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Prospective randomised study comparing non-myeloablative (Flu-TBI) and reduced intensity (FLU-BU-ATG) conditioning for haematological malignancies: a multicentre ITAC study

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RIC have been introduced 10 years ago. However no definitive data exist defining the optimal myeloablative and/or immunosuppressive association. We report the first prospective comparison between 2 popular reduced intensity or non-myeloablative regimens. Pts were randomized between FBA with Fludarabine (30mg/m²/5 days), Oral Busulfan (8 mg/kg over 2 days) and Thymoglobulin (2.5 mg/m²/1 day) and FTBI with Fludarabine (25mg/m²/ 3 days) and 2 Gy TBI. Inclusion criteria were: hematological malignancies, pts non eligible for myeloablative allo SCT, aged above 18, HLA identical sibling and written informed consent. 132 pts have been randomized (FBA: N=67; FTBI: N=65). Groups were well balanced for pt characteristics; Median age 55 (32-66); Male gender: 63%; Diagnosis: acute leukemia: 18%; NHL: 23%; MM: 41%; others: 18%; Disease status: CR=29%; PR and stable disease=63%; refractory disease: 8%. Graft failure was documented in 4 pts (6%) after FTBI. Cumulative incidences (CI) of grade ≥ 2 aGVHD and cGVHD were respectively: 39% (Group A 48%; Group B 29%; p=.03) and 75.2% (FBA 77.8%; FTBI 72.5%: p=NS). With median follow-up of 24 months at time of abstract, 68 pts were alive (FBA: 34; FTBI: 31: p=NS) for a 2 year OS probability estimates of 0.63 [0.50–0.73] for FBA and 0.60 [0.47–0.71] for FTBI (p=NS). At 24 months TRM CI was 0.33 (0.21-0.45) and 0.18 (0.08-0.28) (p=0.076] and Disease Related Mortality (DRM) CI was 0.05 (0.0-0.10) and 0.20 (0.10-0.31) for FBA and FTBI respectively (p=0.015). An analysis was conducted in homogenous subpopulations with sufficient individuals (N>50): pts younger (N=76) or older (N=56) than 55 years, Multiple Myeloma (N=53) and non CR situation (N= 93). In each populations, there was no difference for OS between FBA and FTBI studies. However Disease RM was higher after FTBI for pts above 55 (.00 (.0-.05) vs .26 (.08-.44); p=.008), pts with MM (.13 (.01-.25) vs .23 (.08-.38); p=.03), pts non in CR (.05 (.0-.11) vs .21 (.09-.33); p=.03). QOL was assessed over a 1-year period with the EORTC QLQ-C30 questionnaire. FBA has a stronger negative impact on patients' QOL during the treatment administration which disappeared 80 days after the SCT. One year analysis is under analysis. In conclusion these 2 regimens allow similar high 2-year OS for advanced hematological malignancies in rather aged population. However FBA is associated with better disease control and FTBI with a trend for lower TRM but higher rejection in this time frame.

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Unrelated donors, no prior chemotherapy and low CD3 content of the graft increase the rate of graft failure after stem cell transplantation with reduced-intensity conditioning

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Objectives: Stem cell transplantation (SCT) after reduced intensity conditioning (RIC) is routinely used as a curative approach for older and medical impaired patients with haematological malignancies. In contrast to SCT with conventional conditioning, graft rejection (GR) remains an important issue. We analyzed patients with SCT after 2 Gy total body irradiation (TBI) with or without fludarabine (FLU) conditioning to identify risk factors for GR.

Patients and Methods: 380 patients with a median age of 59 (range 17 – 74) years, underwent allogeneic SCT (BM=11, PBSC=369) from a related (n=122) or unrelated (n=258) donor for AML (n=102), Ph+CML (n=34) NHL/MM (n=109), MDS/MPS (n=98) or other diseases (n=37). Conditioning regimen consisted of 2 Gy TBI at day 0 and FLU 30 mg/sqm day -4 to day -2 (n=354) followed by Cyclosporine A and Mycophenolate Mofetil post transplant.

Results: 30 (7.9%) patients developed primary (n=25) or secondary graft failure (n=5) defined as a T cell chimerism <10% donor cells. In univariate analysis older age (p=0.097), no iv chemotherapy prior to SCT (p=0.054), unrelated donor (p=0.007), bone marrow (p=0,007), low CD3 cells (p=0.001) and CD34 cells (P=0.018) in the graft were identified as predictors for GR. In multivariate analysis only low CD3 cells in the graft as continouos variable, no iv chemotherapy prior to SCT and the use of an unrelated donor remained significantly associated with GR. The relative risks (RR) to experience GR were 1.7, 2.7 and 3.7, respectively. Higher doses of CD3 cells were not associated with a increased incidence of acute GvHD grad II-IV until day 100 (p=0.5).

Conclusion: Low CD3 content of the graft, no previous iv chemotherapy and the use of an unrelated donor in comparison to a related donor were three independent risk factors associated with graft rejection. Since more CD3 cells in the graft reduce the risk of GR without subsequent acute GVHD, we recommend to specifically request CD3 cells in patients without prior chemotherapy and unrelated donor.

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Co-transplantation of mesenchymal stem cells might mitigate acute GvHD without abrogating graft-versus-tumour alloreactivity after allogeneic transplantation with non-myeloablative conditioning

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Background: Results of nonmyeloablative HCT in pts with HLA-mismatched donors have been disappointing due to high incidence of graft rejection and severe acute GVHD. Recent studies have suggested that infusion of mesenchymal stem cells (MSC) the day of HCT might promote engraftment and prevent acute GVHD after myeloablative allogeneic HCT. However, some studies suggested that MSC co-infusion might abrogate graft-versus-host alloreactivity and graft-versus-tumor effects. This prompted us to investigate whether MSC infusion a few hours before HCT could allow nonmyeloablative HCT from HLA-mismatched donors to be performed safely (i.e. with a 100-day incidence of nonrelapse mortality < 35%).

Methods: 20 patients with hematological malignancies were given MSC (1-2 x 10E6 cells/kg) from third party donors a few hours before PBSC from HLA-mismatched unrelated donors, after conditioning with 2 Gy TBI and fludarabine 90 mg/m. Postgrafting immunosuppression included tacrolimus (day -3 to +180; tapered by day +365) and mycophenolate mofetil (tid days 0 to +42). HLA-compatibility was assessed at the HLA-A, -B, -C, -DRBI and DQBI loci: 13 pairs were mismatched for at least one HLA class I antigen (including 4 pairs who were also mismatched for 1 HLA-class II antigens (n=3) or 1 HLA-class I allele (n=1)), 1 pair was mismatched for 2 HLA class II alleles, while 6 pairs were mismatched for a single HLA class I (n=3) or HLA class II (n=3) alleles.

Results: Median follow-up for surviving patients was 288 (range, 76-571) days. One patient with secondary AML had primary graft rejection, while the remaining 19 patients had sustained engraftment. Median donor T-cell chimerism levels on days 28, 100, 180 and 365 after HCT were 90%, 98%, 96%, and 98%, respectively. Grade II, III and IV acute GVHD were seen in 5,

2 and 1 patients, respectively, while 7 experienced NIH moderate/severe chronic GVHD. Three of 7 patients with measurable disease at transplantation achieved complete remission on days 41, 104 and 353 after HCT. Two patients died of non-relapse causes on days 74 and 114 after HCT, while 3 died of disease progression. Projected 1-yr overall and progression-free survivals were 77% and 61%, respectively.
Conclusions: HLA-mismatched nonmyeloablative HCT with MSC co-infusion appeared to be safe, with MSC co-infusion possibly mitigating graft-versus-host alloreactivity without abrogating graft-versus-tumor effects. Survival is encouraging.

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Impact of cytogenetics risk on outcome after reduced-intensity conditioning allogeneic stem cell transplantation from an HLA-identical sibling for patients with acute myeloid leukaemia in first complete remission

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Thus far, no large studies have yet assessed the impact of cytogenetics risk on outcome in the context of RIC allo-SCT for AML in CR1.
This report describes the results of 378 AML patients (185 males) transplanted in CR1 using a RIC regimen and reported to the EBMT registry between 2000 and 2007, and for whom detailed cytogenetics data were available. All patients received RIC allo-SCT from an HLA identical sibling. RIC was defined as Busulfan conditioning regimens containing < 8mg/kg total dose, or TBI <6 Gy: The median age at time of allo-SCT was 55 (range, 18-74) y. The median intervals from AML diagnosis to CR1 and from CR1 to RIC allo-SCT were 45 and 155 days respectively. In this series, 21 patients (6%) belonged to the good cytogenetics risk group, while 304 patients (80%) and 53 patients (14%) belonged to the intermediate and poor cytogenetics risk groups respectively. Age, year of transplant, WBC at diagnosis, gender, CMV serostatus, stem cell source, and RIC regimen type were comparable between all three groups. The M5-6-7 FAB subgroup was significantly higher in the poor risk group (30% vs. 20% in the intermediate group).
With a median follow-up of 24 (range, 1-93) months, the KM estimates of 2 years leukemia-free survival (LFS) were 64±-4, 57±3 and 38±7% in the good-, intermediate-, and poor-risk subgroups respectively (P=0.003). In multivariate analysis, cytogenetics was not significantly associated with non-relapse mortality. However, relapse incidence was significantly influenced by the cytogenetics risk groups (P=0.0001) and a higher WBC at diagnosis (P=0.001). Finally, LFS was significantly influenced by the cytogenetics risk groups (P=0.004), a higher WBC at diagnosis (P=0.006), and year of transplant (P=0.04).
Despite its retrospective nature, results from this large study strongly suggest that RIC allo-SCT from an HLA-matched sibling donor is a valid option for AML patients in CR1 not eligible for standard allo-SCT. As it has been shown in the setting of myeloablative conditioning allo-SCT, patients from the poor cytogenetics risk group had increased relapse incidence and decreased LFS rate after RIC allo-SCT. Therefore, prospective strategies such as use of new drugs, intensification of conditioning regimen, post HST immunotherapy should be investigate to improve current results in this group.

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Haplo-identical allogeneic haematopoietic cell transplantation in adults using reduced-intensity conditioning and CD3/CD19-depleted grafts

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Haploidentical hematopoietic cell transplantation (HHCT) with a new regimen using reduced intensity conditioning (RIC) and immunomagnetic CD3/CD19 graft depletion may allow HHCT with lower toxicity, faster engraftment and immune reconstitution. Furthermore CD3/CD19 depleted grafts contain not only CD34+ stem- and progenitor cells but also graft-facilitating cells, CD34- progenitors, dendritic- and natural killer cells.
A multicenter phase I/II study of HHCT using RIC with fludarabine (150-200 mg/m²), thiotepa (10 mg/kg), melphalan (120 mg/m²), OKT-3 (5 mg/day, day -5 to +14) and CD3/CD19 graft depletion was initiated. No G-CSF or GVHD-prophylaxis was applied if the graft contained $<5x10^4$ CD3+ cells/kg.
To date, 53 patients with median age of 46 years (range, 19-65) have been enrolled. Diagnoses were AML (n=35), ALL (n=7), NHL (n=6), MM (n=3), and CML (n=2). Patients were “high risk” because of refractory disease (n=30) or relapse after preceding HCT (auto=8, allo=15). Twenty-five patients were transplanted in complete, twenty-six in partial remission. Grafts contained a median of 7.0×10^6 (range, $3.4\text{-}18x10^6$) CD34+ cells/kg, 3.9×10^4 (range, $0.4\text{-}44x10^4$) CD3+ T cells/kg and 2.8×10^7 (range, $0.02\text{-}37.3x10^7$) CD56+ cells/kg. The regimen was well tolerated with maximum acute toxicity being CTC-grade 1-2 mucositis. Five cases of reversible peripheral neuropathy and three cases of progressive multifocal leukencephalopathy (PML) occurred in heavily pretreated patients. Engraftment was rapid, with median time of 12 days to >500 granulocytes/µL (range, 9-50) and 11 days to >20000 platelets/µL (range, 7-38). Full donor chimerism was reached after median of 14 days (range, 7-215). Four patients experienced rejection/non-engraftment, two were rescued by a second CD3/CD19 depleted graft from another haploidentical donor. Incidence of grade II-IV acute GVHD was 49% (grade II=16, III=6 and IV=4) and 13% for chronic GVHD (limited, n=5, extensive, n=2). TRM in the first 100 days was 11/53 (21%) and overall 21/53 (40%). Overall survival is 16/53 patients (30%) with 503 days median follow-up of patients alive (range, 76-1205). This results in a Kaplan-Meier estimate 1-year survival of 37%. Thirty patients were transplanted from a KIR-mismatched donor, without significant impact on survival.
This regimen is promising in high risk patients lacking a suitable HLA-matched donor. To evaluate the treatment protocol earlier during the course of disease a new study is in preparation.

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Up-front allogeneic stem cell transplantation as part of induction or salvage therapy in primary high-risk and relapsed acute myeloid leukaemia

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Objectives: High risk acute myeloid leukemia (AML) as well as relapsed disease after conventional chemotherapy remains a challenging disease category. Immediate allogeneic hematopoietic stem cell transplantation (HSCT) during aplasia after