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Retinoids as Potential Chemopreventive Agents in Squamous Cell Carcinoma of the Head and Neck^{1,2}

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Although newer combined modality approaches, including neoadjuvant cytotoxic chemotherapy, for patients with squamous cell carcinoma (SCCA) of the head and neck have produced high initial complete response rates, they have not improved overall survival for patients with advanced disease. Vitamin A plays an essential role in the normal differentiation of epithelial tissues. Retinoids, analogs of vitamin A, are active in certain premalignant and malignant disorders including SCCA. Six studies, including one recently reported placebo-controlled randomized trial, have demonstrated the efficacy of retinoids in oral leukoplakia. Two studies (totalling 48 patients) have shown significant retinoid activity (67% overall complete response rate) in patients with aggressive, recurrent laryngeal papillomatosis. Two trials (including a randomized phase II trial) of isotretinoin in advanced, refractory SCCA of the head and neck have produced an objective response rate of 16%, which is comparable to that reported in single-agent studies with cytotoxic drugs. There is a need for further study of retinoids in head and neck cancer. The high initial response rates with current therapy and the high subsequent risks of local recurrence and of developing second primary tumors in head and neck cancer patients offer an excellent opportunity to investigate the use of retinoids as adjuvant therapy for this malignancy. © 1989 Academic Press, Inc.

INTRODUCTION

With over 40,000 new cases and causing 13,000 deaths in 1986, squamous cell carcinoma (SCCA) of the head and neck accounts for 5-6% of all cancers in the United States (1). Epidemiologic data indicate an increasing incidence of this malignancy and implicate exogenous factors such as tobacco and alcohol use as major (and synergistic) risk factors (2-6). Extraordinarily high incidences of head and neck SCCA in parts of Southeast Asia and India are attributed to chewing and smoking tobacco (5, 6). Recently, the increasing use of smokeless tobacco by younger people in the United States has resulted in a higher frequency of premalignant and malignant oral lesions in this age group (2, 6-8).

Standard initial treatment for this disease consists of local therapy with surgery and/or irradiation, which is inadequate to cure the majority of patients with ad-

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vanced local and regional SCCA of the head and neck. Previously, chemotherapy had been reserved for recurrent disease after local therapy (9). However, extensive prior therapy, reduced performance status, reduced nutritional status, and decreased tumor vascularity frequently led to a reduced response to chemotherapy. Therefore, newer initial treatment approaches, including neoadjuvant (cytoreductive or induction) chemotherapy, have been tested and have produced encouraging response rates (9-11). Cisplatin and 5-fluorouracil (5-FU) constitute one especially promising regimen, which has produced overall response rates of 40 to 89%, with complete response rates of 4-20% in prospective randomized trials (10, 11).

Although producing high response rates, traditional and newer neoadjuvant treatment approaches have not improved survival for patients with advanced SCCA of the head and neck. Multiple concurrent medical problems, often aggravated by toxic therapeutic approaches, account for 20% of the deaths among these patients. Currently patients with advanced (stage III and IV) disease have a 5-year survival of only 0-40% (9, 10). The major causes of death after therapy are the development of local recurrences (60%), distant metastases (20-30%), and second primary tumors (10-40%) (9-13). The concept of "field cancerization" (i.e., diffuse mucosal membrane initiation and promotion) by exogenous factors such as tobacco and alcohol may explain the development of second primary epithelial tumors in the upper aerodigestive tract (13, 14). This concept also suggests the need for an effective preventive agent.

BIOLOGICAL PERSPECTIVE

Vitamin A plays an essential role in the normal differentiation of epithelial tissues (15). Retinoids, the synthetic and natural analogs of vitamin A, are active in certain premalignant and malignant epithelial disorders and are active *in vitro* against SCCA and in animal models against SCCA of the head and neck (13, 15-18). Retinoids appear to be more effective against SCCA and other cancers with the characteristics of histologically well- or moderately well-differentiated lesions and a reduced tumor burden (i.e., reduced tumor cell number) (15-17).

Although the precise mechanism of retinoid action remains unclear (15) the recent discovery of specific genes and their products, specific, high-affinity nuclear retinoic acid receptors, advances our knowledge of this mechanism (19, 20). The two newly identified retinoic acid receptors are strikingly homologous to the glucocorticoid and thyroid hormone receptors, which suggests a unifying hypothesis for both receptor structure and hormone action. It is now possible to speculate that the interaction of retinoids with their intracellular receptors induces a cascade of regulatory events that results from the activation of specific sets of genes by the hormone/receptor complex.

New laboratory data concerning retinoid effects on epidermal growth factor (EGF) receptors are of interest in regard to the mechanism of action of retinoids (15, 17, 21-24). EGF modulates cell proliferation, possibly via protein kinase C or other protein kinases (25). Recently, Lotan *et al.* (26) showed that retinoic acid can inhibit the growth of head and neck SCCA 1483 cells. Further study of 1483 cells by Lotan's group showed that retinoic acid significantly suppressed EGF

receptor mRNA, EGF kinase activity, and EGF binding (24). This selective suppression of EGF receptor gene activity may be responsible for retinoids' *in vitro* and *in vivo* growth-inhibitory effects on head and neck SCCA. In non-SCCA cells, Jetten (23) demonstrated that retinoic acid can significantly increase the binding of EGF, which also correlated with growth inhibition in the mouse fibroblast 3T6 cell line and with differentiation in embryonal carcinoma cell lines. It is interesting to note that the growth-inhibition effect from increased EGF binding capacity is also found (unrelated to retinoid administration) in the vulva A431 SCCA cell line (21). All together, these data indicate that EGF receptor modulation may be a key aspect of retinoids' antiproliferative activity. Depending on the specific cell type, retinoids may inhibit cell growth in SCCA and certain other cell types through the various retinoid effects of increasing, decreasing, or making defective the cell's EGF receptor activity.

ASSOCIATED TOXICITIES

The spectrum of retinoids' side effects and toxicity is comparable to that of vitamin A (15). Most frequently observed are mucocutaneous dryness and musculoskeletal complaints. The synthetic retinoids tend to have fewer central nervous system side effects and less severe hepatotoxicity in comparison with natural vitamin A used at similar doses. However, chronic toxicity resulting from retinoids includes increased liver function tests, vertebral osteophyte formation and abnormalities in reproductive function (15, 16). Severe teratogenic effects have been documented in infants exposed to retinoids *in utero* (15, 16). Therefore, women of childbearing potential should be excluded from clinical retinoid trials.

As yet not much research has been done to compare different oral retinoids' toxic side effects. Differences have been observed, however, and they seem to be due to differences in the chemical structure (e.g., the retinamides which lack a free carboxyl group have markedly reduced skin toxicity) and the tissue storage, distribution, and metabolism of the various vitamin A analogs (15). Therapeutic ratios also differ among the synthetic retinoids. For instance, the half-life of etretinate is longer than that of isotretinoin, implying that etretinate has more severe potential teratogenic effects. Etretinate has the higher therapeutic index, however, and appears to produce fewer lipid and skeletal abnormalities than isotretinoin and other retinoids produce (15, 16).

RETINOIDS IN PREMALIGNANCY (ORAL LEUKOPLAKIA AND LARYNGEAL PAPILLOMATOSIS)

The best data supporting retinoids' potential role in the control of SCCA of the head and neck come from the study of two premalignant lesions—oral leukoplakia and laryngeal papillomatosis. Oral leukoplakia is defined as a raised white patch or plaque on the oral mucosa that cannot be removed by scraping and cannot be classified clinically or microscopically as any other disease entity (5, 6, 27–29). Biopsy usually reveals the histologic finding of hyperkeratosis. Dysplastic changes can be present. Placing oral leukoplakia in the category of premalignant lesions is based on the following data: (a) epidemiological studies conducted in Asia show that almost all new cases of oral cancer arise in areas with an endemically high incidence of leukoplakia; (b) a large number of oral carcinomas are

associated histologically with leukoplakic changes; and (c) prospective study of leukoplakia patients has revealed a significant incidence of malignant transformation to SCCA of the oral cavity. Leukoplakia can be safely monitored noninvasively and has a malignant transformation rate to oral cancer of <1.0% to >15.0%, depending primarily on the degree of dysplasia and duration of follow-up (5, 6, 27-29). Epidemiologic studies in humans have shown that increased intake of retinol may be associated with a reduced incidence of leukoplakia and possibly of oral cancer (16, 30, 31). Retinyl acetate retards the development of leukoplakia and oral cancer in hamsters (32) and in other animal models (33). Surgical excision and/or cryosurgery are the current standard therapies for this preneoplastic lesion.

Six trials, including a recently reported placebo-controlled randomized trial, have demonstrated the efficacy of retinoids in oral leukoplakia. Koch (34) used isotretinoin (24), tretinoin (27), or etretinate (24) to treat 75 evaluable patients with multifocal advanced leukoplakia. Patients received 70 mg per day orally of one of these retinoids for 8 weeks and were followed for 2 to 6 years after stopping therapy. The overall response rates (complete and partial responses) were 87% for isotretinoin, 59% for tretinoin, and 91% for etretinate. All responses occurred within 2 to 3 weeks. Etretinate was the least toxic. No patient receiving etretinate required discontinuation of therapy, whereas 4% of the isotretinoin and 11% of the tretinoin patients discontinued treatment because of toxicity. Relapses occurred in 55% of the isotretinoin, 57% of the tretinoin, and 51% of the etretinate patients, over 50% in each group. Most relapsing patients relapsed within 1 to 2 months of stopping therapy.

On the basis of his initial results, Koch (35) performed a second study involving 45 evaluable patients which compared treatment with oral etretinate to treatment with oral etretinate plus topical etretinate paste for 6 weeks. The response rates were high in both groups, with 84% overall responses in the combined treatment group and 72% in the oral etretinate alone group.

Cordero *et al.* (36) reported a 100% response rate to etretinate in 3 leukoplakia patients, including 1 patient with an erosive leukoplakia lesion who had a complete response. Another small study of 5 patients with snuff-induced leukoplakia also produced a 100% response rate (37). In the most recently reported nonrandomized study, 11 patients were treated with isotretinoin lozenges, which produced an 82% response rate including three complete responses (38).

Hong *et al.* (39) recently conducted a randomized placebo-controlled study of isotretinoin in oral leukoplakia. Their patients received 2 mg/kg per day for 3 months. The response rate was 67% in the treated group, compared to only 10% in the placebo group. Again, relapse generally occurred 2 to 3 months after stopping therapy. Because of the highly significant difference in response rates between the retinoid and placebo groups, this study was prematurely terminated after 44 patients, with the results confirming the five other positive nonrandomized retinoid trials discussed above.

Retinoid treatment of the hyperproliferative lesion laryngeal papillomatosis has been investigated in two trials. We employed isotretinoin at 1-2 mg/kg per day in

6 patients with recurrent laryngeal papillomatosis and achieved four responses, three complete and one partial (16, 40). Bichler (41) reported similar results (67% complete response rate) with etretinate at 1 mg/kg per day in 42 patients who had moderate-to-severe laryngeal papillomatosis. Although these positive results occurred with extant disease, a recent small randomized study by Bell *et al.* (42) attempted adjuvant treatment of laryngeal papillomatosis with retinoids, which did not prevent recurrence. The favorable results of retinoids against oral leukoplakia, supported by the two positive laryngeal papillomatosis studies, clearly bolster the role for retinoids as potential chemopreventive agents for head and neck cancer.

CLINICAL TRIALS IN ADVANCED SCCA OF THE HEAD AND NECK

The positive laboratory studies and encouraging preliminary clinical data in certain premalignant and malignant SCCA lesions, including positive results in 19 refractory head and neck cancer patients included in our broad phase II study of isotretinoin (43), led us to conduct a multi-institutional randomized phase II trial of isotretinoin in patients with advanced SCCA of the head and neck (44). To eliminate selection bias from our evaluation of the efficacy and toxicity of this drug, we randomized patients to receive either isotretinoin or methotrexate. We observed a 16% objective response rate in the 19 isotretinoin-treated patients. In addition to these 19 patients, 19 more from the earlier broad phase II trial (43) have been treated with isotretinoin for head and neck SCCA. A total of six objective responses were achieved in both studies, also producing an overall response rate of 16%. This response rate compares with established single-agent response rates of 15% with 5-FU, 18% with bleomycin, and 24% with cisplatin.

In addition to being randomized to receive either isotretinoin or methotrexate, patients in our more recent study were stratified according to the major prognostic factors for recurrent disease. Overall, these patients had extremely poor prognoses, with 15 (40%) of the 38 evaluable patients 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 a lower-than-expected objective response rate of 5%. Response to methotrexate is reported to range between 8 and 63% (44).

As cited here and elsewhere in the literature (15, 16), retinoid studies generally remark on relapses occurring in responding patients within 2 to 3 months of stopping therapy. This relapse pattern suggests that maintenance therapy is required with this class of drugs.

FUTURE DIRECTIONS

One avenue of future study with retinoids in SCCA of the head and neck should be to advance our positive phase II single-agent results through definitive phase III studies. If significant single-agent retinoid activity is established, combination studies of isotretinoin with other chemotherapeutic (cytostatic and/or cytotoxic) agents and/or irradiation should be pursued (45). Two such studies have already

been reported, one conducted in Japan (46) and the other in England (47). Although both studies produced promising results, their designs were flawed by small patient numbers and study designs lacking controls. Therefore, these studies' findings require further testing by well-designed prospective trials to evaluate objectively the contribution of the retinoid to response.

The high initial complete response rate with current therapeutic modalities and high subsequent risks of developing second primary tumors and local refractory recurrences create an excellent opportunity for employing retinoids as adjuvant therapy for this malignancy (13). We agree with Hong's and his co-workers' suggestion (39) that adjuvant treatment in the control of SCCA of the head and neck may be the most important potential role for these comparatively nontoxic oral drugs.

Future investigation and study of retinoids in SCCA of the head and neck should pursue the following issues:

(1) Retinoids in advanced SCCA of the head and neck as single agents and in combination with cytotoxic drugs, differentiation agents, biological modifiers, and/or irradiation.

(2) Adjuvant therapy with retinoids to reduce local recurrences and metachronous second or third primary upper and lower aerodigestive tract lesions (13). [Study of this is currently underway at the M.D. Anderson Cancer Center as a double-blind randomized trial with isotretinoin at a dose of 50 to 100 mg/m² for 12 months (10).]

(3) Postinduction low dose (maintenance) retinoid trials of premalignant lesions of the oral cavity.

(4) Retinoid treatment of high-risk individuals (without definite premalignant lesions) based on heavy carcinogen exposure, such as heavy tobacco and alcohol users with established relative risks of 10–20 for oral and laryngeal carcinoma (2–4), and/or intermediate biologic marker studies (13, 48–50).

(5) The role of natural vitamin A compounds such as β -carotene and retinol. Epidemiologic and laboratory studies clearly support the use of carotenoids (e.g., β -carotene) as chemopreventive agents in several neoplastic processes including oral leukoplakia/oral SCCA (16, 48–56). The precise metabolic relationship between carotenoids and retinoids is unclear (16). Recent work has indicated, however, that β -carotene may be an important source of retinoic acid in retinoid target tissues by providing retinoic acid both directly and indirectly through the generation of retinol (a precursor of retinoic acid *in vivo*) (57). Interest in these compounds has increased further by the recognition of a need for long-term prevention or adjuvant retinoid therapy in many disorders, the modest clinical toxicity with retinoids (e.g., dry skin, cheilitis), and the high cost of synthetic retinoids. Clinical trials of β -carotene with or without retinol in patients with leukoplakia and erythroplakia currently are being conducted at the University of Arizona and elsewhere (13, 48–51, 55, 56). If it is effective in reversing or preventing the recurrence of these lesions, β -carotene could play a major role in the prevention of head and neck cancer since its intake can be readily and inexpensively increased by dietary changes or supplementation.

(6) Newer synthetic derivatives such as the relatively nontoxic retinamides and the third-generation retinoidal benzoic acid derivatives called arotinoids (15, 58). The arotinoids are far more potent than currently used retinoids and so may be extremely valuable for chemopreventive therapy requiring smaller (i.e., microgram) doses of drugs with higher therapeutic ratios (15).

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