

[Abstract 50]

LYMPHOPLASMACYTIC CELLS AND MAST CELLS ARE TARGETS FOR IMATINIB MESYLATE (GLEEVEC, GLIVEC) IN WALDENSTROM'S MACROGLOBULINEMIA.

Olivier Tournilhac^{1,3}, Daniel Ditzel Santos^{1,3}, Lian Xu¹, Evdoxia Hatjiharissi^{1,3}, Yu Tsu Tai^{1,3}, Laurie Catley^{1,3}, Zachary Hunter¹, Andrew Branagan¹, Renate Burger^{1,3}, Reshma Shringarpure^{1,3}, Joshua Boyce^{2,3}, Kenneth C Anderson^{1,3} and Steven P Treon^{1,3}. ¹ Bing Program for Waldenstrom's Macroglobulinemia, Dana-Farber Cancer Institute; ² Brigham and Women's Hospital and ³ Harvard Medical School, Boston, MA, 02115, USA.

Recently, we demonstrated that in Waldenstrom's macroglobulinemia (WM), clonal lymphoplasmacytic cells (LPC) appear to derive growth and survival signals from excess mast cells (MC) present in the bone marrow (BM). (Tournilhac et al, JCO 2004 22:571S). We therefore have sought agents which could target both LPC and MC. One such candidate is imatinib mesylate which has shown activity in certain mast cell disorders likely on the basis of its ability to target the tyrosine kinases, CD117 (Stem Cell Factor Receptor, c-kit), and Platelet Derived Growth Factor Receptor (PDGFa-R). By flow cytometric analysis, we demonstrated CD117 expression on sorted LPC from 17/22 (76.2%) WM patients, above 20% in 13 cases, whose expression we confirmed by RT-PCR analysis. Moreover, we also demonstrated expression of PDGFa-R along with its ligand PDGFa in BM LPC from 16/18 (88.9%) and 7/10 (70%) WM patients. In addition to CD117, we found by RT-PCR analysis a PDGFa expression in LAD and HMC-1 MC lines and in KU the basophilic cell lines KU as well as in sorted BM MC (FcER1⁺ CD117⁺) from 3/10 (30%) WM patients. Importantly, co-culture of sorted LPC from WM patients along with 0.5% paraformaldehyde fixed LAD cells or *ex vivo* expanded (EVE) BM MC induced proliferation of sorted LPC from WM patients, which was inhibited at pharmacologically achievable levels of imatinib mesylate with an IC₅₀ of 0.5-10 μmoles/L. Moreover, imatinib mesylate inhibited the LAD, HMC-1 and KU cell lines as well as EVE cord blood MC or EVE BM MC at an IC₅₀ of 0.01-1 μmoles/L. Lastly, imatinib mesylate also inhibited proliferation of both MC and LPC when unfixed LAD or *ex vivo* MC were incubated with WM LPC with an IC₅₀ of 1-10 μmoles/L. These studies therefore demonstrate that both LPC and MC are therapeutic targets for imatinib mesylate, and provide the framework for clinical studies evaluating its use in WM.