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Reduced Intensity Allogeneic Stem Cell Transplantation for Hematologic Malignancies

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High dose myeloablative therapy with allogeneic hematopoietic transplantation is an effective, yet risky treatment for hematologic malignancies. The therapeutic benefit of allogeneic marrow transplantation for many diagnoses is largely related to an associated immune-mediated graft-vs.-malignancy effect. This realization has recently led to development of less toxic, nonmyeloablative preparative regimens to achieve engraftment and allow development of graft-vs.-malignancy effects as a primary form of therapy. Nonablative regimens have clearly reduced regimen-related toxicity and also is associated with a lower rate of GVHD and treatment related mortality. This approach allows hematopoietic transplantation in patients considered ineligible for myeloablative preparative regimens because of advanced age or the presence of comorbidities. Infectious complications also appear to be reduced. Neutropenia is reduced or eliminated by most nonablative regimens.

Myeloid Leukemias

Giralt et al initially evaluated use of standard dose purine analog based chemotherapy (fludarabine 30 mg/m²/d x 4 days, cytarabine 1 g/m²/day x 4 days and idarubicin 12 mg/m²/d x 3 days) as a nonablative preparative regimen in elderly or debilitated patients with advanced myeloid leukemia. This regimen was sufficiently immunosuppressive to allow engraftment of matched sibling transplants. The projected disease-free survival of patients who were in remission or had <10% bone-marrow blasts at the time of transplant was 40% beyond 2 years. The outcome of patients with refractory leukemia at transplant was poor; <10% remained in remission at

one year. Giralt et al subsequently reported a study combining melphalan (180 mg/m²) and fludarabine (125 mg/m²) for treatment of advanced acute leukemia; this is a more intensive regimen that should be considered a “reduced toxicity” ablative regimen. It is sufficiently immunosuppressive to allow for engraftment from unrelated donors as well as matched siblings. The additional cytoreduction resulted in improved disease-free survival in AML patients, particularly in those transplanted in relapse, suggests that cytoreduction of the malignancy by the preparative regimen is important in AML. Patients with refractory relapse have 25% extended disease free survival, and 56% of patients with chemotherapy sensitive disease remained in continuous remission beyond one year. These results are similar to those achieved with ablative preparative regimens in younger, but otherwise similar patients.

Champlin et al reported a comparison of the nonablative fludarabine-idarubicin-cytarabine regimen with the reduced intensity ablative regimen of melphalan-fludarabine in older or medically infirm patients with chronic myelogenous leukemia in late chronic or accelerated phase. The actuarial risk of relapse was only 8% with melphalan-fludarabine vs. 82% with nonablative fludarabine-idarubicin-cytarabine. The melphalan-fludarabine regimen was also more toxic, and relapse-free survival was 37% vs, 15% for the two groups. These data indicate that cytoreduction of the malignancy by the preparative regimen reduces the risk of relapse in myeloid leukemias. Slavin and coworkers reported use of a reduced intensity preparative regimen consisting of busulfan (8 mg/kg), fludarabine

and antithymocyte globulin in younger patients. Results of this regimen have been particularly encouraging in CML with 83% disease free survival.

Lymphoma, CLL and Hodgkin's disease

Low grade lymphomas, mantle cell lymphoma and chronic lymphocytic leukemia are highly sensitive to graft-vs.-malignancy effects. Khouri et al reported the use of fludarabine (90-125 mg/m²) plus cyclophosphamide (2 g/m²) with or without rituximab has been effective to achieve engraftment and durable complete remissions. A recent update of this regimen documented extended disease free survival in 70% of patients with follicular lymphomas, mantle cell lymphoma and transformed large cell lymphomas. This approach has also been highly effective in patients with chemosensitive relapse after autologous stem cell transplantation with 90% disease free survival in this group. These data compare favorably to high dose cyclophosphamide-total body radiation regimens in which treatment related mortality rates typically exceed 40%. A recent update using the fludarabine-cyclophosphamide-rituximab preparative regimen has 100% survival in patients with follicular small cleaved cell lymphoma or CLL and 92% in mantle cell lymphoma. Patients with high risk Hodgkin's disease, usually with relapse following an autologous stem cell transplant have 70% PFS using a melphalan-fludarabine nonablative preparative regimen; similar results have been obtained with matched sibling or unrelated donor transplants.

Inclusion of rituximab in the preparative regimen has improved engraftment and reduced the risk of GVHD; results of these studies involving the fludarabine-cyclophosphamide-rituximab preparative regimen compare favorably to a recent EBMT report using regimens not involving rituximab. Rituximab has also been useful to induce molecular complete remissions of CLL in patients with recurrent disease post transplant, and may induce antibody dependent cellular cytotoxicity, augmenting immune graft-vs-malignancy effects.

Multiple Myeloma

Multiple myeloma is also sensitive to graft-vs-malignancy effects, although less so than the indolent lymphomas and Hodgkin's disease. Nonablative stem cell transplants have reduced the risks of morbidity and mortality in myeloma patients compared to full dose ablative regimens, but there is a high risk of disease progression in patients transplanted with active disease. Encouraging results have been reported using a tandem approach, using high dose therapy and autologous stem cell transplantation for initial cytoreduction, after full recovery this is followed by a nonmyeloablative allogeneic transplant to induce the immune graft-vs-myeloma effect. This strategy is better tolerated than a single ablative transplant and preliminary data regarding disease control is encouraging.

Summary

Nonablative allogeneic stem cell transplantation is a highly effective potentially curative treatment for lymphoid malignancies. The approach is associated with mild toxicity and a low risk of GVHD and treatment related mortality, allowing treatment of patients up to at least age 75 years. This modality should be considered in patients with indolent malignancies (follicular lymphomas, mantle cell lymphoma, and CLL) after failure on initial chemotherapy and in selected high risk patients with large cell lymphomas and Hodgkin's disease, usually after relapse following autologous transplantation.