

The In Vitro, In Vivo and clinical activity of Apatone[®] against prostate cancer

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Abstract

The purpose of these studies was to evaluate the Apatone for its antitumor activity against prostate cancer and to explore the mechanism(s) responsible for its cytotoxicity. Apatone exhibited tumor specific cytotoxicity against 4 human prostate cancer cell lines in an MTT assay. Electron micrographs revealed that, following Apatone treatment, tumor cells died by a unique form of cell death called autophagy which entailed the self-excision of cytoplasmic pieces which were devoid of organelles and seceded from the perikarya via aligned vesicles. Apatone treatment induced a G₁/S cell cycle block, diminished DNA synthesis, increased hydrogen peroxide production, decreased cellular thiol levels and increased intracellular Ca²⁺ levels. Electrophoretic analysis of DNA revealed a spread pattern of degradation due to the sequential and caspase 3 independent activation of DNase I and DNase II. Apatone administration to nude mice significantly reduced tumor growth rate ($p < 0.05$) without inducing significant bone marrow toxicity, changes in organ weight or pathological changes in these organs. In a Phase I/IIa study, Apatone was given every 5 to 6 hours for 12 weeks with PSADT as the primary endpoint. Thirteen of 17 patients had significant increases in PSA doubling time ($p \leq 0.05$). Subsequently, two “non-responders” who had large body mass index values were given BMI adjusted Apatone doses and became “responders”. Of the 15 patients who continued on Apatone after 12 weeks, only 1 death occurred after 14 months of treatment. Therapy was not discontinued in any patient due to vitamin toxicity or for safety reasons.

Biography

Dr. Jamison's laboratory has been actively involved in evaluating natural products, drugs and liquid crystalline compounds for their in vitro and in vivo antiviral, antitumor and wound healing activities for the last 20 years. The laboratory has also focused on strategies to improve targeted drug delivery in an effort to produce drugs with greater potency and specificity than those commercially available. This research has led to the publication of over 50 papers and has been funded by over \$1,000,000 of research grants. Dr. Jamison holds one U.S. patent and has 9 patent applications pending.