttransplantation infections between both groups.

The minimum follow-up for surviving patients is now more than 3.6 years (median 6.1; maximum 8.0). The probability for overall survival is 23% among patients randomized to CSP prophylaxis and 26% among patients who received CSP plus MP. Among patients who received CSP alone, 17 relapsed 42-657 (median 81) days after transplantation, compared with 15 patients on CSP plus MP, 57-1343 (median 217) days after transplantation, for cumulative incidences of relapse of 28% and 24% for the 2 respective groups (P = .19). Currently, 12 patients in the CSP arm are surviving in remission (20%), compared with 16 patients (26%) in the CSP plus MP arm (P = .11) (Figure 1).

At the time of last contact, the Karnofsky performance scores were 80-100 (median 100) and 60-100 (median 100) for the CSP-treated and the CSP-plus-MP–treated patients, respectively. One patient in the CSP arm still requires immunosuppressive therapy, compared with 4 patients who had received CSP-plus-MP prophylaxis. One patient in the CSP arm and 4 in the CSP-plus-MP arm developed chronic pulmonary disease. Three patients in the CSP arm developed aseptic necrosis (involving 1-4 joints), requiring joint replacement surgery in 2, compared with 5 patients (involving 1-3 joints) in the CSP-plus-MP arm, requiring replacement surgery in 2.

Thus long-term observations in this randomized trial fail to show any significant advantage to the addition of MP to CSP as GVHD prophylaxis. Although there was a somewhat lower incidence of acute GVHD (accounted for entirely by skin involvement) in patients who received the drug combination, the cumulative incidence of chronic GVHD was significantly increased. Earlier trends toward a reduced incidence of relapse and better relapse-free survival with the drug combination have diminished since our initial report, and neither difference is significant. At the same time, however, the lowest current Karnofsky scores were seen among patients who had received CSP plus MP, and there is a suggestion that more patients in this cohort have developed complications such as aseptic necrosis of the bone and chronic pulmonary disease and have required immunosuppressive therapy for a longer duration.

Very few patients enrolled in this trial were able to avoid the use of MP completely since MP was generally given as initial therapy when GVHD developed. But considering the overall course of these patients, the probability of developing delayed complications, and their current performance status, there is no basis on which to recommend MP plus CSP as a GVHD prophylactic regimen. Although these results do not exclude the possibility that MP may be beneficial when combined with other drugs, data to support such a claim are lacking.

H. Joachim Deeg, Mary E. D. Flowers, Wendy Leisenring, Frederick R. Appelbaum, Paul J. Martin, and Rainer F. Storb
Fred Hutchinson Cancer Research Center
University of Washington
Seattle, WA

References