(p = 0.01). Likewise, the probability or relapse was highest in the MK+ group (72%) as compared to the MK- group (37%), the CN group (24%), or the CBF group (14%) (p = 0.001). There was no statistically significant difference in non-relapse mortality between the four groups.

Conclusions: Our results indicate that cytogenetics is still one of the most important prognostic factors. In particular, the presence of a monosomal karyotype provides a strong negative prognostic prediction for patients with AML undergoing alloSCT. These patients should be referred to alloSCT in early in CR1.

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SYNERGISTIC CYTOTOXICITY OF BUSULFAN AND NUCLEOSIDE ANALOGS IN HUMAN LYMPHOID CELL LINES

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Lymphoid leukemia and Non-Hodgkin's lymphoma (NHL) are heterogeneous diseases, which require various treatment modalities. Although the success of hematopoietic stem cell transplantation (HSCT) for myeloid leukemia has been well documented in the last decade, advances in lymphoid malignancies have been modest and the efficacy of HSCT for these diseases merits further study. To identify potential efficacious pretransplant conditioning therapy for these diseases, we performed *in vitro* cellular studies on the possible synergistic cytotoxicity of the DNA-alkylating agent busulfan (Bu) and nucleoside analogs (NA) clofarabine (Clo), fludarabine (Flu) and gemcitabine (Gem). Daudi (B cell lymphoblast), J45.01 (T cell lymphoblast) and U937 (monocytic/lymphoblast) cells were exposed to these drugs, either individually or in combinations, and analyzed for cell survival by the MTT assay and for protein level and modifications by Western blot analysis. The three cell lines exhibited different drug sensitivities as suggested by the IC_{50} values: Daudi – 40 μM Bu, 80 nM Clo, 30 μM Flu and 2 nM Gem; J45.01 – 100 μM Bu, 60 nM Clo, 0.8 μM Flu and 25 nM Gem; U937 - 160 μM Bu, 20 nM Clo, 1.2 μM Flu and 70 nM Gem. Synergistic cytotoxicities were observed when the drugs were combined at IC_{10} – IC_{20} concentrations with U937 cells being the most sensitive. Exposure of cells to [Gem+Clo+Bu], [Gem+Flu+Bu] or [Clo+-Flu+Bu] for 4 days resulted in 5%-15% survival of U937 cells, 20%-50% of Daudi cells and 45%-80% of J45.01 cells. The effects of these drug combinations on cell survival are consistent with DNA-damage response as indicated by the phosphorylation of H2AX, ATM and SMC1 proteins, and cleavage of PARP-1. The observed methylations of histone 3 may suggest chromatin remodeling which may contribute to the pronounced activity of [NA+Bu] combinations. Interestingly, [two NA + Bu] combinations are much more efficacious than [one NA + Bu]. Exposure of Daudi, J45.01 and U937 cells to [Gem+Bu] for 4 days resulted in 85%, 100% and 78% cell survival, respectively. Similar exposure to [Gem+Clo+Bu] resulted in 50%, 60% and 5% survival and exposure to [Gem+Flu+Bu] resulted in 20%, 80% and 6% survival of Daudi, J45.01, and U937 cells, respectively. Our results suggest that combination of two NA with Bu may be more active than Bu plus one NA. The findings support the introduction of [two NA + Bu] as part of pretransplant conditioning regimen for advanced, aggressive lymphoid malignancies.

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ALLOGENEIC AND AUTOLOGOUS TRANSPLANTATION FOR THE TREATMENT OF ADULT ALL

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Introduction: The Philadelphia chromosome translocation ([Ph+) is the most frequent cytogenetic abnormality detected in adult ALL. Ph+ patients are classified as high-risk, with allogeneic hematopoietic stem cell transplantation (alloHCT) considered the best chance for cure. The role of autologous transplantation (autoHCT) in the treatment of these patients remains controversial. More recently, tyrosine kinase inhibitors (TKIs) have shown promise in treating Ph+ ALL. The long-term outcomes with TKI's plus chemotherapy remain poor, consequently transplantation is still considered standard. At UCSF, Ph+ ALL patients without histocompatible donors are offered autoHCT. In this study we retrospectively analyzed adult ALL patients undergoing alloHCT and autoHCT at UCSF from 1986 to 2009 to identify factors influencing outcome.

Patients and Methods: 121 patients diagnosed with ALL underwent autoHCT or alloHCT at UCSF since 1986. 42 patients were Ph positive; based on cytogenetic and/or molecular methods. The mean age at transplant was 36 overall (15-64), and 43 for Ph+ patients (23-64). Patients received autoHCT or alloHCT based on donor availability. Overall, 43 patients underwent autoHCT, and 78 underwent alloHCT. For the Ph+ subgroup, 13 and 29 received autoHCT and alloHCT respectively. Conditioning consisted of either total body irradiation (TBI) with etoposide and/or cyclophosphamide; or fludarabine with busulfan. AlloHCT patients received standard GVHD prophylaxis, and all patients received ID prophylaxis.

Results: The median disease-free survival (DFS) overall was 1.59 years for patients receiving autoHCT and 1.7 years for those receiving alloHCT. The 5-year probability of DFS was 38% for autoHCT, and 44% for alloHCT with treatment-related mortality of 9% and 36%, respectively. In the subset of Ph+ patients, 5-year probability of DFS was 58% and 40%, respectively, with no significant difference detected. Improved DFS with noted following TKI use (70% in the autologous group, n10; 58% in the allogeneic group, n17). Status at transplantation correlated with probability of DFS. TBI-based regimens and age were not found to influence outcomes.

Conclusion: Our data support the use of alloHCT for the treatment of ALL, including Ph+ patients. The data with autoHCT are encouraging, with impressive results found following the addition of TKI therapy. A larger Phase II study evaluating the role of autoHCT in PH+ ALL appears warranted.

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PURINE NUCLEOSIDE ANALOGS EXERT SYNERGISTIC CYTOTOXICITY WITH THE DNA-ALKYLATING AGENT BUSULFAN IN HUMAN MYELOID LEUKEMIA

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The purine nucleoside analogs fludarabine (Flu) and clofarabine (Clo) were recently shown to have synergistic cytotoxic activity when combined with busulfan (Bu) in AML cell lines and in primary explanted AML cells. We attributed most of this synergism to ATM pathway activation and chromatin remodeling. We have now extended these studies to include gemcitabine (Gem), a pyrimidine nucleoside analog, and determined their efficacy and synergism in myeloid cells including two AML cell lines (KBM3/Bu250[6] and OCI-AML3) and two CML cell lines (B5/Bu250[6] and KBM5). Combination of sub-lethal (IC_{10} – IC_{20}) concentrations of the respective agents [Flu+Clo+Bu] was demonstrated to be synergistically cytotoxic to both AML cell lines and KBM5 but less active against B5/Bu250[6] cells. Similar results were obtained when cells were exposed to sub-lethal concentations (IC_{10} – IC_{20}) of [Clo+Gem+Bu] and [Flu+Gem+Bu] suggesting that replacement of either Clo or Flu with Gem in triple-drug exposure did not result in significantly different phenotypic responses. Western blot analysis indicates DNA-damage response as shown by the activation of ATM and apoptotic pathways in cells exposed to triple-drug combinations. Since chromatin remodeling is involved in the efficacy of [Clo+Flu+Bu] in AML cells, we hypothesize that similar mechanism is involved in the efficacy of [Clo+Gem+Bu] and [Flu+Gem+Bu]. Although limited in sample size, our present and published studies suggest that combination of Bu with two nucleoside analogs as part of pretransplant therapy will be more efficacious against AML. However, the relative resistance of B5/Bu250[6] cells and sensitivity of KBM5 cells to triple-drug combinations suggests varied responses of CML cells. Further experiments using additional CML cell lines and primary explanted CML cells are warranted to define the relevance of [nucleoside analogs+Bu] combinations in pretransplant regimen for CML patients who will undergo hematopoietic