new treatment modalities

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

C. Nabhan,1, W. Fried1, A. Galvez1, P. Venugopal2, J. M. Blum3
1Oncology Specialists, S. C., Lutheran General Hospital, Park Ridge, United States, 2Laboratory of preclinical investigation, Institut Curie, Paris, France, 3Animal Experiments Unit, Institut Curie, Paris, France

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 refractory 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/m² in cohort 1 and subsequent cohorts escalated by 2 mg/m². 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/m². 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. Ne´mati1, C. Mathiot2, I. Grandjean3, O. Lantz2, V. Bordier3, S. Dewulf2, D. Decaudin1, W. Fried1, A. Galvez1, P. Venugopal2, J. D. Bitran1
1Laboratory of preclinical investigation, Institut Curie, Paris, France, 2Tumor Biology, Institut Curie, Paris, France, 3Animal Experiments Unit, Institut Curie, Paris, France

Introduction: We previously reported an increase of tumor growth inhibition following chemotherapy combined with concomitant administration of imatinib mesylate (Decaudin et al., Int J Cancer 2005; 113: 849-856; Rezaei, 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/γc-/- (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 lymphoid Rag2/γc-/- mice, we showed that the effect of imatinib was not dependent on the presence of NK cells. In contrast, serum complement administration 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.