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Retinoids, cisplatin and interferon-alpha in recurrent or metastatic cervical squamous cell carcinoma: clinical results of 2 phase II trials

Abstract

Background: There is no standard treatment for inoperable recurrent or metastatic cancer of the uterine cervix. Retinoids and interferon, in combination with cytotoxic compounds, have been shown to be active in squamous cell carcinoma (SCC). This phase II trial sought to estimate the response rate and the tolerance to a 3-month treatment combining cisplatin, interferon-alpha (IFN-

alpha) and all-trans-retinoic (tRA) or 13 cis retinoic acid (13Cis), in women with recurrent or metastatic cervical SCC. Patients and methods: Between November 1994 and October 1996, 33 patients, who had previously received aggressive treatment, and with metastatic and/or bulky disease were enrolled: 22 received tRA(40 mg/m2/day), 11 received 13Cis (1 mg/kg/day) in combination with IFN-alpha (6.106 UI/day SC) for 84 days plus cisplatin (40 mg/m2 IV, days 1, 28 and 56). Results: All patients were evaluable for response and/or toxicity. Toxicities were easily manageable and were never life-threatening, with major grade 3/4 vomiting (54%) and asthenia (54%). Seventeen patients (52%) stopped or reduced treatment because of toxicity or progression. Six objective responses (18%) were observed. No complete response was recorded. Median response duration was 4 months. Time to progression was 9 months [range 3.3 to 20.9] for responders and 7 months [range 1.7 to 32] for all patients. Conclusions: Regarding toxicity, this regimen should no longer be recommended in previously treated, advanced uterine SCC. However, the consistent response rate reported here may warrant further investigations in an early setting. Retinoid-based treatment with cytokines remains a promising field of research.

Full text

INTRODUCTION

The best method of treatment of metastatic or recurrent carcinoma of the uterine cervix has not yet been established and multimodal therapies including surgery, chemo-radiotherapy or chemotherapy have failed to improve survival rates or produce durable remission [1-3]. In addition, systemic therapy has only a limited role in controlling symptoms associated with loco-regional progression such as sacral plexopathy, ureteral obstruction and thromboembolic events. Thus, new therapeutic drugs must be investigated for control of these symptoms and to prevent disease progression.

Interferon-alpha2a (IFN) and retinoids have shown promising results in a number of squamous cell carcinomas [4]. Retinoids, the natural and synthetic derivatives of vitamin A or retinol, have relevant cellular effects upon differentiation, proliferation and apoptosis [4, 5]. A number of clinical trials have shown their efficacy as chemopreventive and chemotherapeutic agents in head and neck, skin, liver and cervical carcinomas [6, 7]. The high activity of tretinoin, (all-trans-retinoic acid (tRA)), in acute promyelocytic leukemia (APL) has

stimulated further interest [8]. Nevertheless, high recurrence rates suggest that retinoids may have little activity as single agents but may improve the efficacy of other anti-cancer modalities such as radiation or chemotherapy. Interferons are active in several hematological malignancies such as Kaposi's sarcoma, melanoma and renal cell cancer. Preclinical data have demonstrated synergy and molecular interactions between retinoids and interferon [9, 10] both inducing differentiation and/or apoptosis of epithelial cells. Preliminary results with isotretinoin or 13-*cis*-retinoic acid (13Cis) and interferon-alpha in previously aggressively treated patients, with cervical squamous cell carcinoma [11-13] have been promising. Studies of these agents indicate that they may increase the efficacy of chemotherapies such as cisplatin [14-16]. Targets of such synergy could be induction of apoptosis, inhibition of angiogenesis or differentiation of malignant cells. Regarding the activity of cisplatin in cervical carcinoma, strategies combining retinoids, cytokines and chemotherapy represented an attractive approach. We investigated this strategy in recurrent or metastatic cervical carcinoma in terms of response rate, disease-free survival, overall survival and tolerance profile. Two phase II trials have been initiated. Each one combined 13Cis or trans retinoic acid (tRA) with a constant schedule of interferon and cisplatin. We report on these studies for (1) the tolerance of such a combination, and (2) response rates.

PATIENTS AND METHODS

Eligibility criteria

Patients were eligible for this trial if they had a biopsy-proven, locally advanced, unresectable or metastatic squamous cell carcinoma of the uterine cervix (T2b, T3, T4). After a complete physical examination with appropriate laboratory and radiological analyses, all women with the following eligibility criteria were included: (1) age between 18 and 70 years; (2) life expectancy of at least > 3 months; (3) Karnofsky performance status >= 70%; (4) measurable and/or evaluable disease; (5) adequate bone marrow function (neutrophil count > 1,500/mm^3, platelet count > 100,000/mm^3), renal function (serum creatinine < 1.5 x the upper limit of normal value), hepatic function (AST ¾ 1.5 x the normal value, except if due to liver metastasis); (6) no pregnant or lactating women (women of reproductive age had to use adequate contraceptive methods during the study); (7) no uncontrolled brain metastasis, (8) no previous or ongoing auto-immune or mental disease. All patients gave written informed consent in

accordance with French law, the ethical committees of Marseilles approved the protocol.

Treatment plan

Inclusion criteria, treatment plan, toxicity and response evaluation were the same for these two studies, which were performed over a period of 2 years. Results are presented together.

Treatment was administered on an outpatient basis, patients being hospitalized only for severe toxicity. Recombinant interferon-alpha-2A (Roferon A®), all-*trans*-retinoic acid (tRA) and 13 cis retinoic acid (13Cis) were provided by Produits Roche (Neuilly-sur-Seine, France).

Interferon-alpha-2A (IFN-alpha) was given subcutaneously at 6.10^6 units/day for 84 days, tRA was given orally, early in the morning at 50 mg/m^2/day for 84 days (Group tRA), and 13Cis was given orally, in the morning at 1 mg/kg/day for 84 days (Group 13Cis). Intravenous cisplatin was given at 40 mg/m^2/day on days 1, 28 and 56. Dose adjustments were made if required. Platelet or granulocyte toxicity grade 3 warrented a reduction of IFN-alpha to 3.10^6 U/day and cisplatin to 20 mg/m^2/day; if grade 4 hematological toxicity occurred, IFN-alpha and cisplatin were stopped and half doses of tRA or 13Cis were given toxicity had abated. Bleeding or infectious events were indications for complete interruption of therapy. For non-hematological toxicity >= grade 3, treatment was stopped for at least 2 weeks until regression of toxicity. Central nervous system toxicity led to a 50% reduction in the dose of tRA or 13Cis for grade 2, and discontinuation for higher grades. Reappearance of dose limiting toxicity at the lowest permissible dose level resulted in removal from study. Treatment duration did not exceed 12 weeks (84 days) and varied according to response. Patients with potentially operable disease underwent evaluation every 2 cycles in order to determine the date of earliest feasible surgery.

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 bone scans.

Response was assessed after 7 and 12 weeks treatment with "prior-to-inclusion" examinations repeated at each evaluation, except for the bone nuclide scan which was performed only after 12 weeks of treatment. For response evaluation, previously irradiated lesions were considered only in the absence of other lesions.

Response was assessed using World Health Organization (WHO) criteria. A complete response required disappearance of all clinical evidence of disease on two consecutive measurements, at an interval of at least 4 weeks. A partial response required a >= 50% decrease in the sum of the perpendicular diameters of all measured lesions and/or in the size of evaluable lesions on two consecutive measurements, at least 4 weeks apart. In addition, there should be no new lesion or increase in any lesion size. Stable disease was defined as a steady state or response, less than partial response or progression. Progressive disease was defined as an increase of at least 25% of measurable or evaluable lesions and/or the appearance of any new lesion. Treatment was stopped in progressive disease but continued in stable disease or if partial response was experienced. In patients with complete response, the decision was made depending on the metastatic status of the disease at entry to the study.

Treatment toxicity was judged, according to the NCI-CTC criteria, every two weeks using clinical examination and laboratory analysis including blood chemistry, complete blood cell count, liver function test and serum lipid profiles.

RESULTS

Patient characteristics

Thirty-three patients were enrolled in these two studies. Their main characteristics are listed in Table 1. Eleven received 13 cis retinoic acid (13Cis) and 22 received trans retinoid (tRA). The median age was 48 years [range, 30.3-69.1 years]. The Karnofsky index was more than 80% for 27 patients. All 13Cis patients and all but 8 tRA patients (64%) had been treated previously with cisplatin for their initial lesion. Ten patients (5 in each group), (30%), had had progressive disease under previous treatment when they entered the study. Fifteen patients (68%) in tRA group and ten (91%) in the 13Cis group had metastases.

Delivery of therapy

Twenty-two patients received tRA and eleven patients received 13cis retinoic acid. Only 13/22 patients (61%) in tRA group and 7/11 (63%) in the 13cis group continued treatment until day 84 (Table 3). In each group, the median duration of treatment was 9 weeks (range, 2 to 12). The reasons for discontinuing the treatment were as follows: toxicity (4/22 tRA and 2/11 13Cis patients), mainly asthenia (tRA: 3 patients, 13cis: 2), grade 3 cutaneous toxicity (tRA: 1, 13cis: 1), anemia (tRA: 1), progressive disease (3/22 tRA and 1/11 13Cis patients) and other reasons such as patient's decision (1/22 tRA and 1/11 13Cis patients).

In the 13Cis group, seven patients received a reduced dose of interferon-alpha, eight received a reduced dose of 13Cis and five a reduced dose of cisplatin. Twelve patients received full treatment in the tRA group: 19/22 received a reduced dose of interferon-alpha, 16 received a reduced dose of tRA and 9 a reduced dose of cisplatin. Only 14/22 patients received more than 80% of the planned dose for cisplatin, 11/22 received more than 80% of the interferon-alpha and 10/22 received more than 80% of the tRA.

Finally, only 4/11 patients received full 13Cis therapy and 12/22 received full tRA therapy, with neither interruption nor dose reduction.

TOXICITY

All patients received at least two weeks of treatment and were evaluable for toxicity. No toxic deaths occurred during the study or follow-up period (one month after discontinuation of treatment). The main symptoms are listed in Table 2.

The incidence of grade 3 and 4 hematological toxicities was moderate. Eight patients (24%) experienced grade 3 neutropenia, one patient had grade 3 thrombopenia and eight patients had grade 3 or 4 anemia.

The frequent extra-hematological toxicities grade >= 2 included: asthenia in 19 patients (57%) which was severe in 1 case, fever in 15 patients (45%), nausea/vomiting in 18 patients (54%) and hepatic toxicity in 9 patients (27%). Other toxicities were moderate and transient. Flu-like symptoms, allergic

symptoms after administration of tRA and local reactions after administration of interferon-alpha were unusual and regressed spontaneously.

Response

Thirty-two patients had measurable and/or evaluable disease, 8 had had previous irradiation of the lesions in question. One patient received treatment with tRA in an adjuvant setting, following resection of a lung metastasis from a primary cervical carcinoma, and was therefore neither evaluable nor measurable. Two patients in the tRA group with T2b and T3b discontinued this treatment within 3 weeks due to partial response, but underwent radiotherapy followed by surgery. Five patients (three patients in the tRA group and two in the 13Cis group) were not evaluable for response since they discontinued treatment within 7 weeks due to unacceptable toxicity.

Responses are listed in Table 3. At week 7, six patients (18%) had partial response and nine patients had stable disease (27%). At week 12, 2 further patients had partial response while two responders had progression, resulting in the same response rate, while 8/33 patients had stable disease and 7/33 had progressive disease. Among assessable patients, response rate was 23% (6/26) at week 6 and 30% (6/20) at week 12.

Median time to progression was 4 months [range 0.4-17.7 months]. Median overall survival was 7 months [range 1.7-32 months].

Of the 8 responding patients, 7 had metastasis, 7 had previously received chemotherapy and all had a Karnofsky index higher than 80%. All but two received > 80% of the planned dose of retinoid, while only 50% received > 80% of planned dose of IFN-alpha. All but one received 100% of the cisplatin. Median time to progression was 9 months [range 3.3-20.9 months], 2 were progressive before 12 weeks. Median overall survival was 12 months [range 6-32 months] and 2 patients were alive at 28 and 32 months respectively.

DISCUSSION

The aim of this study was to evaluate the tolerance and the efficacy of a combination therapy of retinoid, interferon and low dose cisplatin. Clinical results from this trial were considered moderate, but not totally irrelevant. With

8 objective responses, our trial suggests that interferon and retinoid may potentiate low doses of cisplatin and may have minor but consistent activity in patients with recurrent and aggressively pretreated SCC of the cervix. Indeed, neither IFN-alpha nor retinoic acid as single agents or in combination have shown any activity in squamous cell carcinoma (SCC). This inefficacy led to the early disruption of the New York GOG trial [17], while the SWOG support the lack of recommendation for further use of 13cis or tRA in combination with interferon-alpha in recurrent cervical carcinoma [18]. The present data and those previously observed in a larger population in our institution [19], clearly contrast with the lack of efficacy mainly reported in other SCC. One reason might be the patient selection criteria. In the present trial, we found no difference. Most of our patients had been previously treated. In fact, preclinical data have suggested that the benefit of interferon and retinoid is reserved for chemoprevention and not for the treatment of advanced disease. Our results do not support this hypothesis. Alternatively, the treatment schedule may have influenced the results. It is unlikely that an infra-optimal dose of cisplatin alone (40 mg/m^2 every months) can explain a response rate of almost 24% in these patients. The optimal dose of interferon is un-known, so we proposed the use of a low dose, assessed as effective and only slightly toxic. We did not observe any difference between 13cis and all trans retinoic acid treatment since these two isomers are rapidly and reversibly transformed [20]. It can therefore be suggested that some degree of synergy exists between low-dose tRA, IFN-alpha and cisplatin. This synergy has been assessed *in vitro* [21] where murine retinoids block the production of many cytokines by tumor cells such as: vascular permeability factor/vascular endothelial growth factor-induced microvascular permeability and angiogenesis [23]. It is consistent with the correlation previously found between vascularization, micro-vessel count and responsiveness to INF and RA [24]. The correlation between micro-vessel density and response to retinoid- IFN-cisplatin should be evaluated in order to determine if responders have a specific biological profile.

The mechanism of such an interaction at a cellular level is poorly understood. Retinoic acid receptor beta (RARbeta) is thought to be the key gene in this synergy. Most malignant and premalignant SCC exhibit a reduced level of RARbeta expression [25], while IFN and tRA upregulate its expression, allowing adequate regulation of cell proliferation [26]. Another hypothesis is that retinoids enhance IFN signal transduction predominantly in HPV positive cells [27]. We found no correlation between response and HPV status in this study.

The toxicity observed in this trial was tolerable and included the classical adverse effects of each drug. Potentially overlapping toxicities such as hematological (for IFN-alpha and cisplatin) or hepatic (for tRA and IFN-alpha) were also observed, but were relatively moderate and were similar to those reported by others [9, 12, 28, 30]. No life-threatening event was observed and toxicities were easily manageable. However, side effects or patient refusal justified definitive or temporary discontinuation of treatment in 12 patients and only 18 patients received the planned treatment. Clearly, such treatments have substantial toxicities in patients with advanced and aggressively pretreated disease. Previous studies evaluating combination of retinoids (tRA or 13Cis) and IFN-alpha have reported a pattern of adverse effects qualitatively similar to our results, but toxicities were generally considered moderate and largely acceptable. The substantial toxicities observed in our study could have been due to patient population differences, including previous aggressive treatment or cisplatin. Consistent with our data, a recent phase II study evaluating the combination of tRA with cisplatin-based chemotherapy in advanced, small cell lung carcinoma reported early discontinuation of retinoid administration in the majority of patients because of unacceptable toxicity [30]. A combination of 13cis, IFN and radiotherapy was associated with unexpected toxicity towards the colon mucosae.

CONCLUSION

The correlation between tRA pharmaco-kinetic and clinical effects (response or toxicity) remains controversial. Strategies aiming to prevent early decline in tRA plasma levels have been successful on a pharmaco-kinetic basis, but have not translated into clear clinical benefits. Whatever the schedule of administration, any tRA pharmaco-kinetic parameters can predict a toxicity pattern [31]. It is likely that intracellular parameters (such as qualitative or quantitative patterns of retinoic acid receptor expression), rather than pharmaco-kinetic factors are preponderant in clinical activity.

Regarding the short, median duration of response and the substantial toxicity observed, this regimen can no longer be recommended for previously treated patients with advanced disease. However, the consistent response rate reported here could encourage further clinical studies, since control of high risk, squamous carcinoma of the uterine cervix needs new treatments and strategies. Chemotherapies involving newer drugs [32] have been

disappointing, while new retinoids that have distinctive binding properties and transactivation effects on the various retinoic acid receptor (RAR and RXR) subtypes [33-36] could allow differential modulation of retinoid receptor-induced gene expression and a potentially more favorable efficacy/safety ratio. Retinoid-based therapy, including combination with cytotoxic compounds, remains a promising field of research.

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Figures

Table 1
Patient characteristics

	13 cis	tRA	Total
Patients entered	11	22	33
Median age [range]	48.5	48	
Tumor stage			
T2a		1	1
T2b		3	3
T3		1	1
T4	1	2	3
M1	10	15	25
Karnofsky performans status > 80%	10	17	27
Prior therapy for recurrence	11	14	25
Previous chemotherapy	5	5	10
Previous radiotherapy	5	3	8

Table 2
Toxicity
The highest toxicity during treatment is reported for each patient receiving tRA or 13 Cis. NCI-CTC scale is used

Toxicity grade N patients	Grade 1 tRA/ 13 cis	Grade 2 tRA/ 13 cis	Grade 3 tRA/ 13 cis	Grade 4 tRA/ 13 cis
Alkaline phosphatase	8/4	5/3	1/0	0/0
Nausea/vomiting	4/2	5/4	7/2	0/0
Stomatitis	2/0	1/0	0/1	0/0
Asthenia	2/0	8/3	4/3	1/0
Fever	0/0	10/5	0/0	0/0
Neutropenia	4/3	8/2	4/4	0/0
Anemia	7/1	1/5	0/2	0/1
Thrombopenia	7/2	9/0	4/1	1/0

Table 3
Tumoral response and treatment

	13 cis retinoic acid 11 patients	Trans retinoic acid 22 patients	Total 33 patients
Treatment duration			
12 weeks	7	13	20 (61%)
8-11 weeks	2	4	6 (18%)
7-4 weeks	1	1	2 (6%)
< 4 weeks	1	4	5 (15%)
Response at 7 weeks			
Partial response	2	4	6 (18%)
Stable disease	3	6	9 (27%)
Progression	1	7	8 (24%)
Non-evaluable	5	5	10 (30%)
Response at 12 weeks			
Partial response	2	4	6 (18%)
Stable disease	3	5	8 (24%)
Progression	3	4	7 (21%)
Non-evaluable	3	9	12 (36%)

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Moshe Hacham, Shmuel Argov, Rosalyn M. White, Shraga Segal, Ron N. Apte
IL-1alpha, IL-1beta, organ cytokine expression, young/old age, homeostasis.

The combination of the interleukin-1alpha (IL-1alpha-889) genotype and the interleukin-10 (IL-10 ATA) haplotype is associated with increased interleukin-10 (IL-10) plasma levels in healthy individuals

Sanna Kilpinen, Heini Huhtala, Mikko Hurme
interleukin-1, interleukin-10, gene polymorphism, plasma.

The interleukin-6 G(-174)C polymorphism and the ex vivo interleukin-6 response to endotoxin in severely injured blunt trauma patients

Michael Heesen, Udo Obertacke, F. Ulrich Schade, Brunhilde Bloemeke, Matthias Majetschak
interleukin-6, endotoxin, genetic polymorphism, polymerase chain reaction, whole blood, critical illness.

Comparison of leptin- and interleukin-6-regulated expression of the rPAP gene family: evidence for differential co-regulatory signals

Daniël Broekaert, Sven Eyckerman, Delphine Lavens, Annick Verhee, Wim Waelput, Joël Vandekerckhove, Jan Tavernier
forskolin, IL-6, leptin, rPAP/Reg gene family, signal transduction.

Mice lacking alpha2-macroglobulin show an increased host defense against Gram-negative bacterial sepsis, but are more susceptible to endotoxic shock

Tino Hochepied, Fred Van Leuven, Claude Libert
TNF, shock, acute phase, inflammation, alpha2-macroglobulin.

Tumor necrosis factor-alpha mRNA stability in human peripheral blood cells after lipopolysaccharide stimulation

Lucile Baseggio, Carole Charlot, Jacques Bienvenu, Pascale Felman, Gilles Salles
tumor necrosis factor, mRNA stability, lipopolysaccharide, tristetraprolin.

Caspase-1 levels in biological fluids from patients with multiple sclerosis and from patients with other neurological and non-neurological diseases

Diego Franciotta, Gianvito Martino, Elisabetta Zardini, Roberto Furlan, Roberto Bergamaschi, Maira Gironi, Alessandra Bergami, Giovanna Angelini, Fabrizio De Benedetti, Patrizia Pignatti, Gianna Moscato, Vittorio Cosi
asthma, cerebrospinal fluid, juvenile idiopathic arthritis, sputum, synovial fluid, THP-1 cells.

Divergent effects of tumor necrosis factor-alpha and lymphotoxin-alpha on lethal endotoxemia and infection with live Salmonella typhimurium in mice

Edi Dharmana, Monique Keuter, Mihai G. Netea, Ineke C.M.M. Verschueren, Bart Jan Kullberg
tumor necrosis factor, lymphotoxin, salmonella typhimunium, knock-out mice.

Th1/Th2 cytokine balance and nitric oxide in cerebrospinal fluid and serum from patients with multiple sclerosis

María del Carmen Rodríguez-Sáinz, Silvia Sánchez-Ramón, Clara de Andrés, Margarita Rodríguez-Mahou, M Angeles Muñoz-Fernández
cytokine, nitric oxide, multiple sclerosis, cerebrospinal fluid, oligoclonal bands, Igs.

Retinoids, cisplatin and interferon-alpha in recurrent or metastatic cervical squamous cell carcinoma: clinical results of 2 phase II trials

Anne-Chantal Braud, Laurence Gonzague, François Bertucci, Dominique Genre, Jacques Camerlo, Gwenaelle Gravis, Anthony Goncalves, Vincent Moutardier, Frédéric Viret, Dominique Maraninchi, Patrice Viens
all-trans-retinoic acid, 13 Cis retinoic acid, interferon-alpha, cervical squamous cell carcinoma.

Circulating macrophage colony stimulating factor as a marker of tumour progression

Raymond S. McDermott, Laurent Deneux, Véronique Mosseri, Jacques Védrenne, Krishna Clough, Alain Fourquet, José Rodriguez, Jean-Marc Cosset, Xavier Sastre, Philippe Beuzeboc, Pierre Pouillart, Susy M. Scholl
CSF-1, tumour progression, metastasis, de-differentiation.

The effect of interleukin-1beta (IL-1beta) and tumor necrosis factor-alpha (TNF-alpha) on granulocyte

macrophage-colony stimulating factor (GM-CSF) production by neuronal precursor cells

J. Benjamin Dame, Nasser Chegini, Robert D. Christensen, Sandra E. Juul

IL-1beta, TNF-alpha, GM-CSF, neuron, mRNA, protein.

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