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Clinical report

Phase II study of a combination of low-dose cisplatin with 13-*cis*-retinoic acid and interferon-α in patients with advanced head and neck squamous cell carcinoma

Gwenaelle Gravis, François Pech-Gourgh,[1] Patrice Viens, Claude Alzieu,[2] Jacques Camerlo, Sandrine Oziel-Taieb, Michel Jausseran[1] and Dominique Maraninchi
Medical Oncology Department, [1]Head and Neck Surgery Department, and [2]Radiotherapy Department, Institut Paoli-Calmettes, 13273 Marseille Cédex, France.

Preclinical and clinical data have suggested antitumor efficacy in squamous cell carcinoma (SCC) of interferon (IFN)-α and 13-*cis*-retinoic acid (13-c-RA) as single agent with greater activity in combination. Cisplatin was added to potentiate activity. Twenty-three patients with pretreated advanced or metastatic head and neck squamous cell carcinoma were given a combination of IFN-α (6×10^6 U/day, 84 days s.c.), 13-c-RA (1 mg/kg/day, 84 days) and cisplatin (40 mg/kg/day, day 1, 28 and 56). Seventeen patients had discontinuation of treatment and three patients received overall treatment without dose reduction. Hematological toxicity was more frequent; only three patients experiencing grade 3 or higher extra-hematological toxicity. Four out of 14 evaluable patients were in response, with one in complete pathological response. Median duration of response was 6 months with a 9 month median survival. Association of IFN-α, 13-c-RA and cisplatin induces modest but definite antitumor activity with moderate and manageable toxicity. Further studies of different combination modality therapy with chemotherapy and differentiating agents need to be performed in less pretreated patients. [© 1999 Lippincott Williams & Wilkins.]

Key words: Cisplatin, combined modality therapy, head and neck carcinoma, interferon-α, retinoids, squamous cell carcinoma.

Introduction

Sixty percent of newly diagnosed squamous head and neck cell carcinomas (HNSCC) are patients with advanced stage disease with a 5-year survival rate of less than 25%.[1] For these patients, surgery and/or radiotherapy and/or chemotherapy are the standard primary curative treatments. Most of these patients have recurrences within 2 years of initial treatment and more than 30% will also develop distant metastases.[2] Survival benefits are small when chemotherapy is used in advanced and or metastatic HNSCC. Two randomized trials demonstrate a significant improvement in overall survival for patients treated with cisplatin-based chemotherapy.[3,4] The most active drugs include methotrexate, cisplatin, bleomycine and 5-fluorouracil. Single-agent cisplatin has an overall response rate of 30%. Identification of the chemotherapy most active in treatment of advanced or recurrent disease has led to active-agent combination studies. Response rates from 40 to 80% are reported, and approximately half are complete responses with response duration from 4 to 7 months and survival duration from 6 to 8 months.[5,6] A major impediment to the treatment of recurrent HNSCC is the paucity of active agents.

The poor results associated with traditional treatments have led to investigation into the use of new drugs. Biologic response modifiers such as interferon (IFN) have been used. The IFN effect includes cell differentiation, cell proliferation, antiangiogenesis, antiviral and immunomodulatory effects. The response rate to IFN in HNSCC ranges from 0 to 58%.[7] Retinoic acid (RA) as well as other active vitamin A derivatives and their synthetic analogs (retinoids) regulate many important biological processes including inducing cell differentiation, inhibiting cell proliferations, and angiogenisis, differentiation, morphogenesis, growth, metabolism and homeostatis.[8] They have been found to induce terminal differentiation in various cell systems, epithelial cells, myeloid cell lineage and connective

Correspondence to G Gravis, Oncology Unit, Institut Paoli-Calmettes, 232 Bd Sainte-Marguerite, 13273 Marseille Cédex 09, France.
Tel: (+33) 04 91 22 35 37; Fax: (+33) 04 91 22 35 45;
E-mail: oncomed@marseille.fnclcc.fr

tissue fibroblasts. RA induces apoptosis, which can lead to tumor regression. Cell culture has shown that retinoids induce differentiation and apoptosis in human promyelocytic leukemia (HL60).[9] Antiproliferative and differentiating effects of RA on squamous cell carcinoma cell lines have been demonstrated *in vitro*. Preventive and inhibitory effects of c-RA on carcinogenesis have been shown in animal experiments, and in clinical trials they were found to be effective in prevention of oral premalignant lesions and second primary cancers in the upper aerodigestive tract. Retinoids have been studied in recurrent HNSCC with a 15% response rate with 13-*cis*-RA (13-c-RA).[10]

Combination of RA and IFN-α enhanced antiproliferative and differentiating effects when compared to either agent used alone.[11,12] Several clinical studies have demonstrated antitumoral efficacy of the association in several squamous cell carcinoma tumors.[10,13] Our aim was to add one of the most active cytotoxic agent chemotherapies to an association of 13-c-RA and INF-α. The rationale for adding cisplatin in this study is based on experimental findings. INF-α increased cytotoxicity of cisplatin in a murine model of human non-small cell lung cancer.[14]

In vitro studies with combination RA and cisplatin demonstrated a synergistic effect on squamous cell carcinoma cell lines.[15] The goal in using a moderate dose of cisplatin (40 mg/m^2) versus a standard dose (100 mg/m^2) was to increase the cytotoxic and apoptotic effect with no major toxicity. Our aim was to evaluate feasibility, safety and response in a phase II study using a combination of IFN-α, 13-c-RA and cisplatin in patients with advanced squamous cell head and neck carcinoma for whom local therapy had failed and/or in whom distant metastases existed.

Patients and methods

Patients

To enter the study, patients had to have histological proven squamous cell head and neck carcinoma. Advanced inoperable and/or metastatic squamous cell carcinoma of the cervix, lung, upper aerodigestive tract and esophagus could be included in this study. To enter the study, patients gave written informed consent, and had to have estimated life expectancy >3 months, be younger than 71 years old, a good Karnofsky scale $>70\%$ and had to have bidimensionally measurable lesion or at least evaluable lesion. Exclusion criteria included pregnant women or nursing women. A negative pregnancy test was required in women of child-bearing age. Patients were excluded if they had non-controlled brain metastases, and non-adequate hepatic, renal and/or hematopoietic function. Before the study began, a complete medical history was obtained from each patient who underwent a physical examination with appropriate laboratory and radiological analyses. In accordance with French law the protocol was approved by the CCPPRB of Marseille (Ethical Committee). Between May 1993 and June 1995, 23 patients with HNSCC were enrolled in this phase II study.

Treatment plan

Treatment was administered on an outpatient basis and patients were rehospitalized only for severe toxicity. Recombinant IFN-α-2A (Roferon A) was provided by Produits Roche (Neuilly-sur-Seine, France). IFN-α-2A was given subcutaneously at 6×10^6 U/day for 84 days, 13-c-RA was given orally at 1 mg/kg/day for 84 days. Cisplatin was given i.v. at 40 mg/m^2/day, on days 1, 28 and 56. Dose adjustments were made, if needed. Platelets or granulocytes toxicity grade 3 induced reduction of IFN-α to 3×10^6 U/day and cisplatin to 20 mg/m^2/day; if grade 4 hematologic toxicity occurred IFN-α and cisplatin were stopped and half dose of 13-c-RA was given until restoration of adequate hematologic function. Bleeding of infectious events implied complete interruption of therapy. For extra-hematologic toxicity $\geqslant$grade 3, treatment was stopped for at least 2 weeks until regression of toxicity. Central nervous system toxicity induced 50% reduction of 13-c-RA for grade 2 and discontinuation for grade $\geqslant3$. Overall planned duration of therapy was 84 days unless discontinued for severe toxicity and/or disease progression.

Criteria for response and toxicity

Before treatment, all patients underwent standard clinical evaluations, which included medical history and physical examination, complete blood count, chest X-ray, computed tomography scan to evaluate disease extent, and nuclear medicine bone scans. Response was assessed after 7 and 12 weeks of treatment by physical examination and other radiological studies as appropriate. Standard response criteria were used. A partial response was taken as a 50% or greater reduction in tumor area as measured in two perpendicular dimensions and a complete response was defined as a complete disappearance of the entire tumor, with no apparition of new lesions. Toxicity was monitored through both clinical and

laboratory evaluation every 2 weeks and more frequently in the case of apparition of toxicity. Laboratory analyses performed to monitor toxicity included: blood chemistry, complete blood cell count, liver function test and serum lipid profiles. Treatment toxicity was judged according to WHO criteria.[16]

Results

Patient characteristics

Results are summarized in Tables 1 and 2.

Between May 1993 and June 1995, 23 patients with HNSCC who had failed prior therapy were treated by a combination of IFN-α, 13-c-RA and cisplatin. There were 21 men and two women with a median age of 63 years (range: 46–76); characteristics are listed in Table 1. The most frequent localization of the primary lesion was the oral cavity (48%) and the squamous cell lesion was well differentiated in 57%. Fifteen patients received treatment for a first evolutive disease and eight patients for their second evolutive disease (Table 2). All patients received previous therapy for their initial lesion: 19 underwent surgery, 21 received radiotherapy and 12 received chemotherapy including 11 cisplatin-based chemotherapies associated with 5-fluorouracil in nine of them. All experienced relaspe, 14 at the initial site, five in the initial localization as well as in a new metastatic site and four had distant metastases. Eight patients were progressing after treatment of relapse when they were included in the study. For 15 patients, combination of IFN-α, 13-c-RA and cisplatin was the first treatment of relapse (eight patients) and/or metastases (seven patients).

Table 1. Patient characteristics

	No.	%
Patients	23	
Median age (range)	63 (46–76)	
Sex		
men	21	91
women	2	9
Primary tumor site		
oral cavity	11	48
pharynx	8	35
larynx	2	9
maxillary sinus	1	4
unknown	1	4
Tumor differentiation		
well differentiated	13	57
moderately differentiated	1	4
could not be assessed	9	39
Tumoral status at time of treatment		
locally evolutive disease	12	52
local and regional lymph node metastases	5	22
metastatic disease	6	26

Delivery of therapy

Overall, delivery of the 84 days of therapy was poor in these patients with advanced and progressive disease. Seventeen of 23 patients discontinued therapy. Reasons for discontinuation were disease progression in four patients and patient refusal for three others: for these seven patients discontinuation of therapy occurred at a median of 35 days after initiation (range: 0–77 days). Therapy was discontinued for toxicity in an additional 10 patients, which occurred at a median of 30 days (range: 5–84 days). Dose reduction, with or without interruption of treatment, was required for 13 patients. Finally, only three patients received full therapy without dose reduction.

Median received dose of IFN-α was 38% (range: 5–100%) given for a median duration of 49 days (range: 4–84 days). Median delivered dose of 13-c-RA was 58% (range: 6–100%) for a median duration of 55 days (range: 5–84). Sixty-seven percent of the planned dose of cisplatin was administered (range: 33–100%).

Toxicity

Only 21 patients were evaluable for toxicity because two patients received less than 1 week of treatment (Table 3). Hematologic toxicity grade 3 or higher occurred in 11 patients. One patient experienced leukocyte toxicity. Four patients had neutrophil

Table 2. Treatment received before entering the study

	No.	%
Treatment for initial disease	23	100
surgery+radiotherapy+chemotherapy	10	43
surgery+radiotherapy	7	30
radiotherapy+chemotherapy	2	9
radiotherapy	2	9
surgery	2	9
Treatment for relapse	8	35
surgery+radiotherapy+chemotherapy	1	4
surgery+radiotherapy	2	9
radiotherapy+chemotherapy	1	4
surgery	3	13
radiotherapy	1	4
none	0	0

toxicity, four patients had anemia and two patients developed platelet toxicity. Lymphopenia of grade 3 or higher was more frequent, occurring in 11 patients with a median duration of 28 days (range: 15–77 days). Extra-hematologic toxicity grade 3 was observed in three patients: consisting of nausea and vomiting (one patient), mucositis (three patients), and skin toxicity (one patient). Other toxicities were: elevated triglyceridemia in three patients and fever in three patients. Constitutional symptoms such as fatigue in two patients or weight loss in four patients were observed, but it was difficult to separate treatment toxicity from the effects of underlying malignancies. Hepatic toxicity was mild, with five patients who had grade I and one patient grade II toxicity. Eight patients required hospitalization for toxicity. No life-threatening effects occurred. Overall toxicities were easily manageable, even if frequent, and resolved promptly after dose reduction or discontinuation of therapy.

Response and survival

Response was evaluated in only the 14 patients who received at least seven weeks of treatment. Overall, four of 14 patients responded (29%) with one complete response (CR) and three partial responses (PR): one patient had the appearance of clinical residual disease but surgical excision showed pathological CR and three other patients with PR (Table 4). The four responders were men with a median age of 54 years (range: 46–67): two patients had cancer of the oral cavity (T4N2M0 and T3N0M0), one larynx (T2N0M0) and one pharynx (T4N3M0). All had a well-differentiated tumor. Treatment for initial disease was surgery and radiotherapy (two patients), associated with chemotherapy (one patient) or radiotherapy alone (one patient). Median time from diagnosis to relapse was 15 months (range: 5–36). All of these patients were in local relapse without distant metastatic localization. Two out of four patients were treated for relapse, by surgery (one patient), combined with radiotherapy (one patient). The median received dose of IFN-α, 13-c-RA and cisplatin for these patients was, respectively, 81% (62–100%), 90% (82–100%) and 93% (67–100%) with a median duration of therapy of 76 days (range: 70–84). Median duration of response was 6 months (range: 5–30) with median survival of 9 months (range: 8–38) from initiation of treatment. Median survival of the non-responders and of the whole group were, respectively, 7 months (range: 3–20) and 7 months (range: 6 days to 39 months).

Discussion

Treatment for recurrent and/or metastatic head and neck carcinoma with single or combined modality therapy will cure a small fraction of patients. If 30% response can be achieved with chemotherapy, median duration of response is 2–4 months with 6 month overall survival. To improve efficacy, further investigational single or combined modality therapies are ongoing. In this phase II study we evaluated tolerance and efficacy of a combination of low-dose cisplatin and differentiating agents 13-c-RA and IFN-α-2b in 23 patients with advanced HNSCC.

Our results show that such combination therapy was difficult to maintain for the planned 84 day duration of therapy, because most patients could not receive full dose regimen in time and 10 of 23 needed to discontinue therapy for toxicity. However, despite the frequency of toxic events, partially due to the local and general status of these advanced patients, none was life threatening and toxicities were easily manageable after dose reduction or discontinuation. Similar

Table 3. Grade toxicity > 2, WHO criteria (21 of 23 patients assessable for toxicity)

Toxicity	WHO grade	%	Median duration days (range)
Leukocytes	3–4	5	56
Granulocytes	3–4	19	28 (15–56)
Lymphocytes	3–4	52	28 (15–77)
Hemoglobin	3–4	19	15 (15–84)
Platelets	3–4	10	15
Digestive	3	5	45
Mucositis	3	14	15 (15–63)
Fatigue	3	10	28 (28–70)
Skin	3	5	63

Table 4. Tumoral response (14 patients assessable for response)

	Week 7	Week 12	Global response
CR	—	1 (7%)	1 (7%)
PR	1 (7%)	2 (14%)	3 (22%)
SD	6 (43%)	1 (7%)	2 (14%)
PD	5 (36%)	6 (43%)	8 (57%)
Non-evaluable	2 (14%)	4 (29%)	

CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease.

toxicities have been previously described with the use of 13-c-RA and IFN-α in head and neck cancers as well as in other carinomas.[13,17] Compared to other reports of toxic events with such differentiating agents, hematologic toxicity seemed especially frequent in this series: it is possible that the addition of cisplatin to 13-c-RA and IFN-α, even at a relatively low dose, plays a role in such hematologic toxicity, especially in erythrocytic and thrombocytic lineages where the hematologic toxicity of cisplatin is well documented. Cumulative fatigue was observed in this elderly population (median age 63 years) induced by IFN-α, and anemia resulting from both IFN-α and cisplatin.

We confirm with this cohort of patients that a combination of synergistic differentiating agents (13-c-RA and IFN-α) is able to induce a consistent (29%) rate of antitumoral response in relapsed head and neck cancers. It is probably relevant to note that responding patients had less extensive disease, and better tolerance and dose delivery than non-responding patients. With a 6 month median duration of response and 9 month median survival, these results are encouraging for evolutive and pretreated patients. It was surprising to observe that overall responders had well-differentiated tumors. Effect of differentiation induced by RA which is potentiated by IFN-α led us to hypothesize that there is a major antitumoral effect in less differentiated tumors. Perhaps apoptosis induced by RA is more pronounced the more differentiated the tumor.

It is difficult to assess the benefit in tumoral response of the addition of cisplatin to 13-c-RA and IFN-α in the relatively good tumoral response rate of our patients. Several studies reported relatively low response rates of head and neck cancers to 13-c-RA and IFN-α: one of 21 for Voravud *et al.*,[20] none of three for Roth *et al.*[19] and none of 11 for Cascinu *et al.*[18] However, response rates of 50% have been reported in eight patients by Toma *et al.*,[21] using similar strategies without cisplatin in head and neck cancer. Despite encouraging results in a pilot study (OR: 30%) obtained with the combination of cisplatin, fluorouracil and IFN-α in head and neck cancer, a recent randomized trial using the same chemotherapy with or without IFN-α demonstrated no benefit in adding IFN-α in terms of response or survival.[22,23]

Conflicting results reported in the literature can be in part explained by the heterogeneity of the patient populations: even if our data are informative and confirmative of the possibility of inducing tumoral response in head and neck cancer with low-dose cisplatin, 13-c-RA and IFN-α, such a therapeutic strategy was difficult to tolerate in most of our patients, especially those with the most advanced disease. More encouraging results have been observed in squamous cell carcinoma of the skin (68% OR, 25% CR with a 5 month median duration of response) or the cervix (50% OR) with the association 13-c-RA and IFN-α.[13,17]

Conclusion

Addition of cisplatin to 13-c-RA and IFN-α does not lead to a major increase of the tumoral response rate in relapsed advanced HNSCC. However, in heavily pretreated patients, overall response and median duration of response is sufficiently encouraging to initiate further studies of a combination of cytotoxic drugs and differentiating agents, apoptotic inducer or RA with a more differentiating function. They should rather include patients in post-untreated relapse and be of shorter duration than our treatment.

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