Evidence for GVWM following mini-allo in WM.

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Treatment for refractory Waldenstroms Macroglobulinemia is generally palliative in nature and often compromised by increasing marrow toxicity and marrow tumor infiltration, limiting the use of high-dose therapy and autologous hematopoietic stem cell transplantation (HCT). In contrast, the use of allogeneic HCT provides a healthy stem cell source that has not been exposed to chemotherapy, and eliminates the risk of re-infusion of tumor cells. In addition, the donor immune system is capable of recognizing antigenic differences between the donor and patient and is capable of mounting graft vs host immune responses. While this may provide undesirable and sometimes lethal toxicity due to graft-vs-host disease (GVHD), the recognition of hematopoietic antigenic differences between host and donor may also provide anti-tumor activity through graft-vs-tumor effects (GVT).

Previously, allogeneic HCT was restricted to younger, medically fit patients capable of withstanding the myeloablative conditioning regimens utilized. We have witnessed an explosion of reduced intensity regimens along with the recognition that most of the anti-tumor activity is due to GVT.

In Seattle we have developed a non-myeloablative conditioning regimen using 200 cGy total body irradiation (TBI) +/- fludarabine as conditioning regimen that reliably allows allogeneic engraftment from matched related or unrelated donors. This regimen has been used to treat more than 1,000 patients with a variety of hematologic malignancies in a consortium of institutions on protocols coordinated through the FHCRC.

We have now treated 13 patients with relapsed/refractory WM with allogeneic HCT following flu/TBI conditioning from matched related (n=8) or matched unrelated (n=5) donors. Median age was 58 (44-65) years, patients were at a median time from diagnosis of 5.5 years, and had a median of 5 prior treatment courses. All patients engrafted and 54% had acute grade II-IV GVHD (0% grade IV GVHD), and 7/12 developed extensive chronic GHVD. Day 100 non-relapse mortality (NRM) was 8%. Three patients subsequently died (31% overall NRM) from relapsed aggressive NHL, host derived MDS/AML and refractory hemolytic anemia (all present prior to allogeneic HCT). Disease response was observed in 11/12 evaluable patients with 6 CR, 1 near CR, and 4 PR. One patient had no response and one was not evaluable. Median time to CR (n=6) was 11.7 months. The 4 year overall and progression-free survival is 60%. Patients with extensive chronic GHVD had longer survival (p=0.03). Only one responder (1/11) has had progression of WM.

These studies demonstrate the potent ability of allogeneic HCT to induce CR in patients with relapsed/refractory WM through graft-vs-WM immune effects, and may provide a curative treatment option.