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EDITORIAL

Preparative Regimens for Autologous Bone Marrow Transplantation

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THE PREPARATIVE regimen is the chemotherapy and/or radiation treatment used to prepare patients for bone marrow transplantation (BMT).[1-6] For allogeneic BMT, the preparative regimen has several objectives: cytoreduction, ideally eradication of the malignancy; immunosuppression to abrogaic the immunologic resistance to engraftment; and possibly the creation of "space" within the BM microenvironment to allow engraftment of the donor stem cells. The immune-mediated graft-versus-leukemia effect conferred by the allogeneic transplant adds to the antileukemic effect and is an important component to prevent relapse.[7-9] For autologous BMT, immunosuppression is not required, and the preparative regimen is used to provide maximal dose intensive therapy with a goal of eradicating the malignancy. Here, there is no allogeneic graft-versus-leukemia effect and there is the additional concern of leukemic involvement of the stored autologous BM contributing to relapse. Maximally tolerated doses are used, limited by nonhematopoietic toxicity.

Most BMT recipients have received total body irradiation (TBI)-containing regimens, usually in combination with cyclophosphamide based on the original studies in Seattle for allogeneic transplantation.[10] Fractionation of TBI is generally used to reduce toxicity to normal tissues.[11-13] Escalation of the fractionated TBI dose above 12 Gy has decreased the relapse rate but at the expense of increased toxicity, with no benefit in leukemia-free survival.[14] Newer methods of delivering TBI and perhaps better shielding techniques might be able to exploit the dose-response effect. Use of radiolabeled monoclonal antibodies directed at myeloid cell surface antigens or bone seeking radionuclide chelates are an intriguing approach to selectively irradiate hematopoietic cells, minimizing toxicity to normal tissues.[15,16] Addition or substitution of other drugs with TBI, such as cytosine arabinoside, etoposide, or melphalan, has been proposed, but these regimens have not substantially improved results and attempts at intensification of the preparative regimen have often increased treatment-related morbidity and mortality.[17-23]

Santos et al[24] demonstrated that busulfan could be substituted for TBI. Busulfan at 16 mg/kg and cyclophosphamide at 200 mg/kg(BuCy) is an effective regimen for allogeneic and autologous BMT.[24,25] It achieved a low relapse rate in acute myeloid leukemia (AML) and overall survival comparable to cyclophosphamide/TBI regimens. This regimen was modified by Tutschka et al[26] to reduce the cyclophosphamide dose to 120 mg/kg for reduction of toxicity in allograft recipients (BuCy2).[26,27] The addition of other drugs to BuCy has been studied, but presently there is no compelling evidence that any of these regimens represents a therapeutic advance.[28,29] Several randomized trials are underway comparing the relative toxicity and efficacy of BuCy or BuCy2 versus cyclophosphamide/TBI for allogeneic BMT. Although the TBI-containing regimen was superior in one study,[30] preliminary results of other ongoing studies suggest that there is no significant advantage of either regimen for treatment of AML. Alternative preparative regimens including BCNU, cyclophosphamide, and etoposide,[31] or other nitrosourea based regimens[32] have also been evaluated.

Autologous BMT studies have generally used the same regimens developed for allogeneic transplants. This may not be optimal. The immunosuppressive effects needed for allogeneic BMT are not necessary or desirable for autologous transplants. Also, autologous transplant recipients may be capable of tolerating more intensive regimens, because they are not at risk for graft-versus-host disease and have a more rapid immune reconstitution resulting in a lower risk for cytomegalovirus or other infections.

There has been considerable recent interest in the use of etoposide for treatment of leukemias and as an agent in BMT preparative regimens.[33-35] It is a topoisomerase II inhibitor that is synergistic with alkylating agents in some systems.[36] Etoposide has been successfully combined with total body radiation as a preparative regimen for allogeneic BMT,[37,38] although it has not been directly compared with cyclophosphamide/TBI in a controlled trial.

Two articles in this issue of *Blood* report encouraging results with the combination of busulfan at 16 mg/kg and etoposide at 60 mg/kg as a preparative regimen for autologous BMT for AML. Linker et al[39] evaluated this regimen in 58 AML patients receiving 4-hydroperoxycyclophosphamide (4-HC)-treated autologous marrow. For patients in first complete remission, the actuarial relapse rate was 22% and 78% achieved 3-year disease-free survival. In patients with a more

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advanced remission, the relapse rate was 25% and disease-free survival was 56%.

Chao et al[40] studied 50 patients, 34 patients in first remission and 12 in second remission. Those groups were jointly analyzed. The initial 20 patients received unpurged marrow, with an actuarial relapse rate of 62% and a disease-free survival of 32%. The subsequent 30 patients received 4-HC–purged marrow, with a relapse rate of 28% and a disease-free survival of 32%. The subsequent 30 patients received 4-HC–purged marrow, with a relapse rate of 28% and a disease-free survival of 57%. The two groups appeared to be roughly comparable for major prognostic factors. The difference between the purged and unpurged patients was not significant, possibly due to the relatively small sample size, but these data are consistent with other results supporting the efficacy of purging with 4-HC, mafosphamide, or monoclonal antibodies for autologous BMT for AML.[41-43]

The busulfan/etoposide regimen has substantial toxicity. Moderate to severe mucositis, skin toxicity, and hyperbilirubinemia occurred in most patients. Early deaths from treatment complications, primarily hepatic venoocclusive disease or infection, occurred in 17% and 14% of patients, respectively. The highest rate of severe toxicity occurred in patients with advanced leukemia.

Do these studies demonstrate an improved preparative regimen? The data presented are encouraging, but there are a number of factors that complicate analysis of these and other phase II BMT studies. This involves the bias introduced by patient selection and time to treatment. Many patients were referred after initial chemotherapy treatment from outside institutions. There is referral bias; referring physicians send and transplant centers accept patients they believe to be good autologous transplant candidates (ie, generally young patients in good medical condition). Patients with poor performance, ongoing infection, or organ dysfunction are generally ineligible. Each of the studies involved a relatively large fraction of patients with favorable prognostic features, such as M3 subtype, t(15;17), and M4 subtype with inv 16. To undergo autologous marrow harvest, patients must have normal hematopoiesis and adequate marrow cellularity. Although each study involved early transplantation without interceding consolidation chemotherapy, the median interval from first remission to transplant was 3 months in each study. Patients in remission up to 6 months were included; those who relapsed early or had poor hematologic recovery after induction chemotherapy could not be eligible. The number of patients who were ineligible or excluded was not described in either study and the total denominator of potential patients cannot be determined.

Clearly, busulfan-etoposide is an effective regimen for autologous BMT as treatment for AML and deserves further study. The reported results are at least comparable to other preparative regimens. The results presented for patients in first remission are superior to that expected with standard-dose chemotherapy, but, given the biases described in patient selection, this must be confirmed in controlled trials, using intention to treat methodology because many patients achieving remission will be unable to undergo autologous BMT. In one recent study, less than half of the patients designated for autologous transplantation actually received this treatment.[44] Critical comparison of preparative regimens also requires controlled trials with treatment groups stratified for known prognostic factors. The disease-free survival for this regimen with purged autologous BMT also appears comparable to that achieved with allogeneic transplants. Published studies comparing allogeneic and autologous BMT in first remission have generally favored the use of allografts,[44,45] and any conclusions comparing their relative role requires rigorously controlled trials.

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