IBMTR/ABMTR Mortimer M. Bortin Awards for Outstanding Clinical Research

Mortimer M. Bortin, M.D., was one of the founding members of the International Bone Marrow Transplant Registry and served as its Scientific Director for 20 years. The Mortimer M. Bortin Award, established to commemorate Dr. Bortin's contributions to the field of transplantation, is presented each year to investigators submitting abstracts to the Tandem BMT Meetings. The abstracts must address important issues in clinical blood and marrow transplantation and be of outstanding scientific merit. This year three $1,000 awards will be presented on behalf of the Mortimer M. Bortin Fund Awards Committee. The awards are supported by an unrestricted educational grant from Gambro BCT.

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AML PATIENTS LACKING KIR LIGAND FOR DONOR KIR EXHIBIT INCREASED OVERALL SURVIVAL IN HLA-IDENTICAL SIBLING TRANSPLANTS

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Killer Ig-like receptors (KIRs) comprise a group of inhibitory and activating receptors that interact with specific HLA class I ligands and are found on the surface of NK cells. Previous studies have analyzed the HLA genotypes of donor-recipient pairs and have drawn conclusions about the effect of donor KIR on transplant outcome based on ligand presence alone. It is known, however, that the KIR and HLA chromosomal regions segregate independently from each other, thereby laying challenge to studies that have predicted the effect of KIR genotype based solely on HLA genotype. Our studies analyze KIR effects on transplant outcome by examining donor KIR genotypes together with their class I ligands from donors and patients with myeloid and lymphoid leukemias undergoing allogeneic hematopoietic stem cell transplantation at two transplant centers. In AML patients receiving T-cell depleted (TCD) transplants from HLA-identical siblings (MCW n = 76), we found that the *absence* of patient HLA ligand for donor inhibitory KIR is associated with higher overall survival (OS) ($p = 0.027$). This benefit was also noted in AML patients receiving unmodified allografts from HLA-identical siblings (MSKCC n = 27), where the benefit on OS may be specifically related to the lack of HLA-Bw4 epitope for donor KIR3DL1 ($p < 0.0001$), resulting in a decrease in disease relapse ($p = 0.02$). Furthermore, there may be some additive effect of donor KIR2DS3 in the setting of inhibitory KIR ligand absence in AML patients receiving TCD transplants from HLA-identical siblings (MSKCC n = 59, $p = 0.053$; MCW n = 76, $p = 0.029$). These results could be extended to AML patients receiving TCD allografts from unrelated donors, where again lack of Bw4 epitope leads to higher OS ($p = 0.073$) and lower risk for relapse ($p = 0.03$). Interestingly, there was no KIR-driven benefit seen on OS or relapse in CML or ALL patients receiving either TCD, unmodified, HLA-identical related or unrelated allografts.

These data demonstrate an apparent alloreactive effect in AML patients when an HLA ligand for donor inhibitory KIR is absent. This effect is seen even in HLA-identical sibling transplants, implying that auto-reactive NK clones exist in a suppressed or "anergic" state within individuals who may themselves lack the appropriate HLA-ligands for their KIR. However, these NK clones (or their progenitors) are not deleted, as evidenced by their alloreactivity upon regeneration in the HLA-identical sibling recipient.

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DENILEUKIN DIFTITOX (ONTAK) AS TARGETED THERAPY AGAINST STEROID REFRACTORY GRAFT-VERSUS-HOST DISEASE (GVHD) AFTER ALLOGENEIC HEMATOPOIETIC STEM CELL TRANSPLANTATION (HSCT)

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Denileukin diftitox (ONTAK®) is a recombinant fusion protein composed of human interleukin-2 linked to the membrane translocation and catalytic domains of diphtheria toxin. ONTAK has potent selective killing activity against activated lymphocytes that express the high or intermediate affinity interleukin-2 receptor (IL-2R). Monoclonal antibodies that target the IL-2R have demonstrated clinical activity against acute GVHD. ONTAK may be superior to these agents because it does not rely on secondary effector mechanisms for cell kill, and entry of a few molecules into the cytoplasm may be sufficient to induce apoptosis. Furthermore, because ONTAK selectively destroys activated T-cells and spares resting lymphoid populations, valuable immune function and reconstitution potential may be preserved. We have completed a phase I study to assess the dosing of ONTAK in patients with steroid-refractory GVHD after allogeneic HSCT. Thirty patients (3 related donor, 27 unrelated donor) were treated for grade II (n = 10), grade III (n = 15), or grade IV (n = 5) steroid-refractory acute GVHD. Seven received ONTAK at dose level I (9 μg/kg IV on day 1 and 15), eighteen were treated on dose level II (9 μg/kg IV days 1,3,5,15,17,19), five were treated on dose level III (9 μg/kg IV days 1-5, 15-19). At dose level III, 4 of 5 subjects developed dose-limiting toxicity (1 acute renal failure, 3 hepatic transaminase elevation). Therefore, dose level II was deemed the maximum tolerated dose (MTD). In all patients, elevated transaminases resolved promptly upon withdrawal of ONTAK. Only 2 (7%) developed infusional reactions with transient hypotension. Twenty-four patients were evaluable for GVHD response. After 4 weeks, 8 (33%) had complete GVHD resolution (CR) of, 9(38%) had partial response (PR), for an overall response rate of 71%. Among the 9 PRs, 4 subsequently entered CR without additional GVHD therapy, resulting in an overall CR of 50%. Response was highest at the MTD, where 6 (46%) achieved CR, and 3 (23%) had PR, all of whom eventually converted to CR (overall CR = 69%). Of the 24 patients evaluable for GVHD response, 9(38%) are alive, with the longest survivor being GVHD free at 20 months. Our results show that ONTAK at a dose schedule of 9 μg/kg IV on days 1,3,5,15,17,19 is tolerable and has promising activity for steroid-refractory GVHD. Future studies using the MTD are warranted to investigate the potential role of ONTAK as primary treatment of acute GVHD.

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THE GIFT OF LIFE COMES WITH A PRICE: THE IMPACT OF HEMATOPOIETIC CELL TRANSPLANT ON THE LONG-TERM QUALITY OF LIFE OF SURVIVORS AND THEIR SPOUSES

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The impact of hematopoietic cell transplant (HCT) on the quality of life (QOL) of spouse/partners of survivors is understudied. We collected extensive quality of life data from 662 HCT survivors from 40 North American transplant centers registered with the IBMTR/ABMTR. Survivors were randomly selected from four