Antileukemic effect of a synthetic vitamin D3 analog, HY-11, with low potential to cause hypercalcemia.


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1alpha,25-dihydroxyvitamin D3 [1,25(OH)2D3] is capable of inhibiting the proliferation of acute myelogenous leukemia (AML). However, toxicity of hypercalcemia has limited the use of 1,25(OH)2D3 in clinical trials. We have evaluated 11 synthesized vitamin D3 analogs for their ability to inhibit clonal growth of HL-60 myeloid leukemic cells. Among the 11 vitamin D3 analogs, HY-11 (code name) showed the most potent antileukemic activity with 2.5x10(-6) M of IC50, however, it did not affect the cellular growth of normal peripheral blood mononuclear cells until 10(-6) M. Flow cytometric analysis indicated that HY-11 induced the G1 arrest in a dose-dependent manner, which was mediated via inactivation of CDK4 and CDK6 in association with up-regulation of CDKI (cyclin-dependent kinase inhibitor), p27 and Rb protein. Induction of apoptosis was mediated via caspase-3 pathway in HY-11-treated HL-60. In addition, HY-11 enhanced the expression of TGF-beta1, TGF-beta receptor type I and II and vitamin D3 receptor (VDR). VDR-dependent kinase inhibitor), p27 and Rb protein. Induction of apoptosis was mediated via caspase-3 pathway in HY-11-treated HL-60.

1,25(OH)2-16ene-vitamin D3 is a potent antileukemic agent with low potential to cause hypercalcemia.


Compounds that induce cancer cells to differentiate are clinically effective for several types of malignancies. The 1,25-dihydroxyvitamin D3[1,25(OH)2D3(C)] induces leukemic cells, including HL-60, to differentiate and/or no longer proliferate, but it causes hypercalcemia. Development of vitamin D analogs that are more potent in their abilities to affect leukemic cells without causing greater hypercalcemia, may be useful therapeutically. A novel analog [1,25(OH)2-16ene-D3(HM)] has a double bond between C-16 and C-17; it appears to be an extremely effective antileukemic agent with the same or fewer effects on serum calciums. We define the potency of this compound and compare it with seven, previously reported, potent analogs of 1,25(OH)2D3. HM inhibited clonal growth of HL-60 cells by 50% at 1.5 x 10(-11) M. This was about equipotent to 1,25(OH)2-16ene-23yne-D3(V), about 100-fold more potent than many of the other analogs, and 1000-fold more potent than 1,25(OH)2D3. The rank order of leukemic inhibitory activity was: 1,25(OH)2-16ene-D3(HM) > or = 1,25(OH)2-16ene-23yne-D3(V) > 1,25(OH)2-23ene-22ene-24-cyclopentyl-D3(BT) = 22-oxa-1,25(OH)2D3(EU) = 1,25(OH)2-24-homo-D3(ER) > 1,25(OH)2D3(C) > 1,25(OH)2-24- dihomo-D3(ES). The rank order of their effects on induction of differentiation of HL-60 cells, as measured by superoxide production and nonspecific esterase activity, was similar to their antiproliferative activities. In contrast, each analog slightly stimulated proliferation of normal human myeloid clonal growth. Serum calcium levels were the same or slightly less when either 1,25(OH)2-16ene-D3(HM) or 1,25(OH)2D3 (0.0625, 0.125, or 0.25 microgram) was given intraperitoneally to mice for 5 weeks. HM bound to 1,25(OH)2D3 receptors about 1.5-fold more avidly than 1,25(OH)2D3. In fact, the vitamin D3 appears to be the most avid binder to 1,25(OH)2D3 receptors that has been identified to date. In contrast, HM had a greater than 50-fold lower affinity for the D-binding proteins as compared with 1,25(OH)2D3, thus increasing the availability of the compound for target tissues. Further differentiation experiments showed that HM was more potent than 1,25(OH)2D3 in the presence of serum, but was equipotent in serum-free conditions. Taken together, our experiments suggest that 1,25(OH)2-16ene-D3(HM) may be more potent than 1,25(OH)2D3(C) because of its higher affinity to the 1,25(OH)2D3 receptors and its low affinity to the D-binding protein present in serum. HM is an ideal compound for clinical studies including patients with preleukemia and other neoplasia, as well as several skin disorders, such as psoriasis.

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