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Anti-estrogens induce apoptosis of multiple myeloma cells.

Treon SP, Teoh G, Urashima M, Ogata A, Chauhan D, Webb IJ, Anderson KC.

Department of Adult Oncology, Dana-Farber Cancer Institute, Boston, MA, USA.

Previous studies have suggested that multiple myeloma (MM) cells express estrogen receptors (ER). In the present study, we characterized the effects of estrogen agonists and antagonists (anti-estrogens [AE]) on growth of MM cell lines and MM patient cells. In addition to antagonizing estrogen binding to ER, AE can trigger apoptosis. Hence, we also determined whether estrogens or AE altered MM cell survival. Immunoblotting showed that ER-alpha is expressed in 4 of 5 MM cell lines (ARH-77, RPMI 8226, S6B45, and U266, but not OCI-My-5 cells), as well as in freshly isolated MM cells from 3 of 3 patients. 17beta-estradiol (E2) did not significantly alter proliferation of MM cell lines or MM patient cells. In contrast, two structurally distinct AE, tamoxifen (TAM) and ICI 182,780 (ICI), significantly inhibited the proliferation of all 5 MM cell lines and MM cells from 2 of 2 patients (IC50, 2 to 4 micromol/L). Proliferation of these cell lines was also inhibited by the hydroxylated TAM derivative, 4-hydroxytamoxifen (4HTAM), although this derivative was less potent than TAM (IC50, 3 to 25 micromol/L). In contrast, the dehalogenated TAM derivative toremifene (TOR) did not inhibit MM cell proliferation. We next examined the effects of these agents on MM cell survival. TAM, ICI, and, to a lesser extent, 4HTAM and TOR triggered apoptosis in both ER-alpha-positive as well as ER-alpha-negative MM cell lines and patient MM cells, evidenced both by fluorescence-activated cell sorting (FACS) analysis using propidium iodide staining and the TUNEL assay. TAM-induced growth inhibition and apoptosis of ER-alpha-positive S6B45 MM cells was not blocked by coculture with excess E2. TAM-induced apoptosis of S6B45 MM cells was also unaffected by addition of exogenous interleukin-6. Importantly, both the inhibition of MM cell proliferation and the induction of MM cell apoptosis were achieved at concentrations of TAM (0.5 and 5.0 micromol/L) that did not significantly alter in vitro growth of normal hematopoietic progenitor cells. Similar plasma levels of TAM have been achieved using high-dose oral TAM therapy, with an acceptable toxicity profile. These studies therefore provide the rationale for trials to define the utility of AE therapy in MM. Copyright 1998 by The American Society of Hematology.