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CLINICAL AND LABORATORY RESPONSES TO SILDENAFIL IN WALDENSTROM'S MACROGLOBULINEMIA

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Waldenstrom's macroglobulinemia (WM) is an incurable B-cell malignancy. Interestingly, we have observed unusual response activity in five WM patients which appears related to their use of sildenafil, a phosphodiesterase inhibitor used to treat erectile dysfunction. One patient demonstrated a complete remission, while four other patients demonstrated less dramatic, but also unexpected responses associated with sildenafil used at doses of 25-50 mg once to twice a week. In view of these observations, we next evaluated sildenafil for its ability to induce apoptosis of lymphoplasmacytic cells obtained from WM patients. All patients provided written consent for this study which was approved by our institutional review board. Sorted (CD19⁺, light chain restricted) bone marrow lymphoplasmacytic cells obtained from 6 WM patients were cultured in media alone or with sildenafil (kindly provided by Pfizer Pharmaceuticals, Inc.) at 0.01 ug/ml for 24 hours. These studies demonstrated a mean 2.1 (range 1.24-4.8) fold increase in sildenafil specific/spontaneous apoptosis in lymphoplasmacytic cells from 5 of 5 patients, which included those from a patient who demonstrated a clinical response to sildenafil. Importantly, the concentrations at which apoptosis was observed in these studies is within pharmacologically achievable levels for sildenafil. The results of these studies, along with those recently reported by Sarfati *et al* (Blood 101:265) who demonstrated caspase mediated apoptosis of B-chronic lymphocytic leukemia (CLL) cells by sildenafil, provide the framework for investigation of sildenafil and related phosphodiesterase inhibitors in the treatment of WM and other B-cell malignancies.