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Transplantation of PBPC mobilized with chemotherapy and 5 Or 10 μg/Kg/D filgrastim in patients with non-myeloid malignancies: an open, randomized, phase iii study

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It is not known whether increasing the dose of filgrastim after chemotherapy administration may allow collection of more PBPC and lead to faster hematopoietic engraftment after autologous transplantation. A multicentric randomized trial was carried out in patients with breast cancer (stage II-IV), multiple myeloma, NHL and Hodgkin’s disease, aged 10 to 65 years, with minimal (1-4 cycles) or moderate chemotherapeutic pretreatment. Heavily pretreated patients were excluded. Breast cancer patients were mobilized with FEC (Fluorouracil 500 mg/m^2; Epirubicin 100 mg/m^2; Cyclophosphamide 1200 mg/m^2), myeloma and lymphoma patients with Cyclophosphamide 4500 mg/m^2 and Etoposide 450 mg/m^2. Patients were randomized to receive filgrastim 5 or 10 g/kg/d, starting on the 3rd day after chemotherapy. Leukaphereses (n=3) started within 24 hours of WBC recovery to 1 x 10E9/L. After disease-specific high dose chemotherapy, the first 2 leukapheresis products were reinused if the CD34+ cell dose was 0.5 x 10E6/kg. 131 patients were randomized, of which 128 were mobilized (group A, 5 μg/kg, n= 66; group B, 10 μg/kg, n=62) and 112 transplanted. Although the median number of CD34+ cells collected in the first 2 leukaphereses was higher in group B (12.0 x 10E6/kg) than in group A (7.2 x 10E6/kg), this was not statistically significant. No statistically significant differences in median time to sustained unsupported platelet recovery to 20 x 10E9/L (9 days in both groups) or 50 x 10E9/L (13 days in both groups), to sustained neutrophil recovery to 0.5 x 10E9/L (8 days in both groups) or 1.0 x 10E9/L (9 vs 10 days) or in number of days with platelet transusions (3 in both groups) were detected. A post-hoc subgroup analysis showed a difference in median CD34+ cell yield between minimally and moderately pretreated patients (12.2 [95% CI 7.6-15.3] vs 4.1 [95% CI 1.4-6.7] x 10E6/kg in the first 2 leukaphereses) but this did not translate into faster engraftment. In 90% of minimally and 61% of moderately pretreated patients, 2x10E6/kg CD34+ cells could be collected in 2 leukaphereses. These proportions were not different in the 2 groups. In patients with < 0.5 x 10E6/kg CD34+, a 3rd apheresis usually failed to procure enough cells for transplantation but only 6 patients were so not transplanted due to insufficient CD34+ cell numbers. In conclusion, mobilization with chemotherapy + filgrastim 5 μg/kg is very efficient, and the use of filgrastim 10 μg/kg does not seem to provide additional clinical benefit.

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Optimization of erythropoietin therapy after allogeneic Hematopoietic Stem Cell Transplantation (HSCT)

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Defective Ep0 production after allogeneic HSCT is associated with prolonged anemia. Trials with rHuEpo given in the 1st month after allogeneic BMT resulted in accelerated erythroid engraftment and some reduction in Tx requirements. We enrolled 30 recipients, 22 M and 8 F of an allogeneic marrow (n=8) or PBSC (n=22) transplant from an HLA-id sibling (n=15) or alternative donor (n=15), in 3 consecutive trials of rHuEpo therapy. In the 1st trial (n=7), rHuEpo 1400 U/kg/wk was given from day 1 until an Hb 10 g/dl was achieved, for a maximum of 66 days. Compared to 10 controls, erythroid recovery to 1% retics (12 vs 27 d, p=0.0177) and RBC Tx independence (21 vs 40 d, p=0.007) were faster but the number of Tx was not reduced. In the 2nd trial, rHuEpo was given to achieve Hb levels 13 g/dl in 13 pts complaining of persisting fatigue 60 to 1440 days after transplant. The dose was 500 U/kg/wk. Maintenance doses to uphold target Hb ranged from 30 to 275 U/kg/wk. Baseline Hb ranged from 7.1 to 9.2 (median 8.0) g/dl and 10/13 patients were Tx-dependent. Responses were brisk, with Tx independence achieved after a median of 2 ws in 12/13 pts and Hb values of 10, 11, 12 and 13 gr/dl after 6, 7, 10 and 11 wks, respectively. Only 1 pt did not respond and rHuEpo was stopped after 1 mo in another because of severe GI bleeding. In the other 11 pts, Hb increments ranged from 4.3 to 7.4 gr/dl. Hb decreased to a median of 10.0 g/dl within 3 mo of discontinuation of rHuEpo. In the 3rd trial, rHuEpo was started in 10 pts at a dose of 500 U/kg/wk (later doubled in 2 slowly responding pts) on day 35 with the aim of maintaining Hb levels 13 g/dl. Baseline Hb ranged from 6.8 to 9.4 (median 8.4) g/dl and 7/13 patients were Tx-dependent. Responses were brisk, with Tx independence achieved after a median of 1 wk in 9/10 pts and Hb values of 10, 11, 12 and 13 gr/dl after 4, 5, 6 and 9 wks, respectively. One pt with poor marrow function did not respond. Hb increments ranged from 3.8 to 6.1 g/dl in the other 9 pts and maintenance doses were around 125 U/kg/wk. We conclude that the anemia after allogeneic HSCT is exquisitely sensitive to rHuEpo. The clinical benefit is minimal and the cost prohibitive when it is given early posttransplant as used in all trials to date. However, responses rates are > 90% when it is started after day 35. No iron supplements are needed but infections, bleeding, hemolysis and poor graft function are potential causes of delayed response or temporary Hb decrement. While the hematologic benefit is evident, future trials should examine the impact of rHuEpo on quality of life and survival.

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Mobilised blood CD34+ cells co-express less frequently CXCR4 than those residing in the marrow

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Bone marrow (BM) and more recently blood can be used as source of hematopoietic progenitors. In the latter situations CD34+ cells are mobilised to blood with the use of chemotherapy (autologous) or G-CSF (peripheral blood progenitor cells, PBPC). The question arose whether CD34+ cells mobilised to blood differ from those residing in the marrow and whether they can secure life-long hematological reconstitution. To address this question two parameters were chosen namely co-expression of HLADR and CXCR4.

BM and PBPC were analysed for the presence of CD34+ cells having and lacking HLADR (55 BM and 81 PBPC) and CXCR4 (18 BM and 32 PBPC). PBPC did not differ from BM with respect to the fraction of CD34+ cells (1.21%±0.11 vs 1.19%±0.11, for PBPC and BM respectively). However, CD34+HLADR- cells were present in a higher proportion in PBPC than in BM (0.31%±0.04 vs 0.04%±0.01). The fraction of CD34+CXCR4+ cells was not different between BM and PBPC (55 BM and 81 PBPC) and CXCR4 (18 BM and 32 PBPC). PBPC did not differ from BM with respect to the fraction of CD34+ cells (1.21%±0.11 vs 1.19%±0.11, for PBPC and BM respectively). However, CD34+HLADR- cells were present in a higher proportion in PBPC than in BM (0.31%±0.04 vs 0.04%±0.01).
CD34+ cells lacking HLADR antigen constituted 23.1%±2.0 and 13.9%±1.3 of total CD34+ cells population in PBPC and BM, respectively (p=0.001). Similarly, PBPC CD34+ lacked CXCR4 more frequently than BM counter-partners (51.2%±4.9 vs 77.1%±2.8, p=0.002). This data suggests that CD34+ cells lacking CXCR4 and HLADR were more easily mobilised to blood. CXCR4 is a homing receptor and the absence of HLADR antigen characterises not stimulated cells, which may be less adherent to the marrow stroma.