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IMMUNOTHERAPY AND TRANSPLANTATION FOR MULTIPLE MYELOMA: EARLY RECOVERY OF AGGRESSIVE CYTOTOXIC CELLS AND IMPROVED IMMUNE RECOVERY

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Autologous peripheral blood stem cell transplantation (APBSCT) is effective for the treatment of multiple myeloma (MM); however, the majority of patients relapse. Recent evidence shows an improved outcome if absolute lymphocyte count is increased immediately following APBSCT in patients with a hematologic malignancy. We designed a phase II trial evaluating a dose escalation of SQ IL-2 and standard-dose GM-CSF posttransplantation for myeloma patients. Patients (n = 18) received melphalan 200 mg/m^2 with GM-CSF 250 mg/m^2/day beginning on day 5. IL-2 began on day 0 and continued for 5 days per week for 4 weeks. Peripheral blood samples were obtained at baseline (pretransplantation) and every week for 4 weeks posttransplantation and evaluated using flow cytometry for cell subsets with antibodies directed against CD3, CD4, CD8, CD25, and CD56. Control patients (n = 11) consisted of MM patients who received melphalan 200 mg/m^2 with either G or GM-CSF without IL-2. IL-2 at a dose of 1×10^6 U/m^2/day was not tolerated in 2 of 6 patients due to grade 4 fatigue and diarrhea (n = 1) and grade 4 SVT (n = 1). A dose of 6×10^5 U/m^2/day was well tolerated by 12 patients. At this dose, level 3 or greater toxicities included nausea (n = 5), diarrhea (n = 3), anorexia (n = 11), and mucositis (n = 9). Engraftment of neutrophils occurred on day 12 (median; range, 11–17 days) and platelets on day 14 (median; range, 9–74 days). Only 3 of 18 patients have relapsed/progressed, with a median follow-up of 16.4 months. Absolute lymphocyte counts on days 10–15 were increased by 152% in the IL-2 cohort (mean; range, 25%-390%) compared with the control group. At day 21, there was a marked increase in the number of CD8+ CTLs (43% ± 7.5%), CD56 NK cells (78.3% ± 9.1%), and CD8+CD56+ NKT cells (36.8% ± 9.8%) compared with baseline levels. Cytotoxicity of day 21 PBMNCs in the IL-2 cohort was strikingly increased at 28.1%, compared with 5.5% at baseline when tested against a human myeloma cell line (RPMI 8226) using chromium release assays (E:T ratio = 100:1). These results demonstrate a very-well-tolerated regimen of immediate posttransplantation immunotherapy with marked increase in the number and function of early cytotoxic effector cells. The enhanced immune recovery may translate into an improved outcome.

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TOTAL BODY IRRADIATION DOSE AND PULMONARY TOXICITY IN PEDIATRIC PATIENTS

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Background: The optimal dose for pediatric total body irradiation (TBI) before bone marrow transplantation (BMT) is controversial. Higher doses contribute to normal tissue toxicity, whereas lower doses decrease efficacy of the treatment. We compared overall survival (OS), freedom from relapse (FFR), and freedom from life-threatening pulmonary events (FPE) in 2 TBI regimens that have been used on protocols at our institution. **Methods:** Between April 1993 and March 2003, 61 pediatric patients with hematologic disorders were treated on chemoradiotherapy protocols before receiving BMT. Two TBI fractionation schedules were used for these patients. Twenty-nine patients received 12 Gy in 4 fractions, with all but 1 patient receiving cyclophosphamide-based chemotherapy. The remaining 32 patients received 9 Gy in 3 fractions in conjunction with fludarabine-based chemotherapy. The fludarabine regimen began accruing patients in 1998; the lower radiation dose was used because of possible potentiation of TBI-related pulmonary toxicity with fludarabine. The mean follow-up was 24 months for the 12-Gy group and 13 months for the 9-Gy group. Patients with acute lymphocytic leukemia, chronic myelogenous leukemia, or acute myelogenous leukemia composed 83% of the 12- Gy group and 81% of the 9-Gy group. Retrospective review of medical records was performed to grade pulmonary toxicity. Acute and late pulmonary toxicities that were Radiation Therapy Oncology Group grade 4 or 5 were coded as pulmonary events. OS, FFR, and FPE were computed using the method of Kaplan and Meier. **Results:** The 2 regimens did not differ statistically with respect to OS, FFR, FPE or engraftment rate. Actuarial 2-year statistics for the 12-Gy and 9-Gy regimens were as follows: OS, 28% and 40% (P = .25); FFR, 51% and 58% (P = .30); FPE, 55% and 62% (P = .81). The engraftment rates were 90% for the 12-Gy group and 92% for the 9-Gy group (P = .89). **Conclusions:** The transplantation preparative regimen of 9 Gy TBI with fludarabine is at least as effective as that of 12 Gy TBI with cyclophosphamide in terms of FFR and engraftment rate without a significant increase in pulmonary toxicity.

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HEMATOPOIETIC STEM CELL TRANSPLANTATION IS EFFECTIVE CURATIVE TREATMENT IN PEDIATRIC REFRACTORY/AGGRESSIVE LANGERHANS CELL HISTIOCYTOSIS

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Although the new strategies for the management of LCH have been made considerable advances in the outcomes of pediatric patients, the best therapeutic approach for aggressive/refractory multisystem LCH patients remains controversial. Antiproliferative and immunosuppressive therapy in combination with HSCT has been proposed as the appropriate treatment for these patients with poor prognosis. Because of the appreciable morbidity and mortality of allogeneic HSCT, this strategy has heretofore been reserved for the few LCH patients with a very poor prognosis. In this report we describe 4 children, age 14 months (patient 1), 27 months (patient 2), 96 months (patient 3), and 48 months (patient 4), with refractory aggressive MS-LCH who were treated with allogeneic HSCT in our institution between 2001 and 2003. Disease activity score, as well as Karnofsky status, were retrospectively calculated for all patients at diagnosis and before HSCT. All patients presented with MSD progression despite chemotherapy with single or multiple agents or immunosuppressive therapy. Allogeneic HSCT was performed 10, 22, 72, and 47 months, respectively, from onset. Patients 1 and 3 received umbilical cord blood transplantation (UCBT) from HLA 4/6 and 5/6 mismatched unrelated donors. Patients 2 and 4 received bone marrow transplantation (BMT) from related HLA-identical donors. A conditioning regimen including busulfan 4 mg/kg and fludarabin 30 mg/m^2 from day −7 to day −4 and thiotepa 10 mg/kg on day −3 was used as preparative regimen. All patients received horse ATG 15 mg/kg from day −6 to day −2, cyclosporine A 3 mg/kg from day −1 to day +180, and PDN 1 mg/kg until day +30. After HSCT, all patients are alive with a median follow-up of 30 months (51, 39, 19, and 11 months, respectively). The conditioning regimen was well tolerated without major complications. Donor engraftment was demostrated in all 4 patients by PCR DNA analysis, and progressive improvement of disease symptoms were observed after 18, 6, 8,and 6 months, respectively. Patients 1 and 2 are disease-free, patient 3 presented with grade III aGVHD and reduction of esophthalmous and skin lesions, bone lesions are stable as well as for patient 4. Disease progression was not evident in any of the patients during long-term follow-up. We conclude that HSCT is a good curative treatment for these patients with poor prognosis. Progressive clinical improvements were evident for a long time after HSCT. Selection of patients based on early response to conventional chemotherapy and timing of HSCT remains controversial.