The use of non-Myeloablative Allogeneic Hematopoietic Cell Transplantation for Patients with Refractory Waldenstrom's Macroglobulinemia- Replacing High-Dose Cytotoxic Therapy with Graft-versus-Tumor Effects.

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Toxicities and treatment related mortality have limited the use of allogeneic hematopoietic cell transplantation (HCT) to younger, medically fit patients, in contrast to the incidence of diseases such as CLL, Waldenstrom's, NHL and myeloma which are more prevalent in older populations. Based on studies in a canine HCT model, a combination of postgrafting mycophenolate mofetil (MMF) and cyclosporine (CSP) allowed stable allogeneic engraftment after minimally toxic conditioning with low-dose (200 cGy) total-body irradiation (TBI). These findings, together with the known antitumor effects of donor leukocyte infusions (DLIs), led to the development of a non-myeloablative conditioning regimen consisting of fludarabine 90 mg/m2 and 200 cGy TBI followed by matched related or matched unrelated peripheral blood stem cell infusion with post grafting MMF and CSP. Experience with 45 patients with a variety of hemtologic malignancies receiving this regimen (matched related donors) has shown that the treatment is well tolerated with minimal myelosuppression, allowing 53% of eligible patients to have entirely outpatient transplantations. Grades II to III acute graft-versus-host disease (GVHD) occurred in 47% of patients with sustained engraftment. With median follow-up of 417 days, survival was 66.7%, nonrelapse mortality 6.7%, and relapse mortality 26.7%. Fifty-three percent of patients with sustained engraftment were in complete remission, including 8 with molecular remissions (**Blood 97: 3390-3400, 2001).** These trials have been extended to include the use of matched unrelated donors (URD) using a similar treatment regimen. Differences include using an increased dose of MMF, and a longer course of immunosuppression with both drugs pior to extended tapering. Using these two approaches 5 patients with refractory Waldenstrom's macroglobulinemia have been treated. Three patients had matched sibling donors and 2 unrelated donors. Of the three sibling transplants, all 3 patients are alive with 2 in CR, 1 in improving PR, 1-3 years post transplant. One of the 2 URD recipients died in remission from secondary AML (presumably related to the extensive prior therapy). The other patient is to early to determine response. The onset of remission has been gradual, with one patient still in improving PR nearly 3 years post transplant. In summary, non-myeloablative allografting provides new treatment options for patients with refractory Waldenstrom's macroglobulinemia. Longer follow-up is necessary to determine the durability of response and the outcome of GVHD associated complications.