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Vitamin K2 and its derivatives induce apoptosis in leukemia cells and enhance the effect of all-trans retinoic acid.

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Geranylgeraniol, a polyprenylalcohol composing the side chain of vitamin K2 (VK2), was previously reported to be a potent inducer of apoptosis in tumor cell lines (Ohzumi H et al, J Biochem 1995; 117: 11-13). We examined the apoptosis-inducing ability of VK2 (menaquinone 3 (MK3), MK4 and MK5) and its derivatives such as phytonadione (VK1), as well as polyprenylalcohols with side chains of various lengths including farnesol (C15-OH; FO), geranylgeraniol (C20-OH; GGO), and geranylarnesol (C25-OH; GFO) toward leukemia cells in vitro. MK3, MK4, MK5 and GFO (at 10 microM) showed a potent apoptosis-inducing activity for all freshly isolated leukemia cells tested and for leukemia cell lines such as NB4, an acute promyelocytic leukemia (APL)-derived cell line and MDS92, a cell line derived from a patient with myelodysplastic syndrome, although there were some differences depending on the cells tested. In contrast, VK1 showed no effect on any of the leukemia cells. The combination of MK5 plus all-trans retinoic acid (ATRA) resulted in enhanced induction of apoptosis in both freshly isolated APL cells and NB4 cells as compared to each reagent alone. These data suggest the possibility of using VK2 and its derivatives for the treatment of myelogenous leukemias, including APL.