Potential New Pharmaceutics for the Treatment of Waldenstrom's Macroglobulinemia.

JB Zeldis, Celgene Corporation, Warren, NJ 08540 USA

Thalidomide, the first commercially available immune modulatory drug (IMiD), has activity in the treatment of Waldenstrom's Macroglobulinemia as well as multiple myeloma, myelodysplastic syndrome, myelofibrosis with myeloid metaplasia, CLL, and B cell lymphomas. Although its molecular mechanism of action has not yet been elucidated, thalidomide and the IMiDs affect a variety of cytokines and inflammatory mediators including TNFα, IL-1β, IFNγ, IL-6, IL-10, IL-12, and COX-2 and angiogenesis factors such as VEGF and its receptor. The IMiDs also affect adhesion molecules, ICAM-1, ICAM-2, and L-CAM in addition to preferentially stimulating CD8 cells and expanding NK cell populations. Since most IMiDs share these properties, it would be expected that the second generation IMiDs (REVIMID™, ACTIMID™) would have activity similar to thalidomide in Waldenstrom's Macroglobulinemia with an improved safety profile.

TNFα and angiogenesis most likely play a role in promoting the growth and development of Waldestrom's Macroglobulinemia. The SelCIDs are potent phosphodiesterase 4 (PDE-4) inhibitors that inhibit TNFα production and are highly anti-angiogenic. In addition, inhibition of PDE-4 induces apoptosis in human CLL lymphocytes. It is therefore expected that the SelCIDs might have activity in Waldenstrom's tumors.

Jun N-terminal kinase (JNK) is part of a kinase cascade that modulates apoptosis, the induction of an inflammatory response, and modulation of cellular proliferation. In a variety of tumors including multiple myeloma, JNK is induced as part of a protective mechanism. It is hypothesized that the inhibition of JNK activity might allow other chemotherapeutic agents to be more effective. Work is in progress to evaluate this.

Inhibitors of the e_3 sub-unit of ubiquitin ligase may also selectively modulate the expression of receptors, growth factors and transcription factors essential to the growth, survival, and spread of tumors.

We hypothesize that the IMiDs, SelCIDs, JNK inhibitors, and ligase inhibitors will be the basis for a new non-chemotherapeutic approach to the treatment of Waldenstrom's macroglobulinemia and other related diseases.