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AUTOLOGOUS STEM CELL TRANSPLANTATION (ASCT) IN UNTREATED FIRST RELAPSE (REL1) OR FOLLOWING RE-INDUCTION CHEMOTHERAPY (CT) FOR PATIENTS (PTS) WITH ACUTE MYELOGENOUS LEUKEMIA (AML)

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The timing of ASCT for AML after first relapse is controversial. The purpose of this study was to review our results in AML pts in first relapse by comparing outcomes between pts taken directly to ASCT and pts receiving re-induction chemotherapy prior to ASCT. Between January 1990 and March 2003, 37 pts with AML in REL1 or CT underwent ASCT. Survival was analyzed using the Kaplan-Meier (KM) methodology with statistical comparisons using the log-rank test. Univariate predictors of survival were examined using Cox proportional hazard models. Of the 37, 25 and 12 pts underwent ASCT at CT and REL1 (median age 46 vs 42 years), respectively. There was only 1 pt in the CT group who had refractory disease. In the CT group, 18 pts (72%) and 7 pts (28%) had stem cells harvested during CR1 and CR2, respectively. In the REL1 group, all pts had stem cells harvested in CR1. Thirty of 37 pts received cyclophosphamide and total body irradiation (Cy/TBI) for conditioning and the remainder received busulfan and cyclophosphamide (Bu/Cy). There were no statistically significant differences in the baseline characteristics between the two groups. The percentage of bone marrow blasts at first relapse was increased in the CT versus the REL1 group (median 40% vs 15%, p=0.06). KM analysis showed that there was no significant difference between the two groups in time to neutrophil and platelet engraftment. The REL1 group had a significantly shorter time to relapse than CT. The CT group had significantly higher DFS than REL1 and a trend toward better OS with no difference in TRM. The Table details estimated probabilities of these endpoints. Univariate Cox proportional hazard analysis for overall survival showed that younger age at diagnosis and transplantation, unfavorable cytogenetic abnormalities at diagnosis and relapse were significantly associated with a higher risk of death. Higher percentage of blasts in bone marrow at first relapse and shorter duration of CR1 were not significantly associated with death. In a multivariate model, only unfavorable cytogenetic abnormalities at first relapse were significantly associated with an increase risk of death. Although OS between CT and REL1 groups was not significantly different, the time to relapse and DFS were significantly longer for the CT group. Although retrospective and limited by selection bias, this study suggests that there may be an advantage for re-induction chemotherapy for AML in first relapse before ASCT.

	REL1	Post CT	p value*
Probability of Relapse (%)			**0.0075**
1 year	**83.3**	**45.8**	
5 years	**83.3**	**59.9**	
Median time to relapse (mos)	**6.1**	**13.7**	
Overall Survival (OS) (%)			**0.09**
1 year	**41.7**	**68.0**	
5 years	**8.3**	**40.8**	
Median time of OS (mos)	**8.7**	**17.9**	
Disease free survival (DFS) (%)			**0.006**
1 year	**16.7**	**52.0**	
5 years	**8.3**	**39.0**	
Median time of DFS (mos)	**6.1**	**13.7**	
Transplant related mortality (TRM) (%)			**0.50**
1 year	**0**	**4.0**	

*Log rank test comparing distribution of event times over multiple comparisons.

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HIGH AVIDITY CYCLIN E1-DERIVED PEPTIDE-SPECIFIC CTL KILL LYMPHOID LEUKEMIA CELLS AND CROSS-RECOGNIZE A HOMOLOGOUS CYCLIN E2-DERIVED PEPTIDE

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Using a similar strategy that was used to identify PR1 as a leukemia-associated antigen (LAA), we identified two homologous HLA-A2-restricted peptides from cyclin E1 (CCNE1M) and cyclin E2 (CCNE2L) that could be used to elicit peptide-specific CTL from healthy donors. The two peptides differ by a single amino acid at position 7 and have equal binding affinity for HLA-A2, and each elicited peptide-specific CTL with equal efficiency. Because each CCNE1M- and CCNE2L-CTL clone, derived from limiting dilution, cross-recognized the other homologous peptide, we hypothesized that each clone would efficiently kill leukemia that over-expressed either or both CCNE1 and CCNE2 proteins. Sorted high avidity CTL showed higher specific lysis of peptide-pulsed T2 than did low avidity CTL (38.8% vs 31.9% specific lysis, respectively, at E:T 10:1, p = 0.02). The fluorescence decay of tetramer dissociation (ln (peptide/HLA-A2 tetramer)) over time was linear for each clone, showing that avidity was proportional to TCR affinity and tetramer dissociation t1/2 was determined based on first order kinetics. CCNE1M-CTL had higher affinity for CCNE1M/HLA-A2 (CCNE1/A2, t1/2=84.5 min; CCNE2/A2, t1/2=25.3 min) and preferentially killed CCNE1M-pulsed T2 cells (CCNE1, 56.9% vs CCNE2, 38%, respectively, at E:T 10:1). CCNE2L-CTL also had higher TCR affinity for CCNE1M/HLA-A2 (CCNE1/A2, t1/2=29.5 min; CCNE2/A2, t1/2=10.7 min), but showed only slightly higher specific lysis of CCNE1M-pulsed T2 cells (CCNE1, 49.3% vs CCNE2, 44.2% specific lysis, respectively, at E:T 10:1). Each clone specifically lysed HLA-$A2^+$ T-ALL leukemia cells in proportion to both CCNE1 and CCNE2 protein overexpression (CCNE1M-CTL, R^2=0.89; CCNE2L-CTL, R^2=0.88) in an HLA-A2-restricted manner. Both the high and low affinity clones showed equal lysis of T-ALL cells that expressed large amounts of each protein (CCNE1M-CTL, 24.3% vs CCNE2L-CTL , 23.8%, at E:T 10:1). However, high affinity CCNE1M-CTL killed T-ALL cells significantly better than low affinity CCNE2L-CTL (16.8% vs 6.6% lysis, respectively, at E:T 10:1) when the T-ALL expressed a 2.5-fold lower amount of both CCNE1 and CCNE2 proteins. We conclude that the CCNE1M and CCNE2L homologous self-peptides are lymphoid LAA. Furthermore, while the higher TCR affinity of CCNE1M-CTL suggests that the CCNE1M peptide is the more dominant epitope, ultimate target susceptibility is enhanced due to degeneracy of the resulting CTL clones against homologous peptide epitopes.

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NON-MYELOABLATIVE CONDITIONING FOR ALLOGENEIC HEMATOPOIETIC STEM CELL TRANSPLANTATION IN PATIENTS WITH ACUTE MYELOID LEUKEMIA. THE IMPACT OF THE REMISSION STATUS

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Background: Multicentre randomized trials have shown that allogeneic hematopoietic stem cell transplantation (HSCT) is the most effective strategy for preventing relapse in patients in first complete remission (CR) of acute myeloblastic leukemia (AML), offering up to 50% disease-free survival. However in adult patients with good risk AML, allogeneic HSCT is usually indicated in second complete remission or first untreated relapse. We analyzed the outcome of 16 AML patients who received a reduced intensity conditioning regimen for allogeneic HSCT in first or second remission. **Patients and Methods:** Sixteen AML patients (1 M1, 8 M2, 3 M3, 2 M4 and 2 M5), 9 in first CR (FCR) and 7 in second CR (SCR) were included. All patients received Busulfan 4 mg/kg/d/2 days, Fludarabine 30 mg/m^2/d/3 days and cyclophosphamide 350 mg/m^2/d/3 days as conditioning regimen. The median age was 32 years (range 3–56) in both groups. The source of hematopoietic stem cells (HSC) was peripheral blood and donors were HLA