Title
Treatment of advanced squamous cell carcinoma of the head and neck with isotretinoin: a phase II randomized trial.

Journal
Investigational new drugs, 6(1)

ISSN
0167-6997

Authors
Lippman, S M
Kessler, J F
Al-Sarraf, M
et al.

Publication Date
1988-04-01

Peer reviewed

Investigational New Drugs 6: 51-56 (1988)

Treatment of advanced squamous cell carcinoma of the head and neck with isotretinoin: a phase II randomized trial

Scott M. Lippman[1], John F. Kessler[1,6], Muhyi Al-Sarraf[2], David S. Alberts[1], Loretta M. Itri[3], Douglas Mattox[4,7], Daniel D. Von Hoff[5], Lois Loescher[1] and Frank L. Meyskens[1]

The Sections of Hematology and Medical Oncology, The University of Arizona Cancer Center[1]; Medical Oncology, Wayne State University[2]; Department of Clinical Research, Hoffmann-LaRoche, Nutley, NJ[3]; Departments of Surgery[4] and Medicine,[5] University of Texas, San Antonio, USA (present address: [6]David Grant Medical Center (USAF), Travis AFB, CA; [7]Department of Otolaryngology, Head and Neck Surgery, The Johns Hopkins Hospital, Baltimore, MD, USA)

Key words: retinoids, head and neck cancer, squamous cell carcinoma

Summary

Retinoids, the analogs of vitamin A, are active in vitro and in vivo against squamous cell carcinoma in animals and against certain epithelial precancers and cancers in humans. These data led us to design a prospective, multi-institutional, randomized phase II trial of isotretinoin in advanced head and neck squamous cell carcinoma. We randomly assigned 40 patients to receive isotretinoin or methotrexate, the best-studied and most active single agent for this disease. Overall, the study patients had extremely poor prognoses, i.e., low performance statuses and recurring disease after surgery and/or irradiation. Three objective responses (16%), including one complete response, occurred in the 19 evaluable isotretinoin-treated patients. Only one minor response (5%) occurred in the methotrexate-treated group. Toxicity occurred with both drugs, but was manageable and never life threatening in the retinoid group. These results and the established activity of retinoids in oral leukoplakia (a precursor of head and neck cancer) indicate the need for further study of this class of drugs in head and neck cancer.

Introduction

Surgery and/or irradiation have been the only curative treatments for squamous cell carcinoma (SCCA) of the head and neck [1–3]. Newer treatment approaches include the use of cisplatin-based combination chemotherapeutic regimens as an adjunct to surgery and radiation therapy [1,2]. These combination chemotherapies are currently undergoing intensive investigation, however, their role in advanced head and neck cancer remains unclear. They are highly toxic and have not yet produced a clear-cut improvement in survival [4]. Although producing initially high complete response rates, neither traditional nor newer treatment approaches achieve satisfactory survival for these patients. The major causes of death after treatment are the development of local recurrences and second primary neoplasms [5].

Vitamin A plays an essential role in the normal differentiation of epithelial tissues [6–10]. Retinoids, the synthetic and natural analogs of vitamin A, are active in certain premalignant and malignant epithelial disorders [6,9,11] and have *in vitro* [12] and *in vivo* activity in animals [13,14] against SCCA. Several nonrandomized studies have demonstrated that retinoids – including isotretinoin, or 13-*cis* retinoic acid – are active in oral leukoplakia

[15–19] and laryngeal papillomatosis [20,21], precursors of head and neck SCCA, and in certain advanced human malignancies, such as mycosis fungoides [11,22,23] and refractory SCCA of the skin [11,24]. Isotretinoin also has produced responses in refractory head and neck cancers in a nonrandomized broad phase II trial at the University of Arizona [25]. This study's subgroup of 29 patients with advanced SCCA of the head and neck had three partial responses of less than two months duration in the 19 evaluable patients. Clinical trials have established that in general retinoids are well tolerated and less toxic than cytotoxic agents [11]. These laboratory and clinical data led us to conduct a multi-institutional, randomized phase II trial of isotretinoin for patients with advanced SCCA of the head and neck. To eliminate selection bias from our evaluation of the efficacy and toxicity of isotretinoin, patients were randomized to receive either isotretinoin or methotrexate.

Methods

Patient eligibility criteria for this study included measurable histologically confirmed locally advanced or metastatic SCCA of the head and neck, a Karnofsky performance score of $\geq 50\%$ and a life expectancy of at least eight weeks. Other eligibility requirements followed standard Southwest Oncology Group (SWOG) criteria [26] and included adequate renal function (creatinine <2.0 mg/dl) and adequate liver function tests (bilirubin <2.0 mg/dl). Eligible patients must not have received radiation therapy within six weeks prior to starting this trial. We excluded all women with reproductive capacity and persons taking large doses of vitamin A ($>25{,}000$ IU per day).

Four centers – the Arizona Cancer Center (ACC), University of Texas at San Antonio, Wayne State University and University of Kansas Medical Center – participated in this study. In discussing the nature and purpose of the study with patients, we emphasized that each patient would receive either isotretinoin or methotrexate on the basis of random assignment. Each participating institution's review board for human research gave final study-protocol approval and all patients gave written informed consent.

Patients were centrally registered and randomly assigned to receive either isotretinoin (3 mg/kg per day) or methotrexate (15 mg/m^2 IM on days 1, 2 and 3 of each three week cycle). Patients were stratified by the major prognostic factors for recurrent head and neck cancer, which include prior radiation therapy, performance status and prior adjuvant chemotherapy. None of our patients, however, had received previous chemotherapy (either neoadjuvant or for recurrent disease). Hoffmann-LaRoche Incorporated (Nutley, New Jersey) supplied isotretinoin in the forms of 10-, 20- and 40-mg gelatin capsules. Doses and schedules of the two agents were based on data from prior ACC isotretinoin studies [11,25] and SWOG methotrexate studies [26,27]. Dosage modifications resulting from toxicity followed standard criteria for each drug [26,28]. Patients were continued on isotretinoin or methotrexate for as long as tumor response or stabilization of disease was present. Evaluable patients were defined as those completing at least six weeks of treatment with isotretinoin or two courses of methotrexate.

All patients had complete histories, physical examinations and Karnofsky performance assessments before beginning this study. A complete blood count, chemistry panel including renal and liver function tests and serum lipid profiles, and bidimensional tumor measurements were performed every three weeks during the study. The clinical objective response was evaluated by bidimensional measurement of the lesions. Radiographs and scans and/or color photography were performed as indicated to objectively evaluate disease status. A complete response was defined as the disappearance of all measurable disease for at least four weeks. A partial response was defined as a $>50\%$ reduction in the sum of the greatest diameters of all lesions in any patient not achieving a complete response. A response was classified as minor when the decrease in lesion sizes was less than 50% but greater than 25% of the prestudy, or baseline, measurements. Disease progression was defined as a $>25\%$ increase in the size of any lesion or as the appearance of new lesions during treatment. Grading of toxicity followed previously published criteria [26,28].

Table 1. Characteristics of patients in each treatment group

	Methotrexate	Isotretinoin
Total enrolled	20	20
Evaluable	19	19
Age: mean	62	58
(range)	(42–76)	(44–73)
Sex: male	15	18
female	4	1
Primary site		
Larynx	4	4
Oropharynx/Oral	6	8
Nasopharynx	2	0
Other	7	7
Performance status > 60%	12	11
(Karnofsky) ≤ 60%	7	8
Disease sites prior to study		
Local	8	10
Distant*	11	9
Prior surgery	13	15
Prior radiotherapy	15	16
Responses		
Complete	0	1
Partial	0	1
Minor	1	1
Progressive disease	18	16
Survival median	4 months	4.5 months

*Includes patients with locally advanced or locally recurrent disease.

Results

Forty patients were randomized and entered into this study. Two patients, one in each treatment arm, were not evaluable because of unacceptable toxicity causing early withdrawal from treatment. Table 1 lists the patient characteristics found in each treatment group and indicates that these groups were comparable in respect to age, sex, primary site of disease, performance status, prior treatment and disease sites prior to study. The objective response rate in the isotretinoin-treated group was 16% (exact 95% confidence limits = 3% to 39%) with one complete response lasting nine weeks in a patient with local nodal recurrence following laryngectomy, bilateral neck dissection and radiotherapy. Two other responses – one partial and one minor – also occurred among the isotretinoin-treated patients.

In the methotrexate-treated group, the response rate was only 5% (exact 95% confidence limits = 1% to 25%), involving one minor response in a patient with a local recurrence in the skin. No responses of visceral metastases occurred in patients receiving either treatment. Median survival from the start of treatment was four months for the methotrexate-treated patients and 4.5 months for the patients receiving isotretinoin.

Both treatments were associated with significant toxicity. Side effects with isotretinoin, however, were moderate in most cases, consisting primarily of mucocutaneous toxicity with no life-threatening problems. The methotrexate-treated patients primarily experienced gastrointestinal toxicity (nausea, vomiting and mucositis) and myelosuppression, which was severe (< 500 granulocytes) in two patients.

Discussion

This randomized phase II study achieved a 16% response rate of advanced squamous cell carcinoma of the head and neck to isotretinoin. These 19 isotretinoin-treated patients, along with an equal number from the ACC's earlier broad phase II trial [25], bring the total up to 38 evaluable patients with 6 objective responses and an overall response rate also of 16%. This compares to established single-agent response rates of 15% with 5-fluorouracil, 18% with bleomycin and 24% with cisplatin [3]. The present trial's results and those of several other studies showing retinoid activity indicate the need for further study of this class of drugs in SCCA of the head and neck. Also supporting the use of isotretinoin in the management of this cancer is an elegant randomized, placebo-controlled study of isotretinoin in oral leukoplakia reported by Hong *et al.* [29]. Hong's isotretinoin results included an impressive response in 67% of all lesions. Although the Hong study included only 44 patients, its significant results confirmed five other positive nonrandomized retinoid trials involving oral leukoplakia that were conducted in Europe [15–19].

The patients in the present study 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 (reported to range between 8% and 63%) [1–3,26,27]. The three objective responses in the isotretinoin arm, including one complete response, appear meaningful in light of these poor patient profiles and in the setting of a controlled, prospective study.

Another probable cause of methotrexate's poor showing has been revealed by recent clinical data reported since the start of our study [3]. Clinical investigators have now shown that methotrexate is more effective when administered more frequently. Our results may have improved significantly if the current standard schedule of administering methotrexate weekly or twice weekly had been used instead of the every three weeks schedule used in several early Southwest Oncology Group studies [2,26,27].

After accruing 40 patients (20 in each arm), our study was closed because of the poor methotrexate results and growing interest in other treatment regimens. At the time, cisplatin combination regimens were emerging as promising therapy in treating SCCA of the head and neck [1–4]. Nevertheless, our study design makes it possible to draw meaningful conclusions about the activity of isotretinoin, which falls within the range of other single-agent chemotherapeutic drugs with confirmed activity [3].

The toxicities encountered in both study arms were those expected for either isotretinoin [11,28] or methotrexate [3,26]. Although appreciable, the toxic retinoid effects were not life threatening and reversed soon after reducing doses or discontinuing treatment. Initial treatment employed 3 mg/kg/d. More recent results, however, suggest that lower dose (1 mg/kg/d) isotretinoin may be as effective and much less toxic than the high dose regimen [11,24]. Two other new approaches may also reduce retinoid toxicity: 1) combining retinoids with vitamin E, which in recent studies has markedly reduced isotretinoin toxicity [30], and 2) using the highly potent and relatively nontoxic third-generation retinoids, i.e., the retinoidal benzoic acid derivatives or arotinoids [6,10]. Methotrexate, on the other hand, produced severe toxic effects including severe mucositis, myelosuppression, nausea and vomiting, all of which are potentially far more serious than the retinoid's toxicity.

Perhaps the most significant new laboratory data supporting retinoids for treating SCCA concern their effects on epidermal growth factor (EGF) receptors. EGF has been shown conclusively to modulate cell proliferation, possibly through protein kinase-C and other kinases [8,10,31]. EGF binding capacity correlates directly with growth inhibition in certain human SCCA cell lines, such as A431 [32]. 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 [8,10]. In vivo animal models for testing drugs in SCCA of the head and neck further support the use of retinoids in this disease [13,14].

One avenue of future study should investigate the single-agent retinoid activity we achieved. The potent new arotinoids [6,10] should also be studied in treating this disease. If single-agent activity is established, the next step would be to consider combination studies of retinoids with certain other chemotherapeutic agents and/or irradiation which have shown in vitro synergy [10,11]. Two such studies have already been reported [33,34]. Although both studies produced promising results, their findings – based on small patient numbers and uncontrolled settings – 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 and the high risk of developing a second primary tumor and local recurrences (often refractory to salvage therapy) create an excellent opportunity for trials of retinoids as adjuvant therapy. Isotretinoin's activity in this prospective controlled study leads us to agree with Hong *et al.* [29], who established significant retinoid activity in oral leukoplakia, that the most important potential role for these comparatively nontoxic oral drugs in the control of SCCA of the head and neck may be as adjuvant treatment.

Acknowledgements

Supported in part by Public Health Service grants CA-27502, CA-23874, and CA-23074 from the National Cancer Institue, National Institutes of Health, Department of Health and Human Services, and by Hoffmann-LaRoche, Inc.

References

1. Hong WK, Bromer R: Chemotherapy in head and neck cancer. New Engl J Med 308:75–79, 1983
2. Al-Sarraf M: Chemotherapy strategies in squamous cell carcinoma of the head and neck. CRC Crit Rev Oncol Hematol 1:323–355, 1984
3. Million RR, Cassisi NJ, Wittes RE: Cancer of the head and neck. In: DeVita Jr VT, Hellman S, Rosenberg SA (eds) Cancer, Principles and Practice of Oncology. JB Lippincott Company, Philadelphia, 1985, pp 407–506
4. Jacobs C, Wolf GT, Makuch RW, Vikram B: Adjuvant chemotherapy for head and neck squamous carcinoma. (Abstr) Proc Am Soc Clin Oncol 3:182, 1984
5. Hong WK, Doos WG: Chemoprevention of head and neck cancer. Otolaryngol Clin North Am 18:543–549, 1985
6. Bollag W: Vitamin A and retinoids: from nutrition to pharmacotherapy in dermatology and oncology. Lancet 1:860–863, 1983
7. Sporn MB, Roberts AB: Role of retinoids in differentiation and carcinogenesis. JNCI 73:1381–1387, 1984
8. Sporn MD, Roberts AB, Roche NS, Kagechika H, Shudo K: Mechanism of action of retinoids. J Am Acad Dermatol 15:756–764, 1986
9. Lotan R: Effects of vitamin A and its analogs (retinoids) on normal and neoplastic cells. Biochim Biophys Acta 605:33–91, 1980
10. Lippman SM, Kessler JF, Meyskens Jr FL: Retinoids as preventive and therapeutic anticancer agents (part I). Cancer Treat Rep 71:391–405, 1987
11. Lippman SM, Kessler JF, Meyskens Jr FL: Retinoids as preventive and therapeutic anticancer agents (part II). Cancer Treat Rep 71:493–515, 1987
12. Reiss M, Pitman SW, Sartorelli AC: Modulation of the terminal differentiation of human squamous carcinoma cells in vitro by all-trans-retinoic acid. JNCI 74:1015–1023, 1985
13. Huang CC: Effect of retinoids on the growth of squamous cell carcinoma of the palate in rats. Am J Otolaryngol 7:55–57, 1986
14. Burge-Bottenbley A, Shklar G: Retardation of experimental oral cancer development by retinyl acetate. Nutr Cancer 5:121–129, 1983
15. Koch HF: Biochemical treatment of precancerous oral lesions: the effectiveness of various analogues of retinoic acid. J Maxillofac Surg 6:59–63, 1978
16. Koch HF: Effect of retinoids on precancerous lesions of oral mucosa. In: Orfanos CE, Braun-Falco O, Farber EM, Grupper Ch, Polano MK, Schuppli R (eds) Retinoids: Advances in Basic Research and Therapy. Springer-Verlag, Berlin, 1981, pp 307–312
17. Cordero AA, Allevato MAJ, Barclay CA, Traballi CA, Donatti LB: Treatment of linchen planus and leukoplakia with the oral retinoid Ro 10–9359. In: Orfanos CE, Braun-Falco O, Farber EM, Grupper Ch, Polano MK, Schuppli R (eds) Retinoids: Advances in Basic Research and Therapy. Springer-Verlag, Berlin, 1981, pp 273–278
18. Raque CJ, Biondo RV, Keeran MG, Honeycutt WM, Jansen GT: Snuff dippers keratosis (snuff-induced leukoplakia). South Med J 68:565–568, 1975
19. Shah JP, Strong EW, Decosse JJ, Itri L, Sellers P: Effect of retinoids on oral leukoplakia. Am J Surg 146:466–470, 1983
20. Alberts DS, Coulthard SW, Meyskens Jr FL: Regression of aggressive laryngeal papillomatosis with 13-cis-retinoic acid (Accutane). J Biol Response Mod 5:124–128, 1986
21. Bichler E: The role of aromatic retinoid in treatment of laryngeal keratinizing disorders and dysplasias. In: Spitzy KH, Karrer K (eds) Proceedings of the 13th International Congress of Chemotherapy. VH Egermann, Vienna, 1983, pp 201–229
22. Kessler JF, Meyskens Jr FL, Levine N, Lynch PJ, Jones SE: Treatment of cutaneous T-cell lymphoma (mycosis fungoides) with 13-*cis*-retinoic acid. Lancet 1:1345–1347, 1983
23. Kessler JF, Jones SE, Levine N, Lynch PJ, Booth AR, Meyskens Jr FL: Isotretinoin and cutaneous helper T-cell lymphoma (mycosis fungoides). Arch Dermatol 123: 201–204, 1987
24. Lippman SM, Meyskens Jr FL: Treatment of advanced squamous cell carcinoma of the skin isotretinoin. Ann Intern Med 107:499–501, 1987
25. Meyskens Jr FL, Gilmartin E, Alberts DS, Levine NS, Brooks R, Salmon SE, Surwit EA: Activity of isotretinoin against squamous cell cancers and preneoplastic lesions. Cancer Treat Rep 66:1315–1319, 1982
26. Grose WE, Lehane DE, Dixon DO, Fletcher WS, Stuckey WJ: Comparison of methotrexate and cisplatin for patients with advanced squamous cell carcinoma of the head and neck region: a southwest oncology group study. Cancer Treat Rep 69:577–581, 1985
27. Lehane DE, Lane M, Stuckey WJ: A comparison of methotrexate (m), methylCCNU (mc) and bleomycin (b) in patients with advanced squamous cell carcinoma of the head and neck (H&N) region; a southwest oncology group study (Abstr). Proc Am Soc Clin Oncol 21:331, 1980
28. Meyskens Jr FL, Goodman GE, Alberts DS: 13-cis-Retinoic Acid: Pharmacology, toxicology, and clinical applications for the prevention and treatment of human cancer. CRC Crit Rev Oncol Hematol 3:75–101, 1985
29. Hong WK, Endicott J, Itri LM, Doos W, Batsakis JG, Bell R, Fofonoff S, Byers R, Atkinson EN, Vaughan C, Toth BB, Kramer A, Dimery IW, Skipper P, Strong S:

13-*cis* retinoic acid in the treatment of oral leukoplakia. N Engl J Med 315:1501–1505, 1986

30. Besa EC, Abrahm JL, Nowell PC: Increased survival in myelodysplastic syndrome (MDS) patients on high dose long term 13 cis-retinoic acid (RA); decrease of RA toxicity with alpha-tocopherol (AT) (abstract). Proc Am Soc Clin Oncol 6:150, 1987
31. Sahai A, Feuerstein N, Cooper HL, Salomon DS: Effect of epidermal growth factor and 12-0-tetradecanoyl-phorbol-13-acetate on the phosphorylation of soluble acidic proteins in A431 epidermoid carcinoma cells. Cancer Res 46:4143–4150, 1986
32. Behzadian MA, Shimuzu N: Variant of A431 cells isolated by ricin A-conjugated monoclonal antibody directed to EGF receptor: phosphorylation of EGF receptor and phosphatidylinositol. Somatic Cell Mol Genet 11:579–591, 1985
33. Komiyama S, Hiroto I, Ryu S, Nakashima T, Kuwano M, Endo H: Synergistic combination therapy of 5-fluorouracil, vitamin A, and cobalt-60 radiation upon head and neck tumors. Oncology 35:253–257, 1978
34. Thatcher N, Blackledge G, Crowther D: Advanced recurrent squamous cell carcinoma of the head and neck. Results of a chemotherapeutic regimen with Adriamycin, bleomycin, 5-fluorouracil, methotrexate, and vitamin A. Cancer 46:1324–1328, 1980

Address for offprints: F.L. Meyskens Jr., Arizona Cancer Center, 1501 N. Campbell Avenue, Tucson, AZ 85724, USA