positive samples, being underestimated by Ig/TCR method in 25 cases and by m-BCR/ABL quantification in 21 cases. We found significantly more false-negative samples by Ig/TCR approach (70 samples) compared to BCR/ABL quantification (20 samples). Altogether, we tested 219 bone marrow (BM), 130 peripheral blood (PB) and 1 cerebrospinal fluid samples. The PB samples showed significantly worse correlation between the two methods compared to BM ($p=0.02$). In our hands, the quantification of BCR/ABL transcripts appears to be a more reliable method than the generally accepted Ig/TCR-based MRD monitoring as the number of false-negative samples by BCR/ABL quantification is significantly lower. This contention is supported by outcome of our patients who subsequently underwent allogeneic SCT. In this group BCR/ABL positivity preceding allogeneic SCT seems to represent a better predictor of subsequent relapse than Ig/TCR approach.

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FLUDARABINE AND TREOSULFAN; A NOVEL REDUCED-TOXICITY REGIMEN WITH EFFECTIVE ANTI-LEUKEMIA ACTIVITY IN PATIENTS WITH AML AND MDS

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Allogeneic stem-cell transplantation (SCT) is a potentially curative treatment for patients (pts) with AML and MDS. However, it may be associated with significant toxicity. New regimens are continuously explored trying to reduce toxicity while retaining anti-leukemia effect. Treosulfan is a prodrug of a bifunctional alkylating cytotoxic agent used in the past for the treatment of ovarian cancer. In-vitro it mediates cytotoxicity against cell lines of a variety of hematological malignancies including acute leukemia. In escalated doses it shows myeloablative as well as immunosuppressive properties. Initial studies in SCT showed promising results with relatively limited extramedullary toxicity. In the current study we explored a regimen of fludarabine (total dose 150 mg/m2) and treosulfan (12 gr/m2 $\times$ 3) in pts with AML and MDS not eligible for standard SCT. The study included 24 pts, 15 male, 9 female. The median age was 55 years (range, 30-69). Nineteen had AML (8 secondary, 5 to MDS, 1 to myelofibrosis, 1 to breast cancer, 1 to NHL), 5 had MDS. Two pts had a prior autologous SCT (1 for NHL and 1 for AML). All pts had chemo-sensitive or untreated disease at the time of SCT; 11 pts were in CR1, 5 in CR2/3, 6 previously untreated and 2 in untreated relapse. The donor was an HLA matched sibling (n=11) or matched unrelated (n=13). Twenty-one pts engrafted, one later rejected the graft. Three pts died prior to engraftment. The median time to ANC 0.5×10^9/ L and platelet 20×10^9 / L was 15 days (range, 11-21) and 16 days (range, 11-50), respectively. With a median follow-up of 12 months (range, 1-27), 16 pts are alive in CR, one of them in CR 4 months following treatment for post SCT relapse. Eight pts died (relapse-2, organ toxicity – 2, sepsis - 2, CNS bleeding - 1, graft rejection - 1). The cumulative incidence of acute and chronic GVHD was 20% and 41%, respectively. The estimated 1-year overall and disease-free survival were 66% (95% CI, 11-43) and 63% (95% CI, 11-42), respectively. The cumulative incidence of relapse at 1- year after SCT is 11% (95% CI, 3-41) and the cumulative incidence of non-relapse mortality at 1 year is 26% (95% CI, 13-52). In conclusion, the combination of fludarabine and treosulfan is relatively safe, with effective anti-leukemia potential, in pts not eligible for myeloablative conditioning. This regimen merits further study in larger scale studies.

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REDUCED INTENSITY STEM CELL TRANSPLANT (RIST) AS SALVAGE TREATMENT FOR RELAPSE FOLLOWING MYELOABLATIVE ALLOGENEIC TRANSPLANTATION IN ADULT ACUTE MYELOID LEUKEMIA

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Relapse of acute myeloid leukemia (AML) following myeloablative allogeneic stem cell transplantation portends a dismal prognosis. Therapy aimed at enhancing graft-versus-leukemia (GVL) effect, e.g., by donor leukocyte infusion, has limited success in AML, and a second ablative transplant is associated with prohibitive mortality in adults. From April 2001 to March 2006, nine patients, ranging in age from 21 to 57, with high risk myeloid malignancy (7 AML and 2 advanced myelodysplasia) and overt bone marrow relapse less than one year after ablative busulfan/cyclophosphamide conditioning have been treated with a cytoreductive regimen of fludarabine (30 mg/m2/day) and cytarabine (2g/m2/day) for 5 days (-7 through -3) and G-CSF administration (5 ug/kg daily starting day -8) with or without idarubicin (8 mg/m2 days -7, -5, and -3) (8 cases) or fludarabine 30 mg/m2 for 3 days and 200 cGy total body irradiation (1 case). G-CSF mobilized peripheral blood stem cells from their original HLA-matched donor (8 siblings, 1 unrelated) were infused. Graft versus host disease (GVHD) prophylaxis was mycophenolate mofetil for 30 days and cyclosporine with a rapid taper. The mean onset of relapse after the initial ablative transplant was day 172 (range 106-271). Fludarabine-based therapy was well tolerated with no treatment related mortality. Full donor chimerism was established by day 72 (range 26-113) in 6 patients (67%). Five patients died: 2 from relapse without GVHD at day +30 and +301 after RIST (one patient with complex and one with Ph+ cytogenetic abnormalities), 3 from relapse with evidence of GVHD. Four patients survive: one has relapsed at 91 days after RIST and is receiving alternate therapy, while three patients (30%) survive in complete remission at 100+, 635+ and 1795+ days after salvage RIST. In 5 cases (56%), the duration of complete remission after RIST was longer than after the initial ablative transplant. We conclude that fludarabine-based RIST is a safe and effective salvage therapy offering a chance for increased survival with low morbidity in patients relapsing after ablative transplant. In addition, RIST therapy has resulted in long-term disease free survival in over 20% of cases in this study.

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LONGER FOLLOW UP OF PATIENTS (PTS) WITH ADVANCED CHRONIC LYMPHOCYTIC LEUKEMIA (CLL) TREATED WITH NONMYELOABLATIVE CONDITIONING AND ALLOGENEIC HEMATOPOIETIC CELL TRANSPLANTATION (HCT)

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Pts with fludarabine-refractory CLL have a poor prognosis with conventional therapies with median survival of 12 months. We previously reported 2-year overall survival of 60% for 64 pts treated with nonablative HCT from related (n=44) or unrelated (n=20) donors (Sorror et al. JCO 2005, 23: 3819). Here, we present an update on the first 64 pts (median of 48 [range: 24-86] months) and report data on 18 additional pts transplanted between February 2004 and January 2006. The 82 pts were given nonablative HCT from related (n=52) or unrelated donors (n=30). Median pt age was 55.5 (range 42-72) years, and the median number of prior regimens was 4 (range 1-12). Seventy-nine pts were refractory to at least 1 regimen, 72 to fludarabine (FLU), 27 to alkylating agents, 23 to rituxumab, 7 to CAMPATH®, and 3 had failed high-dose autologous HCT. Thirty-six pts (44%) had disease responsive to the last chemotherapy [36% partial (PR) and 7% complete remission (CR)] while 37 were resistant and 9 had untested relapse. Conditioning for HCT consisted of 2 Gy TBI alone (n=13) or combined with FLU (n=69), 90 mg/m^2. All pts received G-PBMC. The incidences of grades II, III, and IV acute GVHD were 40%, 16%, and 2% respectively, and chronic extensive

GVHD was 53% at 4-years. The overall response rate was 74% (53% CR). Unrelated recipients had a trend for higher CR rate than related recipients (Table). Overall, 45 patients are alive; 27 in CR, 1 with minimal residual disease, 7 in PR, 2 with stable disease, and 8 with relapse/progression. Thirty-seven pts died, 17 from progression/relapse, 14 from infections ± GVHD, 2 from cardiac causes, 1 from metastatic lung cancer, 1 from cerebral stroke, 1 from rejection and aplasia, and one during open heart surgery for a valve defect. Estimated 4-year rates of non-relapse mortality, relapse, disease free, and overall survivals were 24%, 32%, 44%, and 55% respectively. Among 31 surviving pts with the longest follow up (24-86 months), 21 had developed chronic GVHD. Fifteen of the 21 (median follow up of 49 months) had immunosuppression discontinued upon resolution of chronic GVHD while 6 (median follow up of 43 months) continued on immunosuppression. The median performance status (PS) of the 21 pts was 90%. Nonmyeloablative HCT resulted in median survival of greater than 4 years for pts with fludarabine-refractory CLL. Pts with longer follow up showed sustained remissions and continuing resolution of chronic GVHD with good performance status.

Table: *Results stratified by donor type*

	Donor		
	Related (n = 52)	Unrelated (n = 30)	*p*
Acute GVHD grade II, III, and IV	39%, 14%, and 2%	43%, 20%, and 3%	0.19
Chronic extensive GVHD at 4-years	51%	56%	0.94
Pts off immunosuppression at 3 years after chronic GVHD	29%	52%	0.16
Pts alive and off immunosuppression at 4 years	29%	70%*	
CR rate at 4-years	47%	63%	0.07
Relapse/progression at 4-years	33%	31%	0.45
Surviving pts	13 CR, 1 MRD, 6 PR, 2 stable, and 4 progression	14 CR, 1 PR, 2 progression, and 2 relapse	
Day-100 non-relapse mortality	8%	10%	0.97
4-year non-relapse mortality	23%	24%	0.97
4-year relapse-related mortality	27%	12%	0.35
4-year disease-free survival	43%	45%	0.59
4-year overall survival	50%	64%	0.62

*This is a temporary spike at exactly 4.0 years. The prevalence at 3.9 and 4.1 years is 53%. MRD indicates minimal residual disease.

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REDUCED-INTENSITY STEM CELL TRANSPLANTATION FOR HIGH-RISK ACUTE LYMPHOBLASTIC LEUKEMIA

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Reduced-intensity allogeneic stem cell transplantation (SCT) relies mainly on graft versus leukemia (GVL) for its efficacy; is increasingly being used for treatment of hematological malignancies. The role of GVL is less defined in transplantation for acute lymphoblastic leukemia (ALL). We report the experience of 21 ALL patients who were treated with fludarabine 25mg/m^2 daily for 5 days and melphalan 140 mg/m^2 followed by Allo-SCT between 5/7/02 and 5/31/06. The indications for the reduced-intensity regimen were: 1) previous Allo-SCT 5(24%), 2) >50 years 7(33%) and 3) decreased organ function 9(43%). The patient/treatment characteristics are: median age 46 years (6-68), remission status at Allo-SCT: 1CR 10(48%), 1RL 3(14%), 2CR 4(19%) and ≥3CR 4(19%), Ph+ ALL 11(52%), donor type: match sibling 7(33%), matched unrelated 14(67%), stem cell source: primed peripheral stem cells 20(95%) and cord blood-double 1(5%), graft versus host disease (GVHD) prophylaxis: cyclosporine(CSA)/methotrexate(MTX) 4(19%), CSA/Mycophenylate(MMF) 9(43%), CSA/ATG 1(5%) and CSA/MMF/MTX 1(5%). Six (28%) patients received tacrolimus and sirolimus. With a median follow-up for alive patients 17.0 months (range: 2.7-47.2), the one-year cumulative probability of overall survival, disease-free survival and relapse rate were 77.4% (95%CI: 57.2, 88.9), 70.9% (95%CI: 52.0, 83.4) and 7.7% (95%CI: 1.3, 38.7) respectively. Incidence of acute GVHD was 50% for grade II-IV and 15% for grade III-IV. Of the patients evaluable for chronic GVHD, 11% developed limited chronic GVHD and 33% developed extensive chronic GVHD. The 100 day non-relapse mortality was 10%. The results of this study show that RI Allo-SCT using fludarabine/melphalan based conditioning is a potential therapeutic approach for patients with high-risk ALL who are not eligible for full intensity transplant.

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FLUDARABINE-BUSULPHAN REDUCED INTENSITY CONDITIONING (RIC) IDENTICAL SIBLING ALLOGENEIC STEM CELL TRANSPLANTATION (ALLO-SCT) IN HIGH RISK ACUTE MYELOID LEUKEMIA AND MYELODISPLASTIC SYNDROME

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Background-purpose: The use of reduced intensity conditioning regimen (RIC) may reduce non-relapse mortality (NRM) and allow long term disease free survival (DFS) and overall survival (OS) through graft versus leukemia (GVL) effect in patients considered not eligible for convenitonal allogeneic stem cell transplantation (Allo-SCT). In this multicenter, prospective study we report our experience wit RIC regimen based on fludarabine and busulfan. **Patients and methods:** We included all 93 consecutive patients with AML and MDS who underwent fludarabine-busulphan RIC-Allo-SCT from an HLA identical sibling, in 6 Spanish centers since 1998 to 2005. Diagnoses were acute myeloid leukemia (AML) (n=59) or myelodisplastic syndrome (MDS) (n=34), median time from diagnostic was 6 (range 1-150) months. Median age was 58 (range 21-70) years. Follow up for survivors was 43 months (3-89). Conditioning regimen consisted of fludarabine 150 mg/m^2 and busulfan 8-10 mg/kg. Graft versus host disease prophylaxis consisted of cyclosporin A and a short course of methotrexate or mycofenolate mofetil. **Results:** These patients received a RIC regimen for advanced age +/-comorbidities (83%) previous SCT +/- advanced age (9%) or active infection, poor PS, or other comorbidities (8%). 56% of patients showed very high risk disease (high risk karyotype, refractory disease or high risk IPSS). Median time to neutrophil and platelet recovery was on day 17 (range7-27) and 11 (range 0-59) days respectively. Thirty three patients developed acute GVHD for a Cumulative Incidence (Cum Inc) of 33% (95% CI 25-44) and 53 out of 77 evaluable patients developed chronic GVHD for a Cum Inc of 54% (95% CI 44-65%). The 100-day and 1-year Cum Inc NRM was 8% and 17% respectively. The 4 Years Relapse Cum Inc was 37% (95% CI 28-50%). The 4-years DFS was 43% (33-53%) for the whole group. The 4-year