557 PHASE I/II TRIAL OF CLOFARABINE IN REFRACTORY AND/OR RELAPSED NON-HODGKIN'S LYMPHOMA (NHL)

C. Nabhan[1], W. Fried[1], A. Galvez[1], P. Venugopal[2], J.D. Bitran[1]
[1]*Oncology Specialists, S. C., Lutheran General Hospital, Park Ridge, United States,* [2]*Hematology and Oncology, Rush University Medical Center, Chicago, United States*

Background: Clofarabine (CLO) is a second generation nucleoside analogue with known activity in acute leukemia and myelodysplasia. Given the lack of standard therapy in refractory and transplant-ineligible relapsed NHL, we investigated the activity of CLO in this patient (pt) population regardless of histology.

Methods: Eligible pts had relapsed and/or refractory NHL, ECOG performance status ECOG <2, and adequate renal, cardiac, liver, and bone marrow function. CLO was given intravenously over 1-hour days 1-5 every 28 days for 6 cycles maximum. All pts received anti-viral and anti-pneumocystis carinii prophylaxis. A 3×3 phase I study design was used with CLO 4 mg/m^2 in cohort 1 and subsequent cohorts escalated by 2 mg/m^2. Once the maximum tolerated dose (MTD) was determined, the phase II portion of this study was initiated at the MTD.All pts were followed until disease progression.

Results: To date, 14 pts have been enrolled with 7 patients each in the phase I and II portions. Including all pts, median age was 78 years (27-84), median number of prior therapies was 2.5 (1-8), and 3 pts (21%) relapsed after autologous stem cell transplantation. Histologies included 4 diffuse large cell, 3 small lymphocytic, 2 anaplastic large cell, 2 mixed large cell/follicular, 1 follicular, 1 refractory marginal zone, and 1 Richter's transformation. Median CLO cycles were 2.5 (1-6). Grade 3/4 non-hematologic toxicities were: 1 (7%) grade 3 pleural effusion and 2 (14%) grade 3 fatigue. All pts required growth factor support and 2 pts on the phase II portion required a dose reduction. Thrombocytopenia was the dose-limiting toxicity at 6 mg/m^2 in 2/6 patients. The MTD and recommended phase II dose was 4 mg/m^2. Responses: 2 (14%) complete responses lasting 4 and 12+ months, 3 (21%) partial responses, 1 minor response, and 1 stable disease. With a median follow up of 5 months (1-13), the median duration of response has not been reached and 6 patients remain alive (42%).

Conclusions: To our knowledge, this is the first report to establish clinical activity with CLO in refractory and/or relapsed NHL.

558 IMATINIB MESYLATE REDUCES RITUXIMAB-INDUCED TUMOR GROWTH INHIBITION *IN VIVO* ON EBV-ASSOCIATED HUMAN B-CELL LYMPHOMA

F. Némati[1], C. Mathiot[2], I. Grandjean[3], O. Lantz[2], V. Bordier[3], S. Dewulf[2], R. Ekue[3], J. Di Santo[4], M. Poupon[1], D. Decaudin[1]
[1]*Laboratory of preclinical investigation, Institut Curie, Paris, France,* [2]*Tumor Biology, Institut Curie, Paris, France,* [3]*Animal Experiments Unit, Institut Curie, Paris, France,* [4]*Unité des cytokines et Développement lymphoïde, Institut Pasteur, Paris, France*

Introduction: We previously reported an increase of tumor growth inhibition following chemotherapy combined with concomitantly administration of imatinib mesylate (Decaudin et al., Int J Cancer 2005; 113: 849-856; Rezai, Decaudin et al., BMC Pharmacol 2007; 7: 13). Inversely, combination of imatinib and rituximab was reported in very few cases of patients and remains controversial.In order to explore this particular combination of targeted therapies, we therefore investigated the *in vivo* impact of rituximab plus imatinib on a B-cell lymphoproliferation.

Material and methods: Combination of the tyrosine kinase inhibitor imatinib mesylate (STI571) and the anti-CD20 monoclonal antibody rituximab was evaluated on an EBV-associated B-cell lymphoproliferative disorder (Decaudin et al. Anti-Cancer drugs 2006;17:685-696) xenografted into SCID or Rag2/g_c -/- (B-, T-, and NK-) mice.

Results: Using SCID mice, we found that imatinib diminished the efficacy of rituximab to inhibit tumor growth *in vivo*. Using alymphoid Rag2/g_c -/- mice, we showed that the effect of imatinib was not dependent on the presence of NK cells. In contrast, serum complement administered after imatinib treatment reversed this inhibitory effect. Finally, using non immunodeficient mice, we observed an *in vivo* decrease of CD4-positive T-cells and mature B-cell lymphocytes after imatinib administration.

Conclusions: We found that imatinib decreased the *in vivo* efficacy of rituximab *via* serum protein components that could influence complement-dependent cytotoxicity. In contrast, this effect was not dependent on the presence of NK cells.

559 HISTONE DEACETYLASE INHIBITOR, SUBEROYANILIDE HYDROXAMIC ACID (SAHA), PROFOUNDLY DECREASE PROLIFERATION OF MANTLE CELL LYMPHOMA IN VITRO AND VIVO

S. Sakajiri[1], T. Kumagai[2], N. Kawamata[2], Y. Terui[1], K. Hatake[1], P.H. Koeffler[2]
[1]*Division of Medical Oncology and Hematology, Cancer Institute Hospital, Tokyo, Japan,* [2]*Division of Hematology/Oncology, Cedars-Sinai Medical Center, LA, United States*

Mantle cell lymphoma is usually resistant to standard chemotherapy. Patients with this disease need high-dose chemotherapy either with or without stem cell transplantation. New modalities of treatment are necessary. Methylation and deacetylation of tumor suppressor genes is frequently observed in human cansers including lymphomas. These genes are silenced by histone deacetylase (HDAC) recruited by methylated DNA in their promoter lesions. HDAC removes acetyl groups from histones and prevents the basic transcriptional machinery access to the target gene, leading to transcriptional repression. HDAC inhibitors (HDACIs) can restore the expression of the tumor suppressor and/or cell cycle regulatory genes in cancer cells and block the cellular proliferation of these cells. In this study, we investigated the in vitro antiproliferative activities of the HDACIs, suberoylanilide hydroxamic acid (SAHA), and valproic acid against 14 human lymphoid cancer cell lines. All of these cell lines were sensitive to the antiproliferative effects of the HDACI. SAHA induced either G1 or G2-M arrest as well as apoptosis. SAHA downreguleted cyclin D1 and D2, and upregulated p53, p21, and p27. Chromatin immunoprecipitation analysis revealed a remarkable increase in the level of acetylated histones associated with the p21 promoter after SAHA treatment. In nude mice, SAHA significantly inhibited growth of a mantle cell lymphoma without major toxic side effects. SAHA is a promising therapeutic agent for mantle cell lymphoma.