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# Retinoids and ovarian cancer.

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Each year, an estimated 26,000 women in the United States are diagnosed with ovarian cancer. During any given year, approximately 14,500 women die from this disease. Ovarian cancer is the seventh most common cancer in women worldwide, after breast, cervix, colon/rectum, stomach, corpus uteri, and lung cancers. In the U.S., ovarian cancer is the second most common gynecologic cancer, and is the fourth leading cause of solid tumor cancer deaths among women. Currently, postoperative chemotherapy of ovarian cancer is still suboptimal. Drug resistance is a common problem resulting in only 20 approximately 30% overall 5-year survival rates. Clearly, continued development of alternative therapeutic strategies is essential for the management of this fatal disease. A number of recent studies have suggested that retinoids may play a potential role as an ovarian cancer chemotherapeutic agent. Retinoids, the natural and synthetic derivatives of vitamin A, have been shown to inhibit the growth of human ovarian cancer cells both in vivo and in culture. This review will initially summarize what is known about the pathological and molecular characteristics of ovarian carcinoma. It will then describe retinoid metabolism and the role of the cellular and nuclear retinoid binding proteins in mediating retinoid action. Following this general review of retinoids and their function, data supporting the role of retinoic acid as a suppresser of ovarian carcinoma cell growth will be presented. Particular attention will be paid to studies suggesting that members of the RB family of proteins and RB2/p130, in particular, are the molecular targets responsible for retinoid mediated inhibition of ovarian carcinoma cell growth. This review will then conclude with a brief discussion of two synthetic retinoids, 4 HPR R(fenretinide) and AHPN/CD437, which have been shown to induce apoptosis in ovarian tumor cells. It will be clear from the studies summarized in this review that retinoids represent a potentially powerful alternative to present chemotherapeutic approaches to the treatment of late stage ovarian cancer.

 

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# Identification of effective retinoids for inhibiting growth and inducing apoptosis in bladder cancer cells.

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PURPOSE: Retinoids modulate the growth and differentiation of normal and malignant epithelial cells in vitro and in vivo, and inhibit bladder carcinogenesis in animal models. Retinoid analogs have been used in several clinical chemoprevention trials of superficial bladder cancer recurrence. There is a clear need to identify new effective retinoids and develop novel approaches for the chemoprevention and treatment of superficial bladder cancer. We investigated the effects of various retinoids on growth inhibition and apoptosis induction in bladder cancer cell lines. MATERIALS AND METHODS: Ten grades 1 to 3 bladder cancer cell lines and the 4 retinoids all-trans-retinoic acid, 9-cis retinoic acid, 4-(N-hydroxyphenyl) retinamide (4HPR) and LGD1069 were used in the study. We compared the ability of these retinoids to inhibit growth, induce apoptosis, affect the expression of nuclear retinoid receptors and modulate apoptosis related genes. RESULTS: Most bladder cancer cell lines did not express retinoic acid receptor beta and were resistant to the effect of all-trans-retinoic acid and 9-cis retinoic acid on growth inhibition and apoptosis induction, even at a concentration of 10(-5) M. The 2 cell lines that expressed retinoic acid receptor beta were constitutively sensitive to the growth inhibitory effect of all-trans-retinoic acid. 4HPR inhibited cell growth by about 90% in all but 1 cell line and induced apoptosis at a concentration of 10(-5) M after a 24-hour treatment. LGD1069 had virtually no effect. All-trans-retinoic acid and 4HPR induced retinoic acid receptor beta expression in 1 bladder cancer cell line. However, the effect of 4HPR on cell growth and apoptosis were not related to the constitutive expression of retinoic acid receptor beta. 4HPR decreased bcl-2 expression in 6 of 8 bladder cancer cell lines but did not change p53 gene expression. CONCLUSIONS: The results demonstrate that 4HPR is the most potent growth inhibitor and apoptosis inducer of the retinoids tested. Lack of retinoic acid receptor beta expression may be responsible for cell resistance to all-trans-retinoic acid but not to the other retinoids.