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Allotransplantation from unrelated and related donors in patients with active disease in the seventh decade of life

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The widely accepted upper age limit for related or unrelated donor transplantation is 60 and 55 years, respectively. Here we present our results of 28 patients with a median age of 63 (range 56-70) years, transplanted from a matched sibling (n=15) or unrelated (n=13) donor. Patients diagnosis were AML/MDS, MDS RA ,CMML, ALL and CLL. Except for 1 pt each in CR1 and CP1 respectively, all patients had active disease with primary refractory AML (n=6), relapsing, advanced CLL and untreated MDS in 9 patients. For conditioning a regimen ("FBM") with fludarabine 5x30mg/m^2, BCNU 2x150mg/m^2 and melphalane 110mg/m^2 was used. GvHD prophylaxis consisted of CSA, and Mtx or MMF and in unrelated transplants patients received ATG-S (Fresenius) 40-60 mg/kg additionally. 1 pt died from mucor day +28 prior to engraftment, all other pts. engraftend with leukocytes $>$0.5x10e9/l day+10 and platelets $>$ 20x10e9/l day+15 in median. Rates of acute GvHD °II-°IV were 33% (43% in related and 20% in MUD transplants). TRM was 25% in the majority due to fungal infection in this heavily pretreated and advanced disease population. 22 pts. (77%) achieved CR, 2 CLL-pts are in PR and in four pts. remission is not evaluable. OS and PFS is 65% and 55%, respectively with a median follow up of 5 months.
Conclusion: Age as such should not be used as exclusion criteria for allogeneic transplantation. Transplantations with a MUD in elderly patients are save and effective. TRM is determined by disease state and pre-treatment. FBM-regimen has high activity in active myeloid and lymphoid malignancies.

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Tailoring post-transplant immune suppression in high-risk acute lymphoblastic leukemia according to quantitative monitoring of residual disease

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Post-transplant GVHD prophylaxis is usually rigidly performed after allogeneic stem cell transplant for acute lymphoblastic leukemia (ALL). For conventional transplant methotrexate (MTX) and cyclosporin (CSA) are used and if no GVHD occurs, CSA is tapered at month 6; unless relapse, no early DLI are usually performed. We have tried to adapt post-transplant immunomodulation in our last 6 high-risk ALL patients. Patients: P1 (early relapse of CD10+ ALL, HLA-identical sibling), P2 (refractory CD10+ ALL, haplo-identical), P3 (refractory Ph+ ALL, HLA-identical sibling), P4 (refractory relapse of Ph+ ALL, haplo-identical), P5 (refractory Ph+ ALL, HLA-identical sibling) and P6 (refractory Ph+ ALL, HLA-identical unrelated). The conditioning regimen consisted of TBI-cyclophosphamide followed by MTX-CSA prophylaxis except for the two haplo-identical transplants where it was TBI-melphalan-ATG-fludarabine-CSA, T-cell depleted graft and no post-transplant immune suppression. Follow-up of residual disease (MRD) was performed using Real-Time PCR (Ph+ patients) or limiting dilution analysis using IgH clonospecific primers. Results: in P1, MRD failed to decrease for 2 months post-transplant (around 1 %) and CSA was withdrawn. Two months later, MRD became undetectable without GVHD. In P2, the same was observed and mini-DLI (1x104 CD3/kg) were performed thrice at one months interval. At 6 months, MRD is undetectable and no GVHD has occurred. In P3, the lack of MRD decrease led us to stop CSA at month 3, the patient is now in molecular remission with limited cGVHD at month 6. In P4, the same reason led us to perform mini-DLI twice and MRD fell under detectable level with a mild and transient elevation of liver enzymes as the only possible manifestation of GVHD. In P5, MRD is currently decreasing and we have not modified GVHD prophylaxis while in P6, aGVHD occurred, the patient was put on steroids and obviously no other immune manipulation was performed. In this patient, possibly due to GVHD, MRD is currently decreasing. We conclude that in high-risk ALL patients, it could be sensible not to apply standard post-transplant GVHD prophylaxis, but instead to modulate it according to data obtained from quantitative follow-up of MRD by PCR, in patients who do not present with GVHD.

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Double reinforcement with fludarabine/high-dose cytarabine enhances the impact of autologous stem cell transplantation in acute myeloid leukemia patients

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Reinforced chemotherapy based on a double high-dose consolidation regimen could be a different way to enhance in vivo purging prior to autologous stem cell transplantation (auto-SCT) in acute myeloid leukemia (AML) patients. We thus investigated the impact on auto-SCT of two different strategies of early intensification performed after an identical induction regimen in adult patients with AML.
140 consecutive AML patients were subsequently enrolled in a program consisting of an identical anthracycline-based induction (ICE) and two different consolidation regimens: one cycle, cytarabine-based (single-NOVIA: 91 patients); two cycles, fludarabine-based (double-FLAN: 49 patients). Seventy/91 patients received single-NOVIA consolidation: 60 were addressed to transplantation procedures [allogeneic bone marrow transplantation (allo-BMT):16 patients; auto-SCT: 44]. Thirty-five out of 49 patients received double-FLAN consolidation: 31 were addressed to transplantation procedures (allo-BMT: 10; auto-SCT: 21). The double consolidation regimen was well tolerated with only minor side effects.
Considering the patients who received auto-SCT after double-FLAN consolidation strategy (the main end-point), their data compare favorably with the single-NOVIA consolidation group. In particular, the differences in relapse rate, DFS at 36 months and DFS considering intention to treat were all statistically significant (p=0.02; p=0.01; p=0.04, respectively) despite the limited number of cases. This suggests that the double-FLAN consolidation strategy exerts a superior antileukemic effect. We do not know, however, whether this superiority is due to the higher overall dosage, to the use of fludarabine or to a combination of these two factors. The impairment of the stem cell potential and PBSC mobilization could be, anyway, a further indicator of the increased activity of this strategy. This makes autologous bone marrow transplantation an obligatory choice for the majority of patients. We conclude that, even considering the observed impairment of stem cell potential, a double-FLAN reinforcement strategy is safe and enhances the impact of auto-SCT for AML patients in first complete remission.