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EARLY POST-TRANSPLANT WHOLE TUMOR CELL VACCINATION ELICITS ANTI-TUMOR T CELL RESPONSES IN PATIENTS WITH ADVANCED CHRONIC LYMPHOCYTIC LEUKEMIA (CLL)

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Vaccination with whole leukemia cells early after allogeneic hematopoietic stem cell transplantation (HSCT) may facilitate expansion of anti-tumor responses. We tested this hypothesis by initiating a phase I study to vaccinate CLL patients between days 30-100 following reduced-intensity (RIC)-HSCT. One cycle of 6 vaccines consisted of $1x10^7$ irradiated autologous CLL cells admixed with irradiated K562 bystander cells secreting the cytokine adjuvant GM-CSF. Of 20 enrolled patients, 15 initiated vaccination. Four of 20 developed GvHD before day 45, precluding vaccination. At a median of 21 months follow-up, all vaccinated patients remain disease-free–an improvement, compared with a historic relapse rate of 50% at 2 years for CLL patients undergoing RIC-HSCT at our center. We thus compared T cell immune reconstitution of study subjects with CLL patients who had undergone RIC-HSCT without vaccines. Recovery of peripheral CD3+ T cell numbers until d100 was similar between vaccinated subjects and 15 transplanted/non-vaccinated CLL controls. Specificity of the reconstituted T cells in vaccinated patients, however, was consistently directed against autologous tumor cells. Five of 5 vaccinated patients demonstrated increased circulating IFN-γ secreting CD8+ T cells by ELISPOT against autologous tumor (mean of 516 vs 184 spots/10^6 CD8+ T cells at d60 (post-vaccine) vs d30 (pre-vaccine)), but not against autologous hematopoietic cells (PHA blasts, 57 spots/10^6 CD8+ cells, d60) nor autologous non-hematopoietic cells (fibroblasts, 108 spots/10^6 CD8+ cells, d60). In contrast, 5 of 5 controls (+HSCT, no vaccine) did not have expanded anti-tumor responses at d60 (mean 51 spots/10^6 CD8+ cells). Moreover, with GvHD, T cell reactivity developed against autologous PHA blasts and fibroblasts (mean 438 and 434 spots/10^6 CD8+ cells at d90, respectively). After vaccination, tumor-reactive CD8+ T cells were consistently polyfunctional, secreting high levels of GM-CSF, TNF-α, and IL-2. By limiting dilution, we isolated T cell clones from PBMC of 4 vaccinated subjects, and confirmed that 30-50% of T cell clones demonstrated specific recognition of autologous CLL, but not of alloantigen-bearing cells. Our studies reveal that early post-transplant CLL/GM-K562 vaccination is associated with induction of immunity against recipient CLL cells, and suggest that this is an effective strategy for tipping the balance of immunity in favor of GvL following nonmyeloablative HSCT.

HEMATOPOIESIS/MESENCHYMAL CELLS

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PLATELET-LYSATE-EXPANDED MESENCHYMAL STROMAL CELLS FOR THE TREATMENT OF RESISTANT GvHD

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Mesenchymal stromal cells (MSC) are multipotent cells with immunomodulatory properties, capable to escape immune rejection allowing their use in an HLA-mismatched setting.

We describe a multi-centre experience, which started in May 2008 and relied on the use GMP-grade unrelated HLA-disparate donors' bone marrow-derived MSCs, expanded in Platelet-Lysate -containing medium. 10 pts (4 to 15 years) transplanted for malignant (N = 8) or non-malignant (N = 2) diseases, received iv MSCs for acute or chronic grade I-IV GvHD, which was resistant to multiple lines of immunosuppression. Twenty MSC infusions were given to 10 pts. The median dose per infusion was 1.2×10^6/kg. Response to treatment was evaluated 28 days after infusion. Overall response (OS) was 75%, with complete response (CR) in 25% of the cases. We further developed a phase 1 study from August 2009 in order to allow an earlier use of MSCs, as second line treatment after steroid failure. 13 pts (7 adults, 5 pediatric) aged 1-58 years received iv MSCs infusions for steroid resistant acute or chronic GvHD grade II-IV. HSCT was performed for malignant (N = 10) or non malignant diseases (N = 3). GvHD presented as acute in 11 cases and chronic in 2, it involved a single organ in 7 pts (5 skin, 2 gut) and multiple organs in the other cases. Pts received 2 to 6 MSC infusions at $1x\ 10^6$/kg recipient body weight MSCs for each infusion. OS was 70 %, and CR 30%. None of the patients affected by chronic GvHD showed any benefit. Both skin and gut GvHD presented a better response rate, skin showing an earlier response (2 to 4 days) compared to gut (5 to 7 days). Patients with multiple organ involvement showed a worse response. In all 34 treated pts, no side affects were observed after MSC infusion. All responder pts could eventually taper ongoing immunosuppression. Seven pts presented GvHD recurrence 2-5 months after infusion. Four pts developed chronic GvHD. 29 out of 34 treated patients are alive and in complete remission from their disease with an average follow-up of 15.5 months from MSC infusion (range 2-29 months). One pt is alive with overt relapse of ALL, 1 pt died from GvHD complications, 3 pts died from infectious diseases. The present study underlines the safety of PL-expanded MSC use in children and adults. MSC efficacy seems to be greater in acute than in chronic GvHD, it represents an optimal second-line strategy and it could be effective even after failure of multiple lines of immunosuppression.

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COTRANSPLANTATION OF THIRD PARTY UMBILICAL CORD BLOOD MESENCHYMAL STEM CELLS TO PROMOTE ENGRAFTMENT IN PEDIATRIC RECIPIENTS OF UNRELATED DONOR UMBILICAL CORD BLOOD

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Background: Graft-promoting effects of mesenchymal stem cells (MSCs) may be particularly useful for transplants showing delayed engraftment, such as unrelated umbilical cord blood transplantation (UCBT). Inherently low immunogenicity of MSCs may open the possibilities to use universal donor MSCs. We here report the use of third party UCB-derived MSCs to enhance engraftment and to prevent rejection in patients undergoing unrelated UCBT.

Methods: Seven patients with high-risk acute leukemia enrolled in the study and the outcome was compared with 22 historical controls with high-risk acute leukemia given UCBT without MSCs. UCB-derived, ex vivo-expanded MSCs were infused at a target dose of 1×10^6/kg in 4 patients and 5×10^6/kg in 3 patients. On day 0, patients received the specified MSC dose just before infusion of the UCB unit.

Results: There was no acute toxicity related to the infusion of MSCs and no sign of ectopic tissue formation. There were no significant differences for age, gender, transplant indication, and number of CD34+ cells and nucleated cells infused between MSC group and control group. Neutrophil engraftment occurred at a median of 19 days (16-21) for MSC group, and at a median 17 days (13-44) for control group (P = 0.76). The probability of achieving a platelet count ≥ 20×10^9/L by 100 days after transplant was 100% at a median of 47 days (33-80) for MSC group, and 76.5% at a median of 51 days (19-231) for control group (P = 0.41). In comparison to controls (13.6% graft failure), all patients who were given MSCs engrafted successfully. The incidence of grade III-IV acute GvHD was 14.3% for MSC group and 5.9% for control group (P = 0.51). The incidence of extensive chronic GvHD was not statistically different between MSC (14.3%) and control group (18.8%, P = 0.79). The incidences of treatment-related mortality (TRM) within 100 days of transplant and veno-occlusive disease (VOD) were 18.2% and 22.7% in control group, whereas none of the patients of MSC group experienced TRM or VOD. Although there was a trend toward improved 2-year event-free survival after transplant in MSC group (75.0%) compared with control group (54.5%), it was not statistically significant (P = 0.33).