The mechanisms of vitamin K2-induced apoptosis of myeloma cells.

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Abstract

BACKGROUND AND OBJECTIVES: Physiologically, vitamin K compounds act as co-factors for γ-carboxylation of selected glutamates at the N-terminus of prothrombin and some other coagulation factors. These congeners have some growth inhibitory effects of human neoplastic cells. Furthermore, vitamin K2 (VK2) cause apoptosis of some leukemic cells. In search for a new candidate agent to use in the maintenance treatment of myeloma, we analyzed the growth inhibitory effects and apoptosis-inducing capacity of VK2 in human myeloma cells.

DESIGN AND METHODS: The growth of myeloma, lymphoma and non-lymphoid cells cultured with various concentrations of VK2 with or without dexamethasone or allopurinol was assayed. Flow cytometry was used to detect apoptotic cells, activated caspase-3 and -9, the generation of superoxide by hydroethidine, and mitochondrial membrane potential (E centym). In addition, the activation of apoptosis-inducing MAPK, p38 and JNK, release of cytochrome c from mitochondria, and change in the relative Bcl-XL/Xs expression balance were analyzed by Western blotting.

RESULTS: Myeloma cells and B-cell lymphoma cells were sensitive to VK2. The growth inhibition was caused by apoptosis and activation of caspase-3. The generation of superoxide, and inhibitory effects of the xanthine oxidase inhibitor allopurinol, were demonstrated in myeloma cells. The phosphorylation of MAPK was increased by VK2 in myeloma cells. In addition, the mitochondrial apoptotic pathway was activated.

INTERPRETATION AND CONCLUSIONS: VK2 may be a good candidate for myeloma patients, particularly patients who are not suitable candidates for intensive cytoreductive chemotherapy due to age and/or complications.

PMID: 16670066