GVH/GVL

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SINGLE PRE-TRANSPLANT TREATMENT WITH GM-CSF-SECRETING MYELOID LEUKEMIA CELL VACCINE COMBINED WITH AUTOLOGOUS-BMT SIGNIFICANTLY IMPROVES SURVIVAL OF MYELOID LEUKEMIA CHALLENGED MICE

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A number of pre-clinical and recent clinical trials have demonstrated the efficacy of tumor vaccines engineered to secrete GM-CSF (GVAX) for the treatment of solid tumors and hematological malignancies. We investigated the graft-versus-leukemia (GVL) effects of a GM-CSF-secreting myeloid leukemia cell vaccine in a murine bone marrow transplantation (BMT) model using the MMB3.19 leukemia cell line, of C57BL/6 (B6) origin. Our approach consisted of a recipient GVAX-preconditioning strategy, prior to transplantation, that differed from current treatment designs in that post-BMT donor immune reconstitution was not required in order to observe a significant GVL response, and a single GVAX injection, as opposed to multiple treatments, was sufficient to significantly improve survival of leukemia-challenged mice. B6 Mice received a single subcutaneous preconditioning infusion of 2×10^5 irradiated GVAX tumor cells. Seven days later, mice were lethally irradiated with 850 cGy and transplanted with 2×10^6 anti-T cell-depleted B6 BM cells, alone or in combination with 4×10^6 donor lymphocytes (DL). On day 1 post-BMT, mice were challenged with 1×10^5 MMB3.19 cells (i.p). Statistical comparisons using a non-parametric log-rank test showed enhanced survival rate in the GVAX-preconditioned group 70 days post-BMT (60% survival), compared to: DL alone (10% survival, MST = 26 d, $P = 0.01$); GVAX given 1 day post-BMT (20% survival, MST = 26.5 d, $P = 0.01$); and preconditioning with irradiated tumor cells (30%, MST = 37.5 d, $P = 0.01$). GVAX-preconditioned mice receiving no DL also had significantly increased survival than DL alone (40% survival, MST = 37.5 d, $P = 0.02$). These results indicate that a single pre-transplant GVAX dose can significantly improve survival of MMB3.19 challenged mice and suggests that after host irradiation, immune cells exposed to GVAX remain capable of mediating significant GVL responses, even in the absence of DL.

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TREATMENT OF STEROID-REFRACTORY ACUTE GVHD WITH MESENCHYMAL STEM CELLS IMPROVES OUTCOMES IN PEDIATRIC PATIENTS; RESULTS OF THE PEDIATRIC SUBSET IN A PHASE III RANDOMIZED, PLACEBO-CONTROLLED STUDY

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Successful treatment of steroid-refractory aGVHD (SR-GVHD) following allogeneic hematopoietic cell transplantation remains a significant challenge. Because of their immunomodulatory properties and safety profile, adult mesenchymal stem cells (MSCs) have been proposed as a treatment for SR-GVHD. Intravenous allogeneic MSC therapy (Prochymal®) for SR-GVHD was independently evaluated in the pediatric subset of a double-blind, placebo-controlled study (Protocol 280).

Methods: Pediatric patients (< 18 yrs) with grade B-D SR-GVHD were randomized to receive Prochymal or placebo in addition to standard of care, including institutionally selected second line agent. Patients received 8 infusions of 2×10^6 cells/kg for 4 weeks (or volume equivalent for placebo), with 4 more infusions weekly in the case of a partial response (PR). The primary endpoint was durable complete response (CR ≥ 28 days); secondary endpoints included incidence of CR, PR and progression through 100 days, survival, and safety.

Results: Twenty-eight children were randomized to Prochymal (50% male, 79% Caucasian) or placebo (71% male, 71% Caucasian), with a median age of 7 yrs (range 1-15) and 10 years (range 1-18), respectively. The dominant transplant graft was cord blood (71% Prochymal, 57% placebo), with mostly unrelated donors (93% vs 79%, respectively). The median duration of aGVHD prior to enrollment was 20 days for Prochymal and 8 days for placebo ($p < 0.05$). At baseline, aGVHD grades B:C:D were 3:8:3 for both arms. For Prochymal, organ involvement was 64% skin, 43% GI, and 36% liver. For placebo patients, organ involvement was 57% skin, 79% GI, and 29% liver. Durable CR was 64% for Prochymal and 43% for placebo. Prochymal improved rates of CR and OR (Table). The median time to CR was 25 days vs 63 days. The 25% percentile of the survival function after study start was 139 days for Prochymal and 50 days for placebo. The safety data showed no infusional toxicity and no evidence of Prochymal leading to ectopic tissue. There were no AEs leading to discontinuation of therapy.

Conclusion: In a SR-GVHD population in which 79% of patients had grade C/D disease, the addition of Prochymal to standard of care doubled 28 day CR rates and reduced progression by half. Response at 28 days correlated with improved 100 day survival. Given increased response rates and a well-tolerated safety profile, MSCs appear to be a safe and effective therapy in the treatment of pediatric patients with SR-GVHD.

Results for SR-GVHD in children following treatment with Prochymal or Placebo

	CR	OR (CR + PR)	Progression	Survival
	Prochymal/ Placebo	Prochymal/ Placebo	Prochymal/ Placebo	Prochymal/ Placebo
Day 28	36% / 21%	64% / 36%	14% / 50%	93% / 86%
Day 42	57% / 21%	64% / 50%	29% / 43%	79% / 79%
Day 100	64% / 29%	71% / 50%	21% / 43%	79% / 50%

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EFFECT OF CYTOTOXIC T-LYMPHOCYTE ANTIGEN 4 (CTLA-4) HAPLOTYPE ON ALLOGENEIC HEMATOPOIETIC STEM CELL TRANSPLANTATION

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CTLA-4 is a negative regulator for activated T cells and the association of CTLA-4 polymorphisms with autoimmune diseases has been reported. The present study evaluated the effect of donor CTLA-4 haplotype on the immune reaction after allogeneic hematopoietic stem cell transplantation (HSCT) such as graft-versus-host disease (GVHD) and graft-versus-leukemia (GVL) effect. We analyzed 147 cases of Japanese HLA-matched sibling recipients and their donors who had undergone allogeneic HSCT for the treatment of hematological malignancies between 1987 and 2006 at the Nagoya University Hospital and the Japanese Red Cross Nagoya First Hospital. All recipients received T-cell-replete transplantation. Cyclosporine and short-term methotrexate were used as GVHD prophylaxis. Genotyping of three single nucleotide polymorphisms (SNPs) in CTLA-4 (-318, +49, CT60) were performed by Taqman-PCR method and/or DNA sequencing method using genomic DNA obtained from donor peripheral blood mononuclear cells (PBMCs). Their haplotypes were determined based on the HapMap database. Multivariate analyses were performed using Cox proportional-hazard model. Age, conditioning, disease risk and graft source were included as covariates. According to the HapMap database, CTLA-4 haplotype (-318, +49, CT60) could be classified into three types (C-G-G, C-A-A, T-A-G) in Japanese population. In this study, the proportion of the haplotype C-G-G, C-A-A, and T-A-G were 59.5%, 30.6%, and 9.9%, respectively. Recipients who received stem cells from a donor with the C-A-A haplotype showed significantly lower disease relapse (HR: 0.53, 95%CI: 0.29-0.96,