Anti-Cancer Drugs, 4, pp. 33–36

Phase II study of 13-*cis*-retinoic acid and interferon-α2a in patients with advanced squamous cell lung cancer

David A Rinaldi,[1] Scott M Lippman,[2] Howard A Burris III,[1] Chy Chou,[2] Daniel D Von Hoff[3] and Waun Ki Hong[2]

[1]Brooke Army Medical Center, San Antonio, TX 78234, USA
[2]University of Texas MD Anderson Cancer Center, Houston, TX 77030, USA. Tel: (713) 792-6363. Fax: (713) 792-6655
[3]Cancer Therapy and Research Center, San Antonio, TX 78284, USA

The combination of interferon (IFN)-α2a and 13-*cis*-retinoic acid (13-cRA) has demonstrated significant antitumor activity in patients with advanced squamous cell cancer of the skin and cervix. We performed a prospective phase II trial of this combination in patients with locally advanced or metastatic squamous cell lung cancer. Twenty-one patients were enrolled on the study. All patients were evaluable for toxicity and 17 were evaluable for response, four with locally advanced and 13 with metastatic disease. One partial response was obtained in a patient with locally advanced disease. Toxicity consisted mainly of constitutional side effects (fatigue, anorexia), which resulted in eight patients coming off-study. The combination of IFN-α2a and 13-cRA is unlikely to exhibit significant clinical activity in patients with metastatic squamous cell lung cancer, but activity in patients with locally advanced disease has not been excluded.

Key words: Interferon, lung cancer, retinoic acid, squamous cell.

Introduction

Lung cancer is the leading cause of cancer mortality in the US.[1,2] Approximately 60–70% of patients with non-small cell lung cancer (NSCLC) present with advanced, unresectable disease. Squamous cell lung cancer (SqCLC) accounts for 40–50% of newly diagnosed NSCLC.[1] Despite extensive clinical testing, only five commercially available chemotherapeutic agents have demonstrated single agent response rates of 16–27% in patients with metastatic NSCLC. These agents include cisplatin, ifosfamide, mitomycin-C, etoposide and vinblastine.[2–4] Combination chemotherapy, while increasing the response rate to 25–49%,[2–4] has demonstrated a significant survival benefit compared with supportive care in only one randomized trial in patients with metastatic NSCLC, 33 versus 17 weeks.[5] In preclinical studies, interferon (IFN)-α2a and 13-*cis*-retinoic acid (13-cRA) have each demonstrated activity against various squamous cell cancer (SqCC) cell lines including lung cancer.[6–9] Additionally, in clinical studies, each agent has exhibited activity against various hematologic and solid tumors.[6,7,10–29] The combination of the two agents has been active in both advanced SqCC of the skin and cervix, with response rates of 68 and 50%, respectively.[30,31] These preclinical data and clinical results with squamous cell tumors of other sites, led to the design of a prospective multicenter phase II trial of the combination of IFN-α2a and 13-cRA in patients with unresectable localized or metastatic SqCLC.

Materials and methods

Patients were required to be at least 18 years old with bidimensionally measurable, unresectable, SqCLC. Additional eligibility criteria included Zubrod performance status of 2 or less, life expectancy greater than 8 weeks, no more than one prior chemotherapy regimen, and adequate bone marrow, liver and renal function. Patients with brain metastases, serious underlying non-malignant disease, alcoholism, drug addiction and uncontrolled psychotic disorders were excluded. Women of childbearing age must have had a negative pregnancy test and followed an accepted method of birth control. The protocol was approved by each institution's Review Board for Human Research. Written informed consent was obtained from all patients.

Pretreatment evaluation included a complete history and physical examination, complete blood count, chemistry profile, urinalysis, chest X-ray and a radiographic evaluation of measurable lesions.

Supported in part by F. Hoffmann-LaRoche Inc., Nutley, NJ. The opinions or assertions herein are the private views of the authors and are not to be construed as reflecting the views of the Department of the Army or the Department of Defense.

Correspondence to SM Lippman

The starting dose of recombinant human IFN-α2a (Roferon-A, Hoffmann-LaRoche Inc., Nutley, NJ) was 3×10^6 units/m^2 daily at bedtime. The starting dose of 13-cRA (Accutane, Hoffmann-LaRoche) was 1 mg/kg/day (rounded to the nearest 10 mg), in two divided oral doses.

Toxicity was assessed according to the MD Anderson Cancer Center Criteria, which includes the National Cancer Institute Common Toxicity Scale.[32] Dose adjustments were made for grade 3 or higher toxicity.

Patients underwent disease assessment every 4 weeks. Standard response criteria were used. A complete response required disappearance of all evidence of disease for at least 4 weeks. A partial response required a 50% or greater decrease in the sum of the products of the diameters of all measured lesions for at least 4 weeks. There also could be no new lesions or increases in the size of any lesions. Progressive disease was defined as greater than 25% increase in the sum of the products of the diameters of the measured lesions or the appearance of any new lesions. Stable disease was defined as not meeting criteria for a partial response or progressive disease. To be considered evaluable for response, patients must have remained on-study for at least 4 weeks, unless evidence of disease progression occurred sooner. For this study, an objective response rate of 30% or higher was considered to be clinically significant. Based on this, accrual was planned in two stages. The first stage would involve 12 evaluable patients. If the response rate was 8% (1/12) or less, the study would be terminated. Otherwise, accrual would continue to a total of 35 patients.

Table 1. Patient characteristics

Characteristic	Number
Total enrolled	21
Total eligible	20
Evaluable for response[a]	17
Sex	
male	13
female	7
Age (years)	
median = 62	
range = 42–74	
Zubrod performance status	
0	5
1	14
2	1
Extent of disease	
locally advanced	5[b]
metastatic	15
lung	8
adrenal	4
liver	3
subcutaneous nodules	2
bone	1
pleura	1
kidney	1
two or more sites	5
Prior therapy	
radiotherapy only (XRT)	6
chemotherapy only	1
chemotherapy–XRT	5
No chemotherapy or XRT	8

[a] Treated for at least 4 weeks.
[b] Four of the five patients had failed initial therapy (one chemotherapy, two radiotherapy and one combined chemotherapy/radiotherapy) and one presented with untreated locally advanced disease.

Results

Twenty-one patients were enrolled in the trial (Table 1). One patient with 'non-small cell' lung cancer was considered inevaluable for response, but evaluable for toxicity since he received 14 weeks of treatment. At the time of treatment, five patients had locally advanced and 15 had metastatic disease. The sites of metastases included lung (eight patients), adrenal gland (four patients), liver (three patients), subcutaneous nodules (two patients), kidney (one patient), pleura (1 patient) and bone (one patient). Five patients had metastases to two or more sites. Six patients had received prior chest irradiation only, one prior chemotherapy only (carboplatin and etoposide), five prior chemotherapy (cisplatin and etoposide) and radiation therapy, and eight patients received no prior chemotherapy or radiation therapy.

Seventeen patients were evaluable for response. Three patients were removed from the study for toxicity in less than 4 weeks and were considered inevaluable for response. There were no major responses in the 13 evaluable patients with metastatic disease. One of the four evaluable patients with locally advanced disease exhibited a partial response which persisted for 8.5 months. No complete responses were observed. The median survival of the entire group was 31 weeks from the start of treatment.

All 21 patients were evaluable for toxicity (see Table 2). Eight patients either refused further treatment or were removed from the trial due to toxicity, without evidence of progression at 2, 3, 3,

Table 2. Side effects of treatment[a]

Effect	Toxicity grade (maximum)			
	1	2	3	4
Fatigue	6	6	5	0
Anorexia	5	6	2	0
Nausea	5	4	1	0
Headache	5	0	1	0
Fevers	3	8	0	0
Dry skin	9	3	0	0
Cheilitis	10	2	0	0
Diarrhea	1	2	0	0
Anemia	5	1	0	0
Leukopenia	3	1	0	0
Neutropenia	1	1	0	0
Vertigo	0	1	0	0
Miscellaneous[b]	4	0	0	0

[a] All patients enrolled were evaluable for toxicity. The ineligible patient with 'non-small cell' lung cancer received 14 weeks of treatment and is considered evaluable for toxicity only.
[b] There was one case each of grade 1 insomnia, dyspepsia, stomatitis and myalgias.

4, 4, 4, 12 and 17 weeks. Constitutional side effects (fatigue and/or anorexia) were reasons for withdrawal in seven of the eight cases. Toxicity was not significantly influenced by the use of prior chemotherapy. Nine patients developed grade 3 toxicity (five fatigue, two anorexia, one headache and one nausea/vomiting). There were no instances of grade 4 toxicity.

Discussion

13-cRA is a member of the large class of vitamin A derivatives (retinoids) that play important roles in normal epithelial cell growth and differentiation.[6,7] Preclinical studies of the retinoids have demonstrated the ability of these compounds to modulate cellular growth and differentiation in multiple cell lines.[8,9,33,34] Clinically, 13-cRA has shown activity in reversing several epithelial premalignancies, and in decreasing head and neck and skin second primary tumors.[26,35] It has also demonstrated major activity in the treatment of patients with advanced squamous cell cancer of the skin[25] and advanced cutaneous T cell lymphoma.[36] It has been disappointing when used alone in patients with NSCLC, with responses in less than 10% of cases.[24]

Single-agent IFN-α2a has produced response rates of 75% or more in patients with hairy cell leukemia, CML in early chronic phase and untreated patients with cutaneous T cell lymphomas.[10,11,19,20,22,28,29] Response rates of 40–50% have been reported with low-grade Non-Hodgkin's lymphomas and untreated multiple myeloma.[14,15,23,25,27] IFN-α2a has not been as effective in patients with solid tumors. The best results have been seen in patients with AIDS-related Kaposi's sarcoma, with objective responses in the 30–40% range using high doses of interferon.[17,18] Overall responses in the 10–20% range have been seen in patients with melanoma and renal cell carcinoma.[10–16] IFN-α2a has been ineffective in SqCLC, with responses in less than 10% of patients.[37–39]

In vitro studies of the combination of IFN-α2a and 13-cRA have shown a greater antiproliferative effect on various SqCC cell lines than with either agent alone.[9] Clinically, this combination has demonstrated substantial activity in patients with SqCC of the skin[30] and cervix.[31]

In 28 assessable patients with previously treated advanced inoperable SqCC of the skin, 19 (68%) responded to treatment, with seven (25%) being complete responders. The response rate varied from 25% (2/8) in those with distant metastases to 85% (17/20) with local-regional disease.[30] The results in patients with SqCC of the cervix have been impressive. In a study of 26 previously untreated patients with locally advanced disease, the response rate was 50% (12 partial responses and one complete response). This included major responses in 66% (10/15) of patients with bulky (10 cm or larger) tumors.[31]

The toxicities of the 13-cRA plus IFN-α2a combination are unique, relative to chemotherapy. The major toxicities observed have been fatigue and anorexia from IFN-α2a, and dry skin and cheilitis from 13-cRA. There have been infrequent significant hematologic side effects.[30,31]

Despite the results in patients with other advanced SqCCs, the combination of IFN-α2a and 13-cRA failed to show major activity in advanced SqCLC. No responses were observed in 13 evaluable patients with metastatic disease. However, one partial response was obtained among four evaluable patients with locally advanced disease. The results of this trial lead us to conclude that the combination IFN-α2a and 13-cRA does not exhibit significant activity in metastatic SqCLC, but clinically meaningful activity in patients with locally advanced disease has not been excluded.

References

1. Minna JD, Pass H, Glatstein E, *et al.* Cancer of the lung. In: Devita VT, Hellman S, Rosenberg SA, eds. *Cancer,*

principles and practice of oncology. Philadelphia, PA: Lippincott 1989: 591–705.
2. Boring CC, Squires TS, Tong T. *Cancer Statistics* 1992. *CA* 1992; **42**: 19–38.
3. Johnson DH. Chemotherapy for unresectable non-small cell lung cancer. *Sem Oncol* 1990; **17**: 20–9.
4. Gralla RJ, Kris MG. Management of non-small cell lung cancer. In: Williams CJ, Whitehouse JMA, eds. *Recent advances in clinical oncology*, New York: Churchill Livingstone 1986: 167–80.
5. Rapp E, Pater JL, Willan A. *et al.* Chemotherapy can prolong survival in patients with advanced non-small cell lung cancer—a report of a Canadian multicenter randomized trial. *J Clin Oncol* 1988; **6**: 633–41.
6. Lippman SM, Kessler JF, Meyskens FL. Retinoids as preventive and therapeutic anticancer agents (parts 1 and 2). *Cancer Treat Rep* 1987; **71**: 391–405, 493–515.
7. Smith MA, Parkinson DR, Cheson BD, *et al.* Retinoids in cancer therapy. *J Clin Oncol* 1992; **10**: 839–64.
8. Munker M, Munker R, Saxton RE, *et al.* Effect of recombinant monokines, lymphokines, and other agents on clonal proliferation of human lung cancer cell lines. *Cancer Res* 1987; **47**: 4081–85.
9. Frey JR, Peck R, Bollag W. Antiproliferative activity of retinoids, interferon A, and their combination in five human transformed cell lines. *Cancer Lett* 1991; **57**: 223–27.
10. Figlin RA. Biotherapy with interferon—1988. *Sem Oncol* 1988; **15** (suppl 6): 3–9.
11. Spiegel RJ. The alpha interferons: clinical overview. *Sem Oncol* 1987; **14** (suppl 2): 1–12.
12. Krown SE. Interferon treatment of renal cell carcinoma: current status and future prospects. *Cancer* 1987; **59**: 647–51.
13. Muss HB, Costanzi JJ, Leavitt R, *et al.* Recombinant alfa interferon in renal cell carcinoma: a randomized trial of two routes of administration. *J Clin Oncol* 1987; **5**: 286–91.
14. Figlin RA, deKernian JB, Mukamel E, *et al.* Recombinant interferon alfa-2a in metastatic renal cell carcinoma: assessment of antitumor activity and anti-interferon antibody formation. *J Clin Oncol* 1988; **6**: 1604–10.
15. Creagan ET, Ahmann DL, Frytak S, *et al.* Three consecutive phase II studies of recombinant interferon alfa-2a in advanced malignant melanoma: updated analysis. *Cancer* 1987; **59**: 638–46.
16. Kirkwood JM. Studies of interferons in the therapy of melanoma. *Sem Oncol* 1991; **18** (suppl 7): 83–90.
17. Krown SE. The role of interferon in the therapy of epidemic Kaposi's sarcoma. *Sem Oncol* 1987; **14**: 27–33.
18. Real FX, Oettgen HF, Krown SE. Kaposi's sacroma and the acquired immunodeficiency syndrome: treatment with high and low doses of recombinant leukocyte A interferon. *J Clin Oncol* 1986; **4**: 544–51.
19. Roth MS, Foon KA. Alpha interferon in the treatment of hematologic malignancies. *Am J Med* 1986; **81**: 871–82.
20. Golomb HM, Jacobs A, Fefer A, *et al.* Alpha-2 interferon therapy of hairy cell leukemia: a multicenter study of 64 patients. *J Clin Oncol* 1986; **4**: 900–5.
21. Quesada JR, Alexanian R, Hawkins M, *et al.* Treatment of multiple myeloma with recombinant A-interferon. *Blood* 1986; **67**: 275–78.
22. Talpaz M, Kantarjian H, Kurzrock R, *et al.* Interferon-alpha produces sustained cytogenetic responses in chronic myelogeneous leukemia: philadelphia chromosome-positive patients. *Ann Int Med* 1991; **114**: 532–38.
23. Foon KA, Sherwin SA, Abrams PG, *et al.* Treatment of advanced non-Hodgkins lymphoma with recombinant leukocyte A interferon. *N Eng J Med* 1984; **311**: 1148–51.
24. Grunberg SM, Itri LM. Phase II study of isotretinoin in the treatment of advanced non-small cell lung cancer. *Cancer Treat Rep* 1987; **71**: 1097–98.
25. Lippman SM, Meyskens FL. Treatment of advanced squamous cell carcinoma of the skin with isotretinoin. *Ann Int Med* 1987; **107**: 499–502.
26. Hong WK, Lippman SM, Itri LM, *et al.* Prevention of second primary tumors with isotretinoin in squamous-cell carcinoma of the head and neck. *N Eng J Med* 1990; **323**: 795–801.
27. Lippman SM, Kessler JF, Al-Sarraf M, *et al.* Treatment of advanced squamous cell carcinoma of the head and neck with isotretinoin: a phase II randomized trial. *Invest New Drugs* 1988; **6**: 51–56.
28. Olsen E, Rosen S, Vollmer R, *et al.* Interferon alfa-2a in the treatment of cutaneous T-cell lymphoma. *Proc Am Soc Clin Oncol* 1987; **6**: 189 (abs 746).
29. Covelli A, Cavalieri R, Coppola G, *et al.* Recombinant leukocyte A interferon (IFL-rA) as initial therapy in mycosis fungoides (MF) and Sezary syndrome (SS). *Proc Am Soc Clin Oncol* 1987; **6**: 189 (abs 745).
30. Lippman SM, Parkinson DR, Itri LM, *et al.* 13-*cis*-retinoic acid and interferon-A-2a: effective combination therapy for advanced squamous cell carcinoma of the skin. *J Natl Cancer Inst* 1992; **84**: 235–41.
31. Lippman SM, Kavanagh JJ, Paredes-Espinoza M, *et al.* 13-cis-retinoic acid plus interferon A-2a: highly active systemic therapy for squamous cell carcinoma of the cervix. *J Natl Cancer Inst* 1992; **84**: 341–45.
32. Ajani JA, Welch SR, Raber MN, et al. Comprehensive criteria for assessing therapy-induced toxicity. *Cancer Invest* 1990; **8**: 147–59.
33. Marth C, Daxenbichler G, Dapunt O. Synergistic antiproliferative effect of human recombinant interferons and retinoic acid in cultured breast cancer cells. *J Natl Cancer Inst* 1986; **77**: 1197–202.
34. Hemmi H, Breitman TR. Combinations of recombinant human interferons and retinoic acid synergistically induce differentiation of the human promyelocytic leukemia cell line HL-60. *Blood* 1987; **69**: 501–07.
35. Kraemer KH, DiGiovanna JJ, Moshell AN, *et al.* Prevention of skin cancer in xeroderma pigmentosum with the use of oral isotretinoin. *N Eng J Med* 1988; **318**: 1633–7.
36. Kessler J, Jones S, Levine N, *et al.* Isotretinoin and cutaneous helper T-cell lymphoma (mycosis fungoides). *Arch Dermatol* 1987; **123**: 201–04.
37. Olesen BK, Ernst P, Nissen MH, *et al.* Recombinant interferon A (IFL-rA) therapy of small cell and squamous cell carcinoma of the lung. A phase II study. *Eur J Cancer Clin Oncol* 1987; **23**: 987–89.
38. Sarna G, Figlin R, Callaghan M. Alpha(human leukocyte)-interferon as treatment for non-small cell carcinoma of the lung: a phase II trial. *J Biol Resp Mod* 1983; **2**: 343–47.
39. Grunberg SM, Kempf RA, Itri LM, *et al.* Phase II study of recombinant alpha interferon in the treatment of advanced non-small cell lung carcinoma. *Cancer Treat Rep* 1985; **69**: 1031–32.

(Received 12 October 1992, accepted 16 November 1992)