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Vitamin A Derivatives in the Prevention and Treatment of Human Cancer

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Vitamin A is essential for normal cellular growth and differentiation. A vast amount of laboratory data have clearly demonstrated the potent antiproliferative and differentiation-inducing effects of vitamin A and the synthetic analogues (retinoids). Recent in-vitro work has led to the exciting proposal that protein kinase-C may be centrally involved in many of retinoids' anticancer actions including the effects on ornithine decarboxylase induction, intracellular polyamine levels, and epidermal growth factor receptor number. Several intervention trials have clearly indicated that natural vitamin A at clinically tolerable doses has only limited activity against human neoplastic processes. Therefore, clinical work has focused on the synthetic derivatives with higher therapeutic indexes. In human cancer prevention, retinoids have been most effective for skin diseases, including actinic keratosis, keratoacanthoma, epidermodysplasia verruciformis, dysplastic nevus syndrome, and basal cell carcinoma. Several noncutaneous premalignancies, however, are currently receiving more attention in retinoid trials. Definite retinoid activity has been documented in oral leukoplakia, laryngeal papillomatosis, superficial bladder carcinoma, cervical dysplasia, bronchial metaplasia, and preleukemia. Significant therapeutic advances are also occurring with this class of drugs in some drug-resistant malignancies and several others that have become refractory, including advanced basal cell cancer, mycosis fungoides, melanoma, acute promyelocytic leukemia, and squamous cell carcinoma of the skin and of the head and neck. This report comprehensively presents the clinical data using retinoids as anticancer agents in human premalignant and malignant disorders and outlines the ongoing and planned studies with retinoids in combination and adjuvant therapy.

HISTORICAL PERSPECTIVE

Wolbach and Howe [1] were the first to record a relationship between vitamin A and neoplasia in their 1925 report on the effects of vitamin A deprivation and restoration on rat epithelial carcinogenesis. Many other early studies, including that by Abels et al [2] in 1941 which first associated vitamin A deficiencies with established human malignancy, further supported that link between vitamin A and neoplastic disease. Recognition that vitamin A deficiency leads to hyperkeratosis of the skin in humans and to squamous metaplasia in animals spurred an initial interest in treating

cutaneous disorders with this new wonder drug [3,4]; however, early excitement led to overlooking unacceptable toxic effects in many patients, especially acute central nervous system and mucocutaneous toxicities and major chronic reproductive, skeletal, liver, and lipid toxicities [3-7].

Even before vitamin A had been identified, the symptoms of acute hypervitaminosis A were first reported over 100 years ago [7]. These early reports involved the ingestion of polar bear and seal livers by Eskimos and Arctic explorers, which resulted in acute toxic symptoms of severe headache, drowsiness, irritability, nausea, and vomiting, followed 24 hours later by erythema and

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desquamation of the face, trunk, palms, and soles. These symptoms generally resolved in 7–10 days. The earliest pathologically documented evidence of chronic hypervitaminosis A appeared in the skeletal remains of a *Homo erectus* individual disinterred in Kenya.

These severe side effects, especially the hepatotoxicity, led to the search for vitamin A derivatives with improved therapeutic ratios. New drugs, called retinoids, began to be synthesized in the 1950s [8]. Retinoids are the natural (excluding carotenoids) and synthetic compounds having some or all of the biological activities of preformed vitamin A or retinol. Extensive laboratory study since 1950 documents that retinoids often block the phenotypic expression of cancer *in vitro* and inhibit growth and induce differentiation in many malignant cell types [4,9–12].

CHEMICAL STRUCTURE

Retinoids have a basic molecular structure consisting of a cyclic end group, a polyene side chain and polar end group [4] (Fig. 1). Chemical manipulation of the polar end group and the polyene side chain produced the first-generation synthetic retinoids. The most widely studied of these molecules are tretinoin *in vitro* and isotretinoin (13-*cis*-retinoic acid) *in vivo*. The retinamides, such as fenretinide (4HPR), or N-(4-hydroxyphenyl) retinamide, are a group of first-generation retinoids in which the terminal carboxyl group of retinoic acid is replaced by an N-substituted carboxamide group. This new group of drugs has a high therapeutic index in certain animal models (e.g., rat mammary carcinoma) and was relatively nontoxic in human phase I trials.

The second-generation retinoids were developed by altering the cyclic end group. The prototype second-generation molecule is etretinate, which has been extensively studied in Europe and only recently approved in the United States.

Cyclization of the polyene side chain has produced the retinoidal benzoic acid derivatives, or arotinoids, which are potent third-generation retinoids. This is another new class of drugs with high therapeutic indexes now entering clinical tri-

als. The arotinoid TTNPB and its ethylester (Ro13-6298) are less toxic and over 1000 times more potent than first- or second-generation retinoids in several standard screening tests.

Analysis of the structure–function relationships of retinoids (natural, synthetic, and metabolites) and new retinoid-like compounds should help our understanding of the mechanism of retinoid action and provide direction to future clinical study [13–15]. Illustrating the marked specificity of different synthetic analogs is the example of 4HPR, which has a high therapeutic index in rat mammary tumor models but not in rodent skin models [4]. Further illustrating this point are isotretinoin and tretinoin, which, unlike 4HPR, are virtually inactive in the rat mammary model but highly active in the skin models.

MECHANISM OF ACTION

Despite extensive investigation, the molecular mechanisms of action which cause the diverse cellular changes modulated by retinoids remain incompletely understood. Recent research, however, has shed light on a possible basic mechanism of action, which makes it possible to hypothesize a unifying concept of retinoid anticarcinogenic activity [4]. This involves the actions of the protein kinases, including protein kinase-C (PK-C) which has been the focus of significant recent study.

Phorbol esters such as TPA have been established as major tumor promoting agents. Therefore, PK-C, the phorbol ester receptor, plays a critical role in the carcinogenic process and has recently been implicated in the mediation of many phorbol ester-promoted actions such as ornithine decarboxylase induction (which affects intracellular polyamine levels) and epidermal growth factor (EGF) receptor down regulation [16,17]. Activated (membrane-bound) PK-C may transmit signals to the nucleus to regulate gene or oncogene transcription and may act by nontranscriptional actions, such as direct phosphorylation of the EGF receptor.

Recent work by Cope, Verma, Boutwell, and others [17–20] supports the theory that retinoids modulate PK-C activity (Fig. 2). Studying mouse

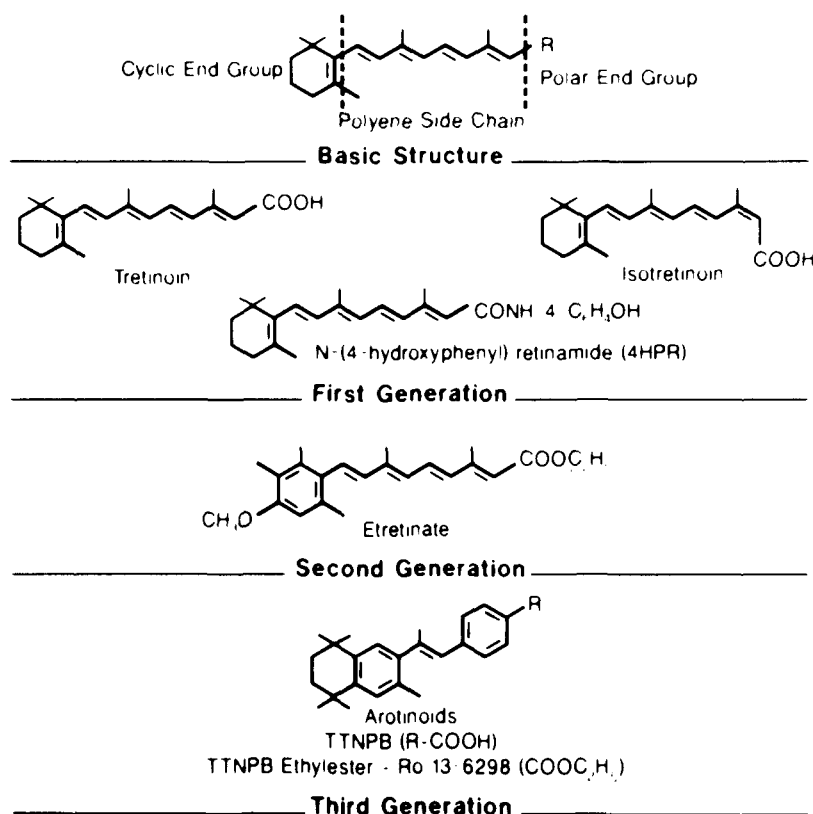


Fig. 1. Chemical structures of the first-, second-, and third-generation retinoids synthetically derived from the basic retinoid skeletal structure. First-generative derivatives include tretinoin, isotretinoin (13-*cis*-retinoic acid or Accutane) and N-(4-hydroxyphenyl) retinamide (4HPR) also known as fenretinide. Etretinate (Tigason) represents the prototype second-generation retinoid. The arotinoid (E)-4-[2-(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthalenyl)-1-propenyl] benzoic acid (TTNPB or Ro13-7410) has demonstrated potent hematopoietic activity. The TTNPB ethyl ester (arotinoid ethyl ester or Ro13-6298) is the only third-generation retinoid available for clinical investigation.

brain PK-C, Cope's group observed that, although unbound cellular retinoid binding proteins (cRBPs), or apo-RBPs, are substrates for PK-C, the bound forms, or holo-RBPs, inhibit PK-C activity. Although the precise way that retinoids interact with PK-C at the molecular level is not known, Cope showed that the retinoids do not inhibit phorbol ester binding to PK-C. Cope also showed that modulation of PK-C alters phosphorylation of cellular retinoid-binding proteins and other specific cytosolic and membrane substrates, which could

explain the regulation of enzyme synthesis, membrane structure, growth factors, binding proteins, gene transcription, postgenomic effects, and extracellular actions. PK-C modulation may also be involved in retinoids' antagonism toward phorbol esters, synergistic activity with other agents (e.g., antiestrogens and selenium), and ability to reverse cytotoxic drug resistance.

Although recent data suggest that PK-C may play a critical role in retinoids' anticancer effects, many questions about PK-C effects remain. At least

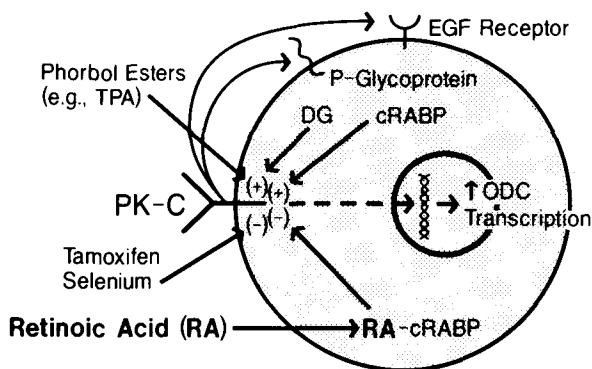


Fig. 2. A schematic of a unifying hypothesis of retinoic acid's anticancer activity at the cellular level mediated through its modulation of a protein kinase-C (see text for details). Abbreviations: TPA = 12-O-tetradecanoylphorbol-13-acetate; EGF = epidermal growth factor; ODC = ornithine decarboxylase; DG = diacylglycerol; cRABP = cellular retinoic acid binding protein; RA = retinoic acid.

three subclasses of PK-C exist, and their precise functions and interaction with retinoids are unclear, possibly varying in different cell types. Lotan showed in murine melanoma cells that PK-C does not play a central role in retinoid-induced growth inhibition [21,22]. It must be noted also that retinoids' biphasic effects on the immune system are difficult to attribute to their interactions with PK-C.

EPIDEMIOLOGY

Vitamin A's critical role in epithelial cell growth and differentiation spawned great interest in developing epidemiologic studies of its relationship to cancer. Over 90% of all human cancers are of epithelial origin. Evidence from several epidemiologic studies suggests the possibility that a relationship exists between cancer risk and dietary intake and serum levels of vitamin A [23]. Some investigators have estimated that dietary factors contribute to 35% of cancers in the United States [23]. Unfortunately, dietary studies do not clearly distinguish between the relative protective effects of retinol and carotenoids (which the body converts in part to retinol). Also, a positive cancer risk relationship with serum retinol levels has not been

uniformly reported, and some unconfirmed studies even indicate that retinoids may increase risk in some cancers (e.g., prostate cancer) [24]. At least in part, the possible anticancer effects of dietary and serum levels of vitamin A depend on interactions with other micronutrients, e.g., selenium, zinc, and vitamin E. An important recent study indicated that supplemental vitamin E significantly reduced retinoid toxicity [25]. These interactions also help to confound the interpretation of epidemiologic studies. Since the epidemiologic and laboratory work alone will never firmly establish the link between cancer risk and dietary and serum levels of vitamin A, carefully controlled clinical trials are the best hope of clarifying this issue [26].

PREVENTION AND THERAPY STUDIES WITH NATURAL VITAMIN A

Several intervention trials indicate that natural vitamin A therapy at clinically tolerable doses appears to have only limited efficacy in the prevention and therapy of human cancer [27,28]. Many other studies over the past 40 years have detailed vitamin A's unacceptable toxicity. Overall, the epidemiologic and clinical studies with systemic natural vitamin A are disappointing. Possibly, the use of topical natural vitamin A has some value. Although hyper- and hypovitaminosis A are well-known health problems, the role vitamin A supplementation may play in preventing cancers in people with normal vitamin A levels is unclear. The immediate future of this class of drugs in human cancer prevention and therapy clearly lies with the use of synthetic retinoids having higher therapeutic ratios.

HUMAN CANCER PREVENTION STUDIES

Accumulating primarily in the skin, retinoids were most widely used initially to manage preneoplastic skin diseases. Including actinic keratosis, keratoacanthoma, basal cell carcinomas, epidermodysplasia verruciformis, and dysplastic nevi, several types of premalignant skin lesions

Table 1. Results of Human Chemoprevention Trials with Retinoids

Malignancy	Retinoid	Evaluable patients	%CR	%PR	%CR+PR	Ref.	
Actinic keratosis	Tretinoin ^a	93	49	51	100	30	
	Tretinoin ^a	60	40	45	85	31	
	Etretinate	46	76	17	93	32	
	Etretinate	44	23	61	84	33	
	Etretinate	15	93	7	100	34	
	Arotinoid	16	0	63	63	35	
Keratoacanthoma	Etretinate	9	67	33	100	32,36-38	
	Isotretinoin	2	50	50	100	39,40	
Basal cell	Isotretinoin	3	100 ^b	0	100	41	
Epidermodysplasia verruciformis	Etretinate	10	10	60	70	42-46	
	Arotinoid	5	0	80	80	47	
Dysplastic nevi	Tretinoin ^a	3	0	100	100	48	
	Isotretinoin	8	0	13	13	49	
Oral leukoplakia	Isotretinoin	24	0	88	88	50	
	Etretinate	24	0	92	92	50	
	Tretinoin	27	0	59	59	50	
	Etretinate ^c	24	29	54	83	51	
	Etretinate	21	24	48	72	51	
	Etretinate	3	33	67	100	52	
	Tretinoin ^a	5	20	80	100	53	
	Isotretinoin ^a	11	27	73	100	54	
	Isotretinoin	24	8	58	66	55	
	Tretinoin ^{a,d}	2	100	0	100	56	
Bronchial metaplasia	Isotretinoin ^{a,e}	16	50	44	94	57	
	Isotretinoin	19	0	0	0	58	
	Etretinate	30	10	77	87	59	
	Etretinate	36	11	89	100	60	
	Laryngeal papillomatosis	Isotretinoin	6	50	17	67	61
		Etretinate	42	67	26	93	62
	Cervical dysplasia ^f	Tretinoin ^a	18	11	22	33	64
		Tretinoin ^a	36	33	64	97	66
		Tretinoin ^a	20	50	NS	50	67
		Retinyl acetate ^a	40	NS	NS	NS	68
Myelodysplastic syndromes (MDS) ^g	Isotretinoin	15	0	33	33	69	
	Isotretinoin	14	0	21	21	70	
	Isotretinoin	18	11	11	22	71	
	Isotretinoin	6	0	67	67	72	
	Isotretinoin	15	7	53	60	73	
	Isotretinoin	1	100	0	100	74	
Superficial bladder carcinoma ^h	Etretinate	5	60	40	100	78	
	Isotretinoin	22	NS	NS	NS	79	
	Etretinate	40	0	50	50	80	
	Etretinate	15	0	73	73	81	
	Etretinate	14	0	29	29	82	

NS = not stated.

^aTopical application of drug.

^bNo tumor recurrence.

^cOral + topical.

^dOral "hairy" leukoplakia in AIDS patients.

^eVulvar leukoplakia.

^fA randomized phase III trial at the ACC, designed to investigate the impressive phase II results, is near completion.

^gAlthough response rates not stated, the results of two recent prospective studies indicate a significant survival advantage in certain MDS subtypes [75,76].

^hThree recent studies indicate a significant effect of retinoids in preventing recurrent superficial bladder cancer [83-85].

have shown substantial responses to retinoids [29-49]. A comprehensive account of numbers of patients, routes of administration and percentages and types of responses to the various drugs employed is presented in Table 1.

Currently, several nondermatologic premalignancies, including oral leukoplakia, bronchial metaplasia, laryngeal papillomatosis, cervical dysplasia, myelodysplastic syndromes, and superficial bladder carcinoma, are receiving more attention in retinoid trials [50-85]. Results of these studies are also presented comprehensively in Table 1. The positive studies including randomized phase III trials, in leukoplakia and superficial bladder cancer, have produced results of major clinical importance. If confirmed by others, the positive results in bronchial metaplasia should pave the way for secondary and tertiary retinoid intervention in heavy smokers and for adjuvant therapy of squamous cell carcinoma of the lung.

THERAPEUTIC ANTICANCER ACTIVITY

In addition to retinoids' more recognized preventive effects, these drugs have shown antitumor activity in several preclinical studies. The growing clinical experience with retinoid therapy in established malignancies totals over 400 patients and includes significant results in basal cell carcinoma, mycosis fungoides, melanoma, acute promyelocytic leukemia, and squamous cell carcinoma of the skin and head and neck. The single-agent data with retinoids in human malignancy is summarized in Table 2 and discussed in detail below.

Basal Cell Carcinoma

As in chemoprevention, the greatest use of retinoids in the therapy of established cancers has been for skin disorders. More than 10 years ago, Bollag and Ott [31] reported that topical tretinoin (0.1-0.3%) produced a therapeutic effect in 15 of 16 patients with basal cell carcinoma. These effects included five complete responses and 10 partial responses. Two of the complete responders recurred within 10 months after treatment. In the

same article, they summarized other early studies of retinoic acid conducted by Belisario [30] and Schumacher and Stuttgen [86]. Sankowski et al [87] utilized topical isotretinoin in 15 patients and achieved similar results. Two complete and 13 partial responses were achieved. In all, 49 patients were treated with topical retinoids, producing 16 complete and 32 partial responses. Therapeutic responses in all four studies occurred within 4-6 weeks and disease usually recurred in the absence of maintenance therapy.

Oral retinoids have also produced objective responses in basal cell carcinoma. Using either etretinate or isotretinoin, three studies involving 56 patients produced a 50% objective response rate, which includes a 9% complete response rate. In a study by Peck [88], 11 patients with multiple basal cell carcinomas were treated with isotretinoin (4.5 mg/kg/day). Prolonged therapeutic responses depended upon the continued intake of the retinoid. We have reported the results of treating five patients with isotretinoin (2 mg/kg/day) for basal cell carcinoma and noted two partial responses, one lasting 18 months and the other 10 months [7,89]. In one of the responders who had vertebral metastases, the need for spinal decompression surgery was averted. In a study involving 20 patients with isolated lesions and 20 with multiple lesions, Grupper and Berretti [32] achieved similar responses with oral etretinate (1 mg/kg/day). Patients with isolated neoplasms relapsed less often (1 of 10) than those with multiple lesions (12 of 14) at 12-months follow-up. As in the studies with isotretinoin, maintenance etretinate appeared necessary to prevent relapse.

These retinoid results appear promising. Ongoing studies are now attempting to determine the most efficacious retinoid form, dose, and treatment schedule for basal cell carcinoma.

Mycosis Fungoides

The broadest experience with retinoids has been in the rare cutaneous T-cell lymphoma called mycosis fungoides. Reported in 1983, our positive pilot data with isotretinoin and many subsequent retinoid trials produced an unprecedented response rate of 62% (21% complete responses) in 92

Table 2. Results of Retinoids in Human Malignancy^a

Malignancy	Retinoid	Evaluable patients	%CR	%PR	%CR + PR	Ref.
Basal cell carcinoma	Tretinoin ^b / Isotretinoin ^b	49	33	65	98	30,31,86,87
	Isotretinoin	16	13	56	69	7,88,89
	Etretinate	40	8	35	43	32
Mycosis fungoides ^c	Isotretinoin	78	14	47	61	90-95
	Etretinate	8	50	0	50	96-99
	Arotinoid (Ro13-6298) ^d	6	67	17	84	100,101
Melanoma	Tretinoin ^a	2	50	50	100	105
	Isotretinoin	20	0	15	15	89
Acute promyelocytic leukemia	Isotretinoin	6	50	17	67	108-111
	Etretinate	1	0	0	0	112
Cutaneous squamous cell carcinoma (SCCA)	Isotretinoin	9	22	56	78	89,120
	Etretinate	4	25	25	50	32
	Arotinoid (Ro13-6298)	1	0	100	100	35
SCCA head and neck	Isotretinoin	38	3	11	14 ^e	89,123

^aThis table only includes malignancies in which retinoid activity has been demonstrated. For retinoid-resistant and less well studied cancers see text.

^bTopical.

^cSee text for discussion of combination studies.

^dGiven parenterally in five patients.

^eThis figure does not include the minor response (see text, p. 276).

patients [90-101]. Preliminary data from Europe have indicated significant activity with arotinoid (Ro13-6298), which produced a response rate of 84% (5/6) including four complete responses (which included isotretinoin-resistant disease) in this malignancy [100,101]. Four other small uncontrolled studies from Europe suggest that combining PUVA with etretinate may improve the response rate over single-agent retinoid treatment [99,102-104]. Large, well-designed trials should investigate this finding further. In 1986 we began an NCI-supported phase II study combining isotretinoin plus recombinant alpha interferon (rαIFN). Also, we have started a promising phase I-II trial combining whole-body electron beam radiation therapy with isotretinoin. This is designed to assess the feasibility and efficacy of combining mucocutaneous-active agents.

Melanoma

We have had a major clinical and laboratory interest in treating malignant melanoma and its

precursor lesion, dysplastic nevus syndrome, with retinoids. Neither disease state has a current effective therapy. Our preliminary data document a remarkable response to topical tretinoin [105] (leading to an ongoing randomized prospective study) and a modest response to oral isotretinoin [89]. These data plus the in-vitro synergy between isotretinoin and rαIFN in cell culture and in the human tumor stem cell assay [4] led us in 1986 to initiate an NCI-supported randomized phase II trial comparing rαIFN to rαIFN plus isotretinoin. The results of an ongoing ACC-based multi-institutional study of adjuvant retinoid therapy may also lead to important therapeutic advances in stage I and II melanoma [106,107].

Myeloid Leukemia

In general, extensive human in-vitro and animal in-vitro data encourage the use of retinoids in leukemia. Acute promyelocytic leukemia (APL) is the most promising leukemic disorder to undergo clinical retinoid trials. In 1983, Flynn et al [108]

described the first APL patient treated with isotretinoin. After a 2-week course, this patient demonstrated a marked elevation of his peripheral granulocyte count. In all, only seven cases have been studied [108–111], all of which involved previously refractory patients. Remarkable responses have been documented in four of these patients, including two patients with prolonged (≥ 1 year) complete responses. Results in several cases including a patient recently treated at the ACC suggest that in-vitro retinoid testing of cultured marrow blast cells may predict clinical response. One of the reported patients, however, had a discrepancy between his in-vitro and in-vivo responses [112]. Tretinoin induced differentiation of his cells in vitro, but etretinate was ineffective clinically. This discrepancy may reflect structure–function specificities of the different retinoids.

In-vitro chronic myelogenous leukemia (CML) bone marrow culture studies with retinoids have produced a dose-dependent decrease in colony and cluster growth and retinoid-induced myeloid differentiation. Although two uncontrolled studies involving 28 chronic-phase CML patients achieved no obvious improvement in complete response rate with isotretinoin [113,114], a large trial with extended follow-up is needed to evaluate the potentially valuable role of retinoids in preventing or delaying blast crisis. Two small studies (16 patients) using retinoids in acute nonlymphocytic leukemia (ANLL) have also been reported [115,116]. If confirmed, the data from one study suggest that retinoids will play a role in the maintenance therapy of childhood ANLL [116].

Squamous Cell Carcinoma of the Skin and Head and Neck

Significant new laboratory data support retinoids for treating squamous cell carcinoma (SCCA) and concern their effects on epidermal growth factor receptors [117–119]. Epidermal growth factor (EGF) has been shown conclusively to modulate cell proliferation, possibly through protein kinase-C and other protein kinases [4,11,117]. EGF binding capacity correlates directly with growth inhibition in certain human SCCA cell lines, such as A431 [118]. Recent laboratory trials have

demonstrated that retinoic acid can significantly increase the number of EGF receptors, which also correlated with growth inhibition in certain cell lines [4,11].

Four patients with refractory cutaneous squamous cell carcinoma were treated with isotretinoin (1 mg/kg/day) [120]. All had major disease regression beginning within 4 weeks of starting therapy. One patient remains in complete remission after more than 23 months, and another patient had nearly a complete initial regression of his massive, fungating neck lesion, with a response that continued for 11 months. The third patient had a complete resolution of his 4×2.5 cm metastatic lesion. The fourth patient had an excellent response (>70% tumor regression) lasting 2 months but relapsed after his dose was reduced because of side effects. This patient then required radiation treatments, after which isotretinoin was resumed at protocol doses and produced another partial response of his hand lesions. Toxicity was generally mild and included reversible mucocutaneous side effects and symptomatic laboratory abnormalities.

In addition to the EGF laboratory data mentioned above, an in-vivo animal model system for testing drugs in SCCA of the head and neck further supports the use of retinoids in this disease [121,122]. Another clinical study also supporting the use of isotretinoin in the management of SCCA of the head and neck is an elegant randomized, placebo-controlled study of isotretinoin in oral leukoplakia, a precursor of SCCA of the head and neck, reported by Hong et al [55]. Hong's isotretinoin results included an impressive response in 67% of all lesions. Although this study included only 44 patients, Hong's significant results confirmed five other positive nonrandomized retinoid trials involving oral leukoplakia that were conducted in Europe (Table 1).

A randomized phase II study of isotretinoin in this cancer achieved a 16% response rate [123]. Now reported in the literature are a total of 38 evaluable isotretinoin-treated patients with head and neck SCCA—19 from this randomized study and an equal number from an earlier broad phase II trial at the ACC [89]. Six objective responses (including one minor response of 25–50% tumor reduction) have been achieved, also producing an overall

response rate of 16%. This compares to established single-agent response rates of 15% with 5FU, 18% with bleomycin, and 24% with cisplatin. Patients in this study were randomized to receive either isotretinoin or methotrexate and were stratified according to major prognostic factors for recurrent disease. Overall, these patients had extremely poor prognoses, with 15 of the 38 patients (40%) having a performance status of 60% or less. The minimal performance status and heavy pretreatment of these patients may partly explain why the methotrexate arm produced its lower-than-expected objective response rate of 5%. Response to methotrexate is reported to range between 8 and 63%. This study achieved three objective responses in the isotretinoin arm, including one complete response, which appear meaningful in light of these poor patient profiles and in the setting of a controlled, prospective study.

Retinoid results in SCCA of the head and neck and, especially, of the skin are promising. A total of only 14 patients with advanced squamous cell carcinoma of the skin have been treated with three different oral vitamin A derivatives [32,35, 89,120]. The overall response rate was 71% (10 of 14 patients), including four complete sustained remissions. Especially encouraging in the absence of any other effective systemic therapy, these data suggest that retinoids certainly deserve continuing trials as this class of drugs may be an effective and well-tolerated therapy for this form of advanced squamous cell carcinoma.

One avenue of future study in SCCA of the head and neck should investigate the single-agent retinoid activity we achieved. If significant single-agent activity is established, combination studies of isotretinoin with other chemotherapeutic agents and/or irradiation should be pursued also. Two such studies of a flawed nature—small patient numbers and uncontrolled settings—have already been reported, one conducted in Japan [124] and the other in England [125]. Both studies produced promising results; however, their findings require further testing by well-designed trials to evaluate objectively the retinoid's contribution to response. The high initial complete response rate with current therapeutic modalities, high risk of developing a second primary tumor and later local recurrences

(often refractory to salvage therapy), create an excellent opportunity for employing retinoids as adjuvant therapy for this malignancy [126,127]. Indeed, Hong et al [55] suggest in their report establishing retinoid activity in oral leukoplakia that adjuvant treatment may have the most important potential role for these comparatively nontoxic oral drugs in the control of SCCA of the head and neck.

OTHER TUMOR TYPES

A large number of patients have been treated with isotretinoin for various malignancies at the ACC. Some of these patients have been previously reported, others have not. Significant objective responses have occurred in two of five advanced cervical cancer patients and in one of 15 ovarian cancer patients who had a >50% decrease in a pelvic mass and resolution of her ascites. Six non-Hodgkin's lymphoma patients have received isotretinoin treatment. An impressive response occurred in the only patient with refractory peripheral T-cell lymphoma. In five patients with minimal-disease choriocarcinoma, two impressive complete responses were documented. One of these has been sustained for 3-1/2 years.

Evaluable cancer patients treated at the ACC with no objective responses to isotretinoin include 17 colon, five bladder, five cervical, 11 breast, 10 sarcomas, five Barrett's esophagus, and a number of other patients. The majority of these had been heavily pretreated. Minor responses in two of 22 patients treated at the ACC with advanced non-small cell lung cancer were recently confirmed by another group of investigators [128]. Cassidy et al [129] have also reported negative results in 18 advanced breast cancer patients. Two months of 0.5–8 mg/kg/day of isotretinoin produced no objective responses. Considerable toxicity occurred in this study and probably resulted from the high dose and rapid escalation schedule. Ziegler et al [130] recently reported a pilot study of isotretinoin (2 mg/kg/day) in six patients with Kaposi's sarcoma associated with the acquired immune deficiency syndrome. Skin toxicity was excessive and all patients' disease progressed.

Also, no objective responses occurred among 15 patients with advanced germ cell tumors treated at Memorial Hospital [131]; however, four patients did have stable disease for at least 8 months. All patients had failed prior cisplatin-containing regimens. One patient, whose original biopsy revealed pure embryonal carcinoma, had mature teratoma at autopsy. These histologic changes may have resulted from his earlier cytotoxic treatment, although retinoid-induced changes have been documented *in vitro* in murine teratocarcinoma cell lines and *in vivo* in mice.

FUTURE DIRECTIONS

Many studies have demonstrated clearly that retinoids, especially the synthetics, have efficacy as single agents in several human malignant and pre-malignant disorders. The future of this class of drugs depends on testing new retinoids as single agents and on combination studies of retinoids with other biological modifiers, cytotoxics, other modalities, and with other retinoids having different spectra of activity and toxicity [4,7,132,133]. Unfortunately, the rush to institute combination studies has led to poorly designed, uncontrolled studies (e.g., in mycosis fungoides and SCCA of the head and neck). Basic researchers, nutritionists, epidemiologists, and clinicians must maintain among themselves a free flow of information in order to specify the disorders most promising for conducting clinical retinoid trials, either in combination or as single agents. At the ACC and elsewhere, a multidisciplinary approach has been started to design controlled prospective combination studies.

New synthetic retinoids currently undergoing laboratory investigation include the retinamides and the arotinoids. With a derivatized carboxyl group, the retinamides (e.g., 4HPR) were relatively non-toxic in phase I trials and have recently entered phase II trials in this country. We have now treated 42 patients at the ACC. Our phase II results to date include modest activity in refractory advanced breast cancer (response rate $3/11 = 27\%$), Kaposi's sarcoma ($2/6 = 33\%$), and melanoma ($1/11 = 9\%$). Although only one patient with mycosis

fungoides has been treated with 4HPR, this patient achieved a definite objective response to 4HPR after failing all known therapy including immunosuppressives, cytotoxics, α -interferon, electron-beam, PUVA, and isotretinoin. Although only minimally active in advanced breast cancer, 4HPR is unequivocally active as adjuvant and preventive therapy in rodent mammary cancer. Therefore, the results of a large ongoing trial in Milan using this drug as adjuvant therapy for breast cancer will be especially important. We also treated 14 preleukemic patients with 4HPR in a recently completed phase II trial producing no responses. Although isotretinoin is modestly active in preleukemia (see Table 1), our negative 4HPR results are consistent with recent *in-vitro* structure-function activity studies, indicating that a free terminal carboxyl group is of critical importance to retinoids' antileukemic activity *in vitro* [4,7]. The arotinoid ethyl ester (i.e., Ro13-6298), which is the only third-generation retinoid currently in clinical trial, appears quite promising even in microgram doses in cutaneous malignancy (e.g., mycosis fungoides) in preliminary data from European studies and is just entering phase I study in the United States.

In addition to the synthetic vitamin A analogues, interest is growing in newly synthesized compounds which are structurally distinct from retinoids and arotinoids but possess potent retinoid-like activity *in vitro* [13-15]. Recent work has also discovered certain metabolites of vitamin A, which are as active as vitamin A *in vitro*, but unlike vitamin A, are water-soluble and less toxic [15]. Further investigation along these lines will lead to a better understanding of retinoids' mechanism of action and may lead to important clinical advances.

As already mentioned, retinoids deserve consideration as adjuvant therapy in SCCA of the skin, head and neck, and lung and as neoadjuvant therapy in cutaneous malignancy. Retinoids chosen on the basis of *in-vitro* sensitivities may also offer equally effective but less toxic alternative treatments in disorders which have highly toxic standard therapies (e.g., childhood neuroblastoma). Because a recurrent theme from the many clinical trials is that most retinoid-responsive neoplastic processes require maintenance therapy to prevent

relapse, the future of retinoids may depend less on screening for efficacy than on screening for toxic effects.

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