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Immunosuppressive non-myeloablative allografting as salvage therapy in advanced Hodgkin's disease

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Many treatment options are now available for patients with recurrent Hodgkin's disease. These include radiation of localized recurrences or non-cross-resistant salvage chemotherapy regimen after failure of first line therapy. For patients with resistant/early recurrent disease, high-dose therapy with autologous stem cell transplantation rescue has been tested extensively in the last decade. Most studies have demonstrated that about one quarter of patients with primary refractory disease may achieve long-term disease-free survival after high-dose therapy.[1-12] A recent retrospective analysis of 175 patients reported by the *European Blood and Marrow Transplantation Group* demonstrated that 30% of these patients achieved complete remission with an actuarial 5-year overall survival and progression-free survival of 36% and 32%, respectively.[13] Unfortunately, despite these results, many of these patients are expected to relapse and to die of their disease. Since these patients are unlikely to be cured, innovative strategies may be required. Among these, attempts to harness the curative potential of allogeneic stem cell transplantation have been largely limited to younger patients because of conditioned-related toxicity and graft-versus-host disease (GVHD). A survey of transplant activity of the *International Bone Marrow Transplantation Registry* (IBMTR) indicated that 297 patients with advanced disease received conventional allografting, 228 of them in Europe.[14] The results with conventional allografting have been generally disappointing.[15-18] Procedure-related mortality resulted to be surprisingly high, varying from 31% to 61%, with most series having more than 50% mortality, which corresponds to a low rate of survival free from relapse.

Recently, new enthusiasm for allografting has arisen from the use of fludarabine-containing regimens (with or without early cyclosporine withdrawal and donor lymphocyte infusion) that provide sufficient immunosuppression for allogeneic engraftment; this means less toxicity than standard high-dose preparative regimens.[19-27] These non-myeloablative allografts (NST) are expected to allow the development of graft-versus-lymphoma reactions with less morbidity than conventional allografts. Since several reports have demonstrated favorable outcomes in small cohorts of lymphoma patients[20,21,23-30,32,33] treated with NST, these transplants have been recently tested as consolidation therapy after autografting.[27,31] In fact, the greater potential benefit of allografting in these high risk patients could be exploited if tumor burden is minimized prior to allograft and conditioning mortality decreased. One method to achieve this would be to combine high-dose therapy and autologous stem cell *rescue* followed by NST, especially in patients with primarily resistant disease and *early* relapsed disease. This strategy attempts to achieve both maximal tumor reduction with high-dose therapy and immune-mediated control of residual disease with allografting.[27] Moreover, high-dose therapy induces significant host immunosuppression, which should contribute to the enhancement of donor engraftment during the allogeneic transplant procedure.

We have recently reviewed our experience in Genoa. Seventeen patients with advanced Hodgkin's disease who had HLA-suitable donors received high-dose therapy with the BEAM protocol (carmustine, etoposide, arabinosyl-cytosine, melphalan) followed by reinfusion of autologous peripheral blood stem cells previously mobilized and cryopreserved. When clinically stable, all patients received fludarabine 30 mg/m^2 and cyclophosphamide 300 mg/m^2 concurrently for three days as the preparative regimen, followed by infusion of fresh, not T-depleted allogeneic peripheral blood stem cells mobilized from an HLA-identical sibling. GVHD prophylaxis consisted of cyclosporine and methotrexate. All patients were transplanted

in conventional rooms. The regimen was well tolerated with no mucositis and no patient requiring intravenous nutrition. Thirteen patients achieved complete donor engraftment (four after donor lymphocyte infusion), three had mixed chimerism and one patient had autologous hematopoietic recovery. Four patients had acute GVHD of grade ≥ 2 (two of them after donor lymphocyte infusion) and 3 patients chronic GVHD, (mild: 2 patients; extensive: 1 patient). Five patients died: three of progressive disease, one of infection and one of progressive disease combined with extensive chronic GVHD. Eleven patients achieved remission (complete: 9; partial: 2). As of March 2001, 11 (65%) patients are alive at a median of 566 days (range, 267-860) after NST. Seven patients maintain remission (complete n=6; good partial remission=1), at a median of 596 days (range, 290-767) after achieving this status. Patients with full chimerism and patients in whom GVHD developed after transplantation had a significantly higher probability of a response.

The median interval of 165 days from NST to regression of lymphoma, the demonstration that Hodgkin's disease regression occurred only after achievement of full donor chimerism and the association of GVHD with regression of lymphoma are all consistent with the occurrence of an antilymphoma effect that was mediated by the donor's T-cells. These results suggest that a graft-versus-Hodgkin effect may exist. The existence of a graft-versus-Hodgkin effect has also been supported by reports that showed lower relapse rates in patients receiving donor lymphocyte infusion[28] and those who develop acute GVHD.[17,18,30]

In conclusion, this dual transplant procedure[34] appears to be most promising in patients with resistant disease or with first relapse after a short first remission. Long-term follow-up of these patients will be required for a full assessment of the efficacy and the risk of late complications.

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