G3139 (BCL-2 antisense oligonucleotide) Therapy in Waldenstrom's Macroglobulinemia: A Targeted Approach to Enhance Apoptosis

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Active therapy of WM has historically been derivative of therapies developed for chronic lymphocytic leukemia (CLL), low-grade non-Hodgkin's lymphoma (NHL), or multiple myeloma (MM). A block in apoptosis is central to the pathogenesis and development of drug resistance in all of these B-cell cancers. The components of the apoptotic program are targets for anticancer therapy. Bcl-2 protein inhibits apoptosis and confers resistance to treatment with traditional cytotoxic chemotherapy, radiotherapy, and monoclonal antibodies. G3139 (oblimersen sodium, Genasense™, Genta Inc., Berkeley Heights, NJ) is an antisense oligonucleotide compound designed to specifically bind to the first 6 codons of the human *bcl-2* mRNA sequence, resulting in degradation of *bcl-2* mRNA and subsequent decrease in Bcl-2 protein translation. G3139 downregulates bcl-2 in MM cells and sensitizes them to cytotoxic therapies including dexamethasone and doxorubicin. G3139 has single agent activity in patients with low grade NHL and CLL. The combination of rituximab and G3139 has been shown to enhance apoptosis in vitro in both CLL and NHL cells and shows a survival benefit in a xenograft model Epstein Barr virus driven lymphoma. The combination of cyclophosphamide and G3139 is curative in xenograft models of NHL. WM has been shown to express the bcl-2 target. Enhancement of the efficacy of anticancer treatments with G3139 represents a promising new apoptosis-modulating strategy that is undergoing evaluation in WM.