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MINIREVIEW

MODULATION OF ABNORMAL GROWTH BY RETINOIDS: A CLINICAL PERSPECTIVE OF THE BIOLOGICAL PHENOMENON

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Extensive *in vitro* and *in vivo* results in animals suggest that vitamin A and its natural and synthetic derivatives (retinoids) can modulate differentiation and proliferation of normal and abnormal cells. Retinoids can suppress the phenotypic expression of malignancy whether promoted by chemicals, radiation, viruses, or sarcoma growth factor as well as inhibit the proliferation of some established malignant cells. These responses may be effected through several mechanisms, including membrane alterations, interaction with an intracytoplasmic receptor(s), direct inhibition of ornithine decarboxylase expression, and *in vivo* modification of host immune responses. Individual retinoids vary markedly in their ability to produce a response in different biological systems. The current data suggest that retinoids may be effective chemopreventative and antitumor agents if used on a rational biological basis. Since classical antitumor therapy is largely based on cytotoxic effects and direct killing, a reorientation in approach will be required to derive maximal clinical benefit from the retinoids.

EXPERIMENTAL BACKGROUND

The investigational background for retinoids as biological modifiers of growth and differentiation (1), chemopreventative agents (2), and antiproliferative compounds (3,4) has been extensively detailed elsewhere (4). Only the background necessary to orient the reader and to form the basis for the discussion of retinoids as antitumor agents will be discussed.

It has long been recognized that vitamin A deficiency leads to reversible epithelial dysplasia and metaplasia (5). This observation led to a consideration of vitamin A as a natural nutritional principle important in the regulation of normal and dysplastic growth (6). The concept that vitamin A might reverse preneoplastic cellular changes developed much later and initially was considered to be potentially important only in reversing preneoplastic lesions induced by chemicals (7). Although quite effective as a suppressor of the phenotypic expression of neoplasia, the natural vitamin A produced a considerable amount of hepatotoxicity (8), and the experimental emphasis shifted to the development of retinoids which retained biological activity but which were not concentrated in the liver (1,9). Several hundred vitamin A analogues have been synthesized and based on their biological and bio-chemical effects (9), it would appear that retinoids may be divided into several major classes (1,3,4). Presently β -trans retinol

(vitamin A), 13-cis-retinoic acid (and trans-retinoic acid), 4-(hydroxyphenyl) retinamide, and an ethyl ester aromatic derivative retinoic acid (R01-9359) represent some of the better-studied retinoid analogues which produce a spectrum of biological activities and toxicities.

The interest in retinoids as potential anticancer agents in man is based on two fundamental experimental observations: 1) in most in vitro and in vivo animal systems these compounds inhibit the phenotypic expression of malignancy (2,10,11) whether the cell or tissue has been promoted by chemicals (7,12), radiation (13), or ultraviolet light and 2) the retinoids inhibit the proliferation of many established malignant cell lines (review, 4) which in many cases are associated with a stimulation of differentiated functions (4,15,16,19). The data in animal systems have been reviewed extensively elsewhere (4), and only information related to human cells will be mentioned here. Extensive in vitro investigations with murine cell lines showed that retinoids inhibited proliferation and stimulated differentiation in melanoma cells (15,17). These studies led to similar investigations with cultured human cells, and in many cases a similar effect was seen, including melanoma (18,19), breast cancer (4,18), and cervical carcinoma (4). Detailed studies by Lotan et al (4) and our group (19) have clearly demonstrated that the effect of different retinoids on melanoma cell proliferation and differentiation are dissimilar and that different melanoma cell lines are differentially affected (18,19). We have also extended these observations to a clonogenic assay system and have found that retinoids can inhibit colony formation of melanoma cells from fresh biopsies (20). Additionally, we have begun to investigate the effect of retinoids on colony formation of other human tumors and find that other cancers also show sensitivity to some retinoids (21). Further quantification of the response of clonogenic human tumor cells to retinoids will be of importance. The responsiveness of malignant cells to retinoids does not seem confined to solid tumors inasmuch as the promyelocytic cell line HL60 terminally differentiates when exposed to 13-cis-retinoic acid (22). Additionally, when 25 myelocytic leukemias were cultured in soft agar two responded to 13-cis-retinoic acid, and it is probably significant that both were from patients with promyelocytic leukemia (S. Collins, personal communication).

USE OF RETINOIDS AS ANTICANCER COMPOUNDS

Retinoids should be considered as possible useful compounds in 3 distinct settings in clinical oncology: in a chemopreventative mode against preneoplasia, in the adjuvant setting when the tumor burden is low, and against advanced malignancies.

With classical cytotoxic agents, activity of the drug is sought against advanced cancers before it would be considered as potentially useful in the adjuvant setting. Certainly, if retinoids are active against advanced cancers, no further rationale is needed to explore their effect in the adjuvant or preneoplasia setting. However, for biological response modifiers such as retinoids this strict criteria may not be appropriate. A rationale for the use of retinoids in preneoplasia and in the adjuvant setting is developed below:

Preneoplasia

Two different therapeutic situations arise when considering the treatment of preneoplasia: (1) locally confined preneoplasia amenable to topical treatment and (2) preneoplasia approachable only by systemic therapy. Examples of these two categories are listed in the table below:

Preneoplastic Conditions Possibly Reversible by Retinoids

Local treatment

Cervical dysplasia
Bladder dysplasia
Oral mucosa dysplasia

Systemic treatment

Preleukemias (including chronic myelogenous leukemia)
Squamous dysplasia of lung
Preneoplastic bowel syndromes

It would seem reasonable that treatment of the best defined entity in each category would be the preferred approach. Cervical dysplasia is probably the most approachable of preneoplasias amenable to local treatment inasmuch as its natural history is clear, accessibility is excellent, lesions are macroscopically identifiable, and long-term application of retinoid via a mechanical delivery system is practical. Optimal treatment regimens will need to be carefully defined as animal studies suggest that constant application of retinoid is required for suppression of preneoplasia, which may be technically difficult in humans. Chronic myelogenous leukemia (CML) represents an ideal situation in which to test the long-term effect of retinoids. CML appears to be a true preneoplasia with a highly predictable course which requires systemic treatment and which is easily accessible (blood and bone marrow) for evaluation.

Adjuvant setting

The treatment of a malignancy in the adjuvant setting with retinoids should rely on results of *in vitro* studies and, if available, evidence of therapeutic effect on the advanced cancer. Based on *in vitro* results, melanoma (4,15,17-20), breast cancer (4,18,23), and skin cancer (3) would seem like reasonable candidates. Our preliminary clinical results with 13-cis-retinoic acid against advanced metastatic cancers suggests activity in melanoma, cervical cancer, and squamous cell carcinomas of the skin (F. Meyskens, unpublished results). Since the interaction of retinoids with chemotherapeutic agents may be complex, initial adjuvant studies should probably explore the efficacy of the retinoid alone in one arm of any trial.

Advanced disease

The use of retinoids against advanced cancers will need to be carefully evaluated. At this time it is unclear as to whether the antiproliferative effects of retinoids are largely due to membrane or nuclear mediated events. Certainly, cells which contain intracytoplasmic receptors usually respond to retinoids with an antiproliferative, differentiation response, but cells without receptors may respond also (4). In terms of the whole organism the immunological effects of retinoids will play a role in tumor modulation,

particularly since in vitro the immunological effects of retinoids demonstrate a biphasic response.

The optimal retinoid in in vitro systems varies from cell type to cell type. Based on the presently available results it is likely that the different retinoids will produce as diverse effects as the steroids. Consequently, each major class of retinoids will need to be independently evaluated. Presently, retinol, 13-cis-retinoic acid, trans-retinoic acid, an ethyl ester aromatic analog (ROL-9359), and 4-(hydroxyphenyl) retinamide, have differential actions in many in vitro systems, and early animal in vivo investigations suggest different toxicities.

In addition to their action as single agents, retinoids may be able to potentiate (24,25) chemotherapy. Theoretically, since all retinoids, particularly retinol derivatives, labilize membranes, a synergistic effect with compounds which impair membrane turnover may occur.

The past two decades have proven the efficacy of cytotoxic chemotherapy against certain human cancers. Advances in cell biology suggest that regulation of proliferation and differentiation may be possible by a diversity of simple non-cytotoxic compounds, including butyrate, interferon, ascorbic acid (26), dimethylsulfoxide, and retinoids. A major challenge of the next decade will be to use these compounds intelligently to modify the malignant process.

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