However, increases in coagulation markers have not been reported in mild community acquired pneumonia.[9] Of note, upper airway infections (generally post viral) and poor treatment compliance are also common causes of COPD exacerbation,[1] and severe pneumonia is unlikely in our COPD patients given that specific signs of consolidation and diffuse infiltration were lacking on their chest X-rays and the absence of high grade fever. The lack of prothrombotic conditions in the control patients is probably due to the heterogeneous nature of their diseases, which included respiratory tract infections/mild pneumonia (n=3), asthma (n=4), pulmonary fibrosis (n=3), and obstructive sleep apnea syndrome (n=2).

Activation of the endothelial-coagulative system in the course of acute exacerbations in COPD may result in an increased risk of PTE and contribute to severity of symptoms. Death from PTE occurs in about 10% of patients admitted for an acute exacerbation of COPD.[10] The incidence of fatal PTE in acute exacerbation of COPD appears to be even higher when reported at post-mortem. Pulmonary emboli have been found in up to 30% of patients who died from acute exacerbation of COPD.[11,12] It is remarkable to observe that PTE was clinically suspected in less than half of the cases and that no specific symptoms were described, thus supporting the view that clinical suspicion of PTE in acute exacerbation of COPD is particularly difficult since clinical symptoms of decompensated COPD may closely mimic those of PTE. Thus, micro-thromboembolism may also contribute to clinical symptoms of an acute exacerbation of COPD. Pharmacological thromboprophylaxis should be instituted for the in-hospital management of these patients.

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Second donation of hematopoietic stem cells from unrelated donors for patients with relapse or graft failure after allogeneic transplantation

Allogeneic hematopoietic cell transplantation (HCT) is a potentially curative approach for a variety of hematologic malignant and non-malignant disorders. With the rising number of stem cell transplantations from unrelated donors over the last years,[1] the occurrence of graft failure or disease relapse has increased. Therapeutic options for the majority of these patients include a second HCT using stem cells from the same unrelated donor.

Given the lower stem cell yield obtained by a bone marrow harvest, the easy and convenient access to G-CSF mobilized peripheral blood stem cells (PBSC) has resulted in their preferred usage as the source of hematopoietic progenitor cells.[2] Nevertheless, severe complications have been described.[3] In fact, we described[4] for the first time a significant increase in spleen size after G-CSF stimulation. Although there have been a few single case reports of the occurrence of secondary hematologic malignancies in voluntary stem cell donors after exposure to G-CSF,[5] at the moment long-term safety data for repeated G-CSF exposure for stem cell donors are not available. Additionally, a bone marrow harvest as an alternative donation procedure still harbors a minimal risk of morbidity.

Against this background, it is of importance to address the question whether repeated donations of HSC in case of graft failure or relapse are associated with a clinical benefit for patients thus justifying a possibly increased risk for voluntary donors. Earlier studies on this subject were mainly performed with bone marrow (BM) as stem cell source (SCS) and showed a worse outcome compared to results after first transplantation. Nevertheless, even the use of PBSC does not seem to have a positive

impact on survival.[6-10]

Therefore, we retrospectively investigated within the German bone marrow center (DKMS) database the outcome of seventy (n=70) patients with hematologic malignancies (Table 1) receiving a second HCT using peripheral blood stem cells (n=67) or bone marrow (n=3) from the same unrelated donor. To our knowledge this is one of the largest analyses so far for a second HCT using PBSC from unrelated donors as SCS. All patients and donors had given informed consent prior to HCT or donation respectively. The indications for a second donation of stem cells were either relapse (n=36, median time to relapse 6.2 months [range 1.1-69]) or primary graft failure (n=34). Whereas in 21 patients no conditioning was used, the remaining 49 patients, including all but 4 patients with relapsing disease, received a second cytoreductive preparative regimen. Cumulative incidences of graft versus host disease (GvHD), treatment related mortality (TRM) and relapse were determined. Survival rates were calculated by means of Kaplan-Meier analysis. Univariate log rank comparisons were performed to identify parameters predicting the outcome after second transplantation.

After a median follow-up of 33 months (range 7.9-76.2) after second HCT, a total of 55 patients died due to TRM (63%) or relapse (16%) resulting in a median overall survival for all patients of three months. The OS was significantly better in patients receiving a second donation for graft failure (37 *vs.* 7%, p=0.02) and in patients < 50 years (38 *vs.* 8%, p=0.01) (Figure 1). Time interval between HCT, HLA-disparity, disease type (AML/MDS *vs*. CML/MPS *vs*. ALL), number of infused CD34$^+$ cells/kg, CMV-positivity or graft source at first transplantation had no significant impact (*data not shown*). Additionally, in graft failure patients there was no impact on outcome whether a conditioning prior to second transplantation was used (*data not shown*). This is an interesting observation suggesting that in a certain subgroup of patients with graft failure, a second stem cell boost without repeated conditioning seems to be equally effective. The infusion of CD34$^+$ selected donor cells in patients with poor graft function has been described as a successful strategy by Bagicalupo *et al.*[11] However, due to the limited number of patients results have to be interpreted with caution.

Previous studies using mostly bone marrow for second transplantation showed poor long term survival rates[9,12,13] comparable to our results. It is of note that TRM seemed to be slightly higher (63%) in our cohort compared to previous studies. This is surprising, as in about one third of our patients no additional toxic conditioning was used before second transplantation. One explanation for this observation could be a higher median age of patients in our study. In fact, patients' age can predict the outcome after second transplantation, which supports our findings, although the cut-off value separating the favorable from the unfavorable group was significantly higher in this study. Eapen *et al*. found a better prognosis for patients ≤ 20 years[9] whereas in the study of Michallet *et al.*[10] the cut-off was even lower (<16 years). Recent predictors such as time to relapse after first transplantation, remission status at second transplantation, absence of acute and occurrence of chronic GvHD after second transplantation, or conditioning regimen had no impact in this analysis.

These data show the limited success of a second infusion of HSC from the same donor, especially in older patients and in cases in which relapse of malignancy is

Table 1. Patients' characteristics.

Total	*N. patients*
Age median (range) yrs.	30 (1-59)
MDS/AML	n=31
ALL	n=17
CML/MPS	n=22
Donor unrelated	n=70
CMV-seropositivity donor or recipient	n=52
HLA-disparity	n=19
One antigen/allele	n=14
Two antigens/alleles	n=5
Reason for 2nd HCT	
Relapse	n=36
Graft failure	n=34
Conditioning prior 2nd HCT	
myeloablative	n=13
dose-reduced	n=35
none	n=21
unknown	n=1
Graft source 1st/2nd HCT	
PBSC/PBSC	n=34
BM/PBSC	n=33
PBSC/BM	n=2
PBSC/BM	n=1
GVHD prophylaxis	
none	n=14
CsA/Tac – based	n=37
other	n=7
unknown	n=12
Median follow-up from 2nd HCT in months	32.6 (7.9-76.2)
Median age (range) yrs.	30 (1-59)

CsA: cyclosporine A; Tac: tacrolimus; PBSC: peripheral blood stem cells; BM: bone marrow, HCT : hematopoietic cell transplantation; MDS: myelodysplastic syndromes; AML: acute myeloid leukemia; ALL: acute lymphoblastic leukemia, CML: chronic myeloid leukemia; MPS: myeloproliferative syndrome.

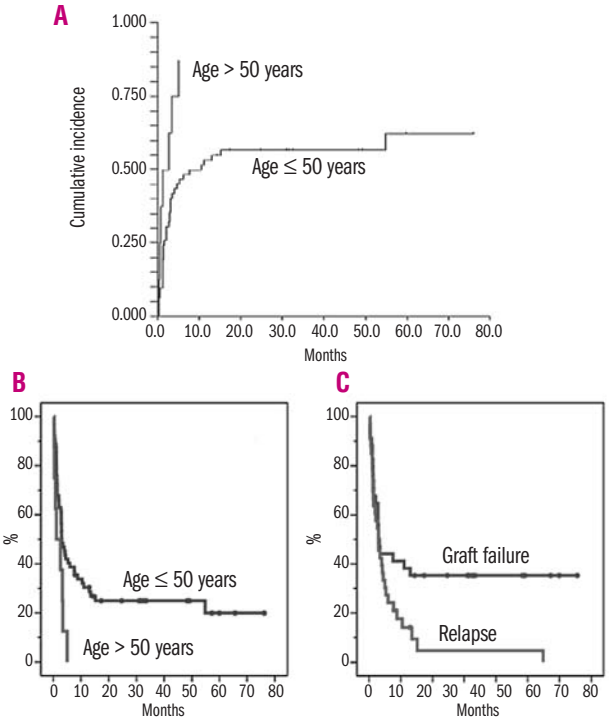

Figure 1. (A, B, C) Treatment-related mortality (A) and overall survival (B, C) according to patient age at and reason for 2nd HCT.

the reason for second transplantation. Given the currently unknown long-term effects of a repeated exposure to G-CSF, the factors mentioned above should be kept in mind whenever a request for a second PBSC donation is considered.

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Extracorporeal photochemotherapy for steroid-refractory graft-versus-host disease in low-weight pediatric patients. Immunomodulatory effects and clinical outcome

Pediatric patients with refractory graft-versus-host disease (GVHD) have been considered for extracorporeal photochemotherapy (ECP). The main problems with ECP in children, especially in the smaller ones, are technical difficulties of leukaphereses with a large extracorporeal volume. Only a few pediatric centers have experience with ECP, mainly with older children.[1,2] We report the clinical outcome in very low-weight pediatric patients who underwent ECP for refractory GVHD and the effect on the lymphocyte subsets. Between September 2003 and April 2007, 11 children with a body weight lower than 25 kg underwent ECP by refractory GVHD. Patients' characteristics are shown in Table 1. GVHD prophylaxis consisted of cyclosporine and methotrexate. Diagnosis (clinical and histological) and classification of GVHD was made according to published criteria.[3] Steroid refractory was defined as failure to respond to 2 mg/kg/day of 6-methilprednisolone after five days (acute GVHD) and flare-up of disease activity upon tapering (chronic GVHD). All patients received cyclosporine A or mycophenolate mofetil and steroids as first-line therapy. ECP was used as second-line treatment in 4 patients who received etanercept prior to ECP. Written informed consent was obtained from all patient's parents and our institution's ethics committee approved the study. Lymphocytopheresis was performed using a continuous-flow cell separator (Spectra, COBE, Lakewood, CO, USA; version 6.1) processing 2 blood volumes as previously reported.[4] The product was diluted with normal saline to a volume of 300 mL by the addition of 3 mL of 8-methoxypsoralen (8-MOP) aqueous solution (Gerot Pharmaceutika, Vienna, Austria) to achieve a product concentration of 200 ng/mL. This final product was transferred to a UVA-permeable bag (MacoPharma, Tourcoing, France), exposed to UVA irradiation (UV-MATIC irradiator, Vilbert Lourmat, France) at a dose of 2 J/cm^2 and reinfused.[5] The average time of ECP procedure was 180 minutes. The machine was primed with packed red blood cells in patients with body weight <15 kg. No standard prophylaxis of hypocalcemia was used.

ECP sessions were performed twice a week (consecutive days) until clinical improvement for acute GVHD. Patients with chronic GVHD were given EPC on two consecutive days (one cycle) at 2-week intervals. Progressive tapering of immunosuppressive therapy and discontinuation of ECP depended on clinical response which was defined according to previously published crtiteria.[6]