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