0%-43%) and 10% (95%CI, 0%-23%) for MRD and CB, respectively (p = 0.6)

Conclusion: The use of allogeneic HSCT with RIC provides favorable disease outcomes in older AML patients in CR1. CB should be considered as an alternative donor source in patients with no MRD donor available.

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SYNERGISTIC CYTOTOXICITY OF CLOFARABINE, FLUDARABINE AND BUSULFAN: RELEVANCE TO MYELOABLATIVE THERAPY

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Clofarabine (Clo) and Fludarabine (Flu) are purine nucleoside analogues (NA) with antileukemia activity. Their synergistic cytotoxicity in the absence or presence of DNA alkylating drug Busulfan (Bu) has not been reported. To determine the efficacy and synergism of these three drugs in Bu-resistant AML cell line (KBM3/Bu250[6]), various combinations were analyzed for their cytotoxicity. Clo, Flu and Bu have IC_{50} values of 0.03 μM, 1.22 μM and 126 μM, respectively. Combination of 0.01 μM Clo and 0.2 μM Flu resulted in 84% cell survival after 4 d; addition of 40 μM Bu to this combination decreased cell survival to 59% suggesting synergism. Cell cycle analysis after 2-day exposure of cells to either 0.015 μM Clo or 0.6 μM Flu showed 6% cells in sub-G1. When combined at the same concentrations, 20% cells were in sub-G1 and 5% were TUNEL-positive. Addition of 80 μM Bu to this combination increased sub-G1 and TUNEL-positive cells to 35% and 15%, respectively. These results suggest synergistic efficacy of Clo and Flu which further improves with addition of Bu. Immunoblot analysis of cells exposed to 0.015 μM Clo + 0.6 μM Flu resulted in significant cleavage of PARP1 and increased γ-H2AX compared with exposure to either NA alone; addition of 80 μM Bu increased the effects two-fold. These results suggest drug-mediated induction of DNA damage response and apoptosis. Inhibition of ribonucleotide reductase (RNR) with 100 μM hydroxyurea (HU) was also synergistic with Clo or Flu. The effects of [Clo + Flu], [Clo + HU] and [Flu + HU] were reversed by 100 μM cytidine. These data support self-potentiation of [Clo + -Flu] combination as a possible mechanism of their synergistic cytotoxicity where both NA inhibit RNR, decrease deoxynucleotide synthesis and make more deoxycytidine kinase available to phosphorylate and activate Clo and Flu. This mechanism may result in enhanced incorporation of Clo and Flu during DNA synthesis. [Clo + Flu] combination also resulted in more significant methylation of histone H3 suggesting increased chromatin remodeling which possibly exposed more DNA to Bu-mediated cross-linking and explains the observed synergism of [Clo + Flu + Bu]. This model is consistent with a dramatic increase in the level of γ-H2AX, an indicator of DNA damage, when Bu was added to [Clo + Flu] combination. Overall, our results suggest that addition of [Clo + Flu] might synergistically improve the cytoreductive efficacy of Bu-based pre-transplant regimen in myeloid leukemia patients.

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EFFECTS OF CHANGES IN CONDITIONING REGIMEN AND SUPPORTIVE CARE ON OUTCOMES IN PATIENTS WITH ACUTE MYELOID LEUKEMIA (AML) AFTER ALLOGENEIC STEM CELL TRANSPLANTATION (ALLO-SCT)

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As in all centers around de world, transplant strategies have change in our center over the time. Here we report the results of a single center, retrospective analysis of outcomes in patients with AML treated with high dose therapy and allo-SCT, from 1994 to 2009, comparing patients treated before and after 2005 when we changed conditioning regimen for AML to Fludarabine-Busulfan and implemented supportive measures as Levofloxacine as prophylaxis, CMV pre-emptive strategy, and EICH prophylaxis with Micofenolate (MMF).

Since 1994, 59 LMA patients have been treated, 57 received peripheral blood HLA identical related grafts and 2 patients received UR cord blood transplants. As conditioning, 3 patients received RIC and 56 full intensity conditioning (BuCy 25 – BuFlu 23 – other 8). Only 3 (5%) had high risk cytogenetics at diagnosis but 40% were considered of high risk at transplantation (44% for BuCy and 39% for BuFlu). Table 1. Describes patient characteristics and outcomes for all patients and BuCy vs BuFlu groups. Of note BuCy and BuFlu groups are very similar except for CMV positivity 56 vs 78% and time from diagnosis to transplant 24 months (2.3-167) vs 14.5 (2.13-33).

BuFlu patients received routine Levofloxacine prophylaxis (78% vs 0% BuCy group), GVHD mainly with Cs-MMF (69% vs BuCy group 28%) and were treated for CMV in a preemptive strategy.

As shown in table toxicity related to the procedure was greatly reduced with BuFlu strategy, having a shorter hospital stay, less fever, diarrhea, requiring less antibiotics and transfusion support. There were no toxic deads in BuFlu group.

For BuCy group, at a median follow-up of 12.8 months (range 0.5-118.), 9 patients are alive in CR (36%), 4 were lost for follow-up (16%) and 12 died (48%). 4 patients (16%) died before day 100 of transplant related causes. Main cause of death was relapse in 7 (58.3%).

For BuFlu group, at a median follow-up of 7 months (range 1-40), 13 (56.5%) are alive in CR, 1 is alive in relapse (4.3%) and 9 died (39.1%). No patient died before day 100. Relapse has been the main cause of dead so far, 4 (33.3%); followed by pulmonary complications, 3 (25%) and EICH related complications 2 (16.7%).

This retrospective analysis suggest benefit of Bu-Flu and newer supportive strategies in early toxicity related to HLA familial allo-SCT over BuCy. Longer follow-up and greater numbers of patients are needed to draw conclusions about its significance in long-term survival.

Patient characteristics and outcomes

	All (N 59)	BuCy (N. 25)	Bu-Flu (N. 23)
Gender (M/F)	32/27	12/13	14/11
Age	34 (6-63)	34.9 (6-55)	33.8 (10-61)
# Previus cycles	4.67 (1-16)	4.5 (1-16)	4.7 (1-9)
CD34+x10-6/kg	3.3 (0.3-11.1)	2.9 (1.1-8)	2.9 (0.8-11)
Hospital stay	32.1 (21-80)	34.7 (22-54)	27.3 (22-40)
% weigth loss	5 (-3.4 – 13.6)	6 (0-12.9)	3.7 (-3.4-12.1)
Neutrophyls graft	13 (6-43)	14 (9-43)	11 (6-14)
Fever (days)	4.1 (0-22)	4.8 (1-20)	1.9 (0-5)
Diarrhea (days)	3.9 (0-21)	5 (0-15)	2.9 (0-21)
TPN (days-% patients)	6.2 (0-25)-61%	8.3 (0-21)-72%	3.1 (0-10)-48%
Antibiotic days	32.4 (0-127)	42.56 (12-127)	17 (0-49)
RBC transfusion	1.8 (0-28)	1.92 (0-14)	0.6 (0-5)
PLT transfusion	4.9 (0-35)	6.5 (1-27)	1.4 (0-18)
Mortality <100 days	6.7%	16%	0%

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UNRELATED DONOR REDUCED-INTENSITY STEM CELL TRANSPLANTATION IS A PROMISING TREATMENT OPTION FOR ELDERLY PATIENTS WITH BLASTIC PLASMOCYTOID DENDRITIC CELL NEOPLASM (BPDC)

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Blastic plasmacytoid dendritic cell neoplasm (BPDC), formerly known as *blastic NK cell lymphoma*, is a rare hematopoietic malignancy preferentially involving skin, bone marrow and lymph nodes. The overall prognosis of BPDC is dismal. Most patients show an initial response to acute leukemia-like chemotherapy, but relapses with subsequent drug resistance occur in virtually all patients resulting in a median overall survival of only 9-13 months. However, anecdotal long-term remissions have been reported in young patients who received early myeloablative allogeneic stem cell transplantation (alloSCT). As the median age at diagnosis is above 60 years, most patients at risk will not be eligible for myeloablative alloSCT. Here we present our experience with reduced-intensity conditioning (RIC) alloSCT from unrelated donors in elderly patients with BPDC.