To the Editor:

Considerable attention has recently been paid to the induction of graft-versus-host (GVH) disease after autologous or syngeneic bone marrow transplantation (BMT) by the administration of low-dose cyclosporine A (CSP). It is hoped that an associated graft-versus-tumor effect will reduce relapses after transplantation. However, this still remains controversial.

In a recent issue, Yeager et al. reported a high incidence of skin reactions in 19 patients with acute myeloid leukemia treated with high-dose busulfan and cyclophosphamide who received escalating doses of CSP after autologous BMT. Fifteen patients (79%) had skin biopsies consistent with histopathologic grade I acute GVH disease during the first 49 days after transplantation, but no lesions of a higher grade were observed. Ten patients also developed a maculopapular rash without erythroderma or bullous lesions—clinically at maximum a grade I acute GVH skin reaction. However, five patients with histopathologic grade I acute GVH skin biopsies had no cutaneous changes clinically. It was not stated in the article how many patients developed cutaneous changes without histopathologic evidence of GVH disease. None of the patients, whether they had a rash or only histopathologic cutaneous abnormalities, developed gastrointestinal symptoms, hepatic dysfunction, or any other sign attributable to acute GVH disease. Skin biopsies were obtained weekly starting on day +7 after BMT, but no biopsies were obtained before the conditioning chemotherapy.

In humans, histopathologic cutaneous changes indistinguishable from those seen in grade I or II GVH disease after allogeneic BMT are common and occur after conventional chemotherapy as well as after autologous or syngeneic BMT. Sale et al. analyzed 300 skin biopsy specimens of patients after autologous, syngeneic, and allogeneic BMT as well as of 17 patients after conventional chemotheraphy, none of whom received CSP. There was a considerable overlap in histopathologic changes between these groups and cutaneous changes consistent with grade II GVH disease were found in two of 17 patients after conventional chemotherapy, in 7 of 8 patients after autologous BMT and in 6 of 22 patients after syngeneic BMT. In a more recent prospective analysis Sviland et al. found grade I or II GVH skin reactions in 18 of 30 patients before BMT and in 7 of 9 patients after autologous BMT without CSP administration. These investigators conclude that grade I or II changes are of little value in diagnosing early GVH disease and that additional clinical clues or greater than grade II changes are required for the histologic diagnosis of GVH disease.

The mechanisms of epidermal cell injury in patients with histopathologic grade I or II GVH skin reactions but without further evidence of GVH disease are not clear. There are reports on the generation of autoreactive cytotoxic T lymphocytes in these patients and a decrease in the CD4/CD8 lymphocyte ratio in lesional skin of three patients with a GVH-like syndrome was observed. However, in a recent prospective analysis imbalances in lymphocyte subsets were found to be a common event during lymphocyte repopulation in peripheral blood as well as in skin and rectum biopsy specimens in patients after BMT, whether there was evidence of acute GVH disease or not.

The absence of biopsies before BMT and the lack of a control group to study the occurrence of cutaneous changes without administration of CSP are major limitations in the study of Yeager et al. The investigators conclude that they were able to induce acute GVH disease after autologous BMT, but did not observe a
benefit for patients with positive biopsies in terms of a reduced relapse rate or improved survival. In fact, 6 of 7 patients who relapsed had histopathologic evidence of GVHD disease during their posttransplant period. As there was no other clinical or histopathologic evidence of GVHD disease apart from the cutaneous changes, the absence of a graft-versus-tumor effect in the study by Yeager et al should raise the question if the observed skin reactions represented a GVH-like cutaneous syndrome rather than the cutaneous manifestations of GVHD disease. And without unequivocal GVH disease, how much do we know about the negative effects of CSP that can also interfere with immunsurveillance in recipients of autologous or syngeneic marrow?

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REFERENCES


RESPONSE

Dr Beyer et al question whether the appearance of the skin reactions observed in patients with acute myeloid leukemia (AML) receiving cyclosporine (CSP) after autologous bone marrow transplantation (ABMT) represent bona fide cutaneous manifestations of graft-versus-host disease (GVHD) or are really “GVH-like” reactions attributable to the pre-ABMT chemotherapy conditioning regimens. They indicate that similar GVH-like cutaneous manifestations have been reported in recipients of conventional chemotherapy without BMT and in some recipients of autologous and syngeneic marrow grafts. However, these1,2 and other3 reports inflate the estimated frequency of these GVH-like skin findings by inclusion of patients who had histopathologic grade 1, as well as grade 2, skin biopsies. We agree that histopathologic grade 1 GVH changes on skin biopsies are nonspecific and can be seen after irradiation or chemotherapeutic agents, with or without BMT. The presence on skin biopsy of dyskeratotic cells without lymphocytic infiltration is not specific for GVHD, although this could be described as histopathologic grade 2 GVHD changes and further overestimate the frequency of autologous GVHD. It is important to re-emphasize three points of our study: skin biopsies were at least histopathologic grade 2 to be considered positive; both dyskeratosis and inflammatory changes were required for a biopsy to be classified as grade 2 GVHD; and all biopsy specimens were reviewed in blinded fashion by a dermatopathologist.

Although the design of our study did not include a simultaneous control non-CSP group, we previously reported that the frequency of spontaneous histopathologic grade 2 GVHD was approximately 7% (7 of 96 patients) after autologous BMT with busulfan/cyclophosphamide or other preparative regimens. In our series of 19 patients receiving CSP after ABMT for AML, the observed frequency of histopathologic grade 2 GVH changes in the entire group (15/19 patients), those with concomitant cutaneous manifestations (10/19), or those with positive biopsies but no cutaneous manifestations (5/19), was statistically significantly greater (P < .001, < .001, and < .025, respectively; chi-square test) than that expected from historical controls who did not receive post-ABMT CSP. In studies of induction of autologous GVHD in patients with non-Hodgkin’s lymphoma or breast cancer at this institution, skin biopsies have routinely been obtained as a baseline before ABMT, and none has shown histopathologic alterations consistent with grade 2 (or greater) GVHD.

Dr Beyer et al raise concerns that CSP administration might adversely affect immune function in recipients of autologous or syngeneic BMT. It is unlikely that the CSP-induced GVH syndrome has substantial adverse effects; the CSP dosage is low and its duration of administration is brief, and the GVH reactions observed have been self-limited and clinically mild. In more than 140 patients receiving short-course CSP after ABMT for AML, non-Hodgkin’s lymphoma, or breast cancer at The Johns Hopkins Oncology Center, we have not seen an increased frequency of post-ABMT morbidity or mortality attributable to opportunistic infections such as viral pneumonitis or to immune-mediated cytopenias.

This letter raises important points that investigators must consider as they develop and evaluate methods to induce GVH in the ABMT setting; as alluded to by Dr Beyer et al, there is a risk of overdagnosis of this syndrome unless stringent objective criteria for its diagnosis are used. As noted above, the possibility that histopathologic alterations are primarily caused by the preparative regimen must be excluded by evaluation of post-ABMT skin biopsies, either in a concomitant or historical control group. At the minimum, the cutaneous histopathologic changes must be at least grade 2; evaluation of biopsies by an experienced dermatopathologist blinded to the clinical status and treatment protocol of each patient is desirable. Determination of autoreactive cytotoxic T lymphocytes and T lymphocyte subsets from patients with induced or spontaneous autologous GVHD will be an essential complementary study to demonstrate the immunoregulatory imbalances already well delineated in the preclinical rodent model of autologous or syngeneic GVHD and documented after CSP-induced autolo-
gous GVHD in patients receiving ABMT for lymphoma. The "gold standard" for clinical investigations, a randomized prospective double-masked trial of autologous GVHD induction, could even be considered; for optimal patient accrual, this study would most likely need to be performed in a multicenter setting. Only with objective clinical and laboratory assessment will we be able to discriminate between true autologous (autoimmune) GVHD and nonspecific "GVH-like" reactions that may occur after ABMT or conventional chemotherapy.

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REFERENCES


Graft-versus-host disease or graft-versus-host-like syndrome [letter; comment]

J Beyer, R Schwerdtfeger and W Siegert