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Eosinophilia in bone marrow after hematopoetic stem cell transplantation: does it indicate the onset of acute graft-versus-host disease ?

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Objective: Acute and chronic graft-versus-host disease (GvHD) are frequent complications after allogeneic hematopoetic stem cell transplantation (HSCT) mediated by alloreactive lymphocytes and proinflammatory cytokines. Acute GvHD has been recognized as TH-1 associated process. Eosinophilia has been linked with a variety of diseases such as allergies and parasitic infections and is associated with a TH-2 response triggered by IL-5. Few studies have explored bone marrow morphologic findings in patients (pts) after HSCT. Eosinophilia in HSCT following BU/CY or TBI/CY preparartive regimens has been regarded by some authors as a valuable indicator of evolution to chronic GvHD. However, the significance of eosinophilia in acute GvHD is presently unknown. Significant CD25 antigen expression on the eosinophilia has been recently demonstrated in pts with acute GvHD.

Patients and Methods: We perform prospectively both bone marrow smear and histologic evaluation at day +30 and day +100 in 237 pts transplanted with allogeneic HSC from July 1987 to September 2000 in our department. Ninety-four of them were diagnosed with AML or MDS, 68 with CML or MPS, 46 with ALL, 16 with NHL and Hodgkin lymphoma and 13 with non malignant hematological diseases. 129 pts (54%) received unrelated HSCT and 106 pts (48%) received related HSCT. 20 pts died before the first bone marrow evaluation at day +30.

Results: A significant eosinophilia of more than 7%, determined at 400 bone marrow cells, was found in 32 pts (15% of pts). Twenty-eight (87,5%) of those pts developed acute GvHD grade II-IV. Four pts died due to severe GvHD, 24 pts developed chronic limited GvHD. Conclusions: In conclusion, bone marrow eosinophilia after HSCT, probably mediated by endogenous IL-2 predicts acute GvHD. The use of allogeneic G-CSF mobilized stem cell grafts in pts, which contain a high number of TH-2 polarized lymphocytes, may contribute to the development of eosinophilia in association with GvHD. However, the functional significance is not known and should be determined.

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Total body irradiation (TBI) with stem cell transplantation (SCT) in multiple myeloma (MM)

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Background: Until recently, TBI has been part of the conditioning regimen prior to SCT. Most centers use fractionated TBI. At the ORCC single fraction has been the standard. This study reports on the toxicity associated with this regimen.

Methods: A retrospective analysis of 52 consecutive patients (pts) having received SCT following melphalan 140 mg/m2 + etoposide 60 mg/kg and 500 cGy TBI.

Results: Allogenic/autologous cells were used in 4/48 (8%/92%) pts. Median age was 53 years (27-66). Prior therapy consisted of chemotherapy (8%); radiotherapy (XRT) and both (17%). Induction chemotherapy of VAD was given to 48 (92%) pts. Median/mean dose rate of XRT was 90/87 cGy/min (79-94). Objective response was seen in 42 (81%) pts (25% CR). Median EFS and OS were 30 and 36 months. 4 pts (8%) had deaths potentially related to regimen toxicity: 1 esophageal bleeding and aspiration secondary to thrombocytopenia 1.5 weeks after TBI (wat); 1 pneumonia 5 wat; 1 multi-organ failure 1.5 wat in a pt with prior amyloidosis and nephrotic syndrome; and 1 renal failure 73 wat. 2 pts had grade (gr) 3, 3 gr 4 transient dyspnea < 2 wat. 1 pt died of respiratory failure secondary to graft vs host disease 41 wat. Infection/febrile neutropenia was documented in 40 (77%) pts. Interstitial pneumonitis was observed in 3 pts and resolved within 3 months. FEV1 and/or DLCO were compromised in 7 of 21 evaluable pts 11-50 wat, which in 2 pts returned to normal within 13 and 22 weeks. 26 (50%) pts had diarrhea/colitis (3 were gr 3); 23 (44%) had nausea/vomiting (6 gr 3); 36 pts (69%) had mucositis/dysphagia (16 gr 3 and 1 gr 4). GI symptoms usually occurred <1 wat and always resolved. 8 (15%) pts had cardiovascular manifestations, all of which resolved but one (arrythmia) 0.5-5 wat. 5 (10%) pts developed endocrine abnormalities: hypogonadism, hypothyrodism (HT) (x2), HT+SIADH and transient diabetes; 35-100 wat. 1 pt had mild elevation in creatinine 72 wat and recovered after 1 year; 4 other pts had transient renal insufficiencies <3 wat. 1 pt has blurred vision wat, 1 optic neuropathy 55 wat, 2 cataracts 46-52 wat.

Conclusions: Results suggest this regimen of single fraction, high dose rate TBI does not appear to result in higher toxicity levels. However the use of TBI containing conditioning regimens in general does not appear to provide superior control rates over chemotherapy conditioning regimens alone. For that reason, this approach was discontinued.

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Allogeneic peripheral blood stem cell transplantation following reduced-intensity chemotherapy for refractory sarcoma

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An immune-mediated graft-versus-tumour (GVT) effect has been recently reported in patients given an allogeneic transplant of hematopoietic stem cells (HSCT) for renal cancer and occasionally in patients with other solid tumors. To evaluate whether refractory sarcomas can benefit from a GVT effect, we are conducting a pilot trial of allogeneic HSCT in patients not amenable to further conventional treatments. The 3 evaluable patients enrolled so far had stage IV, progressive disease: Ewing sarcoma (ES; age 18, lung and bone mets), rhabdomyosarcoma (RMS; age 10, soft tissue and limphnode mets), gastric sarcoma (GS; age 45, liver metas). Preparative regimen consisted of reduced intensity chemotherapy (CT) with fludarabine 30 mg/m2 days from day -5 to day -2 and cytoxan 30 mg/kg days -5 and -4. Patients were transplanted with peripheral blood stem cells from HLA identical siblings (CD34+ cells: 2.4, 4.9 and 6.5x10-6/kg). GVHD prophylaxis consisted of CyA and short-term MTX. All patients experienced mild treatment related complications limited to short-lasting neutropenia and thrombocytopenia </= grade 3 and no organ toxicity. At day +90, 100% donor chimerism was documented by minisatellite PCR in the 2 cases previously treated with intensive CT including autologous HSCT), and mixed donor chimerism was observed in the patient who had previously received only one line of CT (GS). Acute grade 2-3 GVHD occurred in 2 patients. One patient (ES) had initial radiographic evidence of tumor progression (PD) and subsequent 5 months disease stabilisation (SD) after CyA withdrawal and development of GVHD; he died of PD on day 390. GS patient had SD for 6 months post transplant and subsequently had a low progressing disease; he is alive at day +280. Following allogeneic HSCT, the patient with RMS achieved complete remission lasting 5 months, but he subsequently relapsed and died on day 231. We conclude that: 1) allogeneic HSCT following CY/FLU reduced conditioning is feasible in patients with refractory sarcoma; 2) full donor chimerism may be more easily achieved in patients who had received previous intensive CT; 3) tumor regressions or disease stabilisation occurred in these patients thus indicating that a GVT effect can be generated in vivo against sarcoma cells. Two additional patients (1 ES and 1 liposarcoma) received an allogeneic HSCT more recently. The procedure was uneventful and no adverse events were recorded at 1 month post-transplant.

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Allogeneic hematopoietic stem cell transplantation in patients with beta-thalassemia

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Introduction: Beta-thalassemia major is a hereditary disease characterized by a defective synthesis of the beta-chains of the hemoglobin molecule. The course of the disease in childhood depends almost entirely on whether the child is maintained on an adequate transfusion program. Until now the only curative is an allogeneic hematopoietic stem cell transplantation (HSCT). We herein report on nine patients (six children, three adults, median age: nine years) with beta-thalassemia undergoing allogeneic bone marrow-(BMT) or peripheral blood stem cell transplantation (PBSCT).

Methods: The preparative regimens consist of busulfan 3,5 mg/kg orally on four consecutive days, cyclophosphamide 50 mg/kg intravenously on four consecutive days followed by HSCT. Graft versus host disease (GvHD) prophylaxis included cyclosporine A (CSA) starting on day 2 with 5 mg/kg