Pergamon

European Journal of Cancer, Vol. 33, No. 11, pp. 1900–1902, 1997

Printed in Great Britain
0959-8049/97 $17.00+0.00

PII: S0959-8049(97)00263-3

Short Communication

Higher Doses of α-Interferon do not Increase the Activity of the Weekly Cisplatin–Interferon Combination in Advanced Malignant Mesothelioma

L. Trandafir,[1] P. Ruffié,[1] C. Borel,[1] I. Monnet,[3] P. Soulié,[2] D. Adams,[4] E. Cvitkovic[2] and J.P. Armand[1]

[1]Institut Gustave Roussy, 39 Rue Camille Desmoulins, 94805 Villejuif; [2]Service des Maladies Sanguines et Tumorales, Hôpital Paul Brousse, 14 Avenue Paul Vaillant Couturier, 94804 Villejuif; [3]Centre Hospitalier Intercommunal, 40 Avenue de Verdun, 94010 Créteil; and [4]Hôpital de Bicêtre, Avenue du Général Leclerc, 94275 Kremlin-Bicêtre, France

Management of advanced malignant mesothelioma (MM) still requires innovative systemic therapy as its prognosis is poorly affected by currently available chemotherapy. The combination cisplatin and α-interferon (α-IFN) has synergistic antitumoral activity in preclinical models and interesting activity in phase I–II clinical trials. Weekly CDDP (60 mg/m²) and α-IFN (3 MUI/d: d1–d4) in combination was tested in a previous phase I–II study in 23 MM patients, with a 36% objective response rate (ORR). A trial with higher doses of α-IFN in the same combination schedule was conducted to explore an incrementalist hypothesis. Thirty patients with MM received the same CDDP dose (60 mg/m²/w) and doubled doses of α-IFN (6 MUI/d: d1–d4). The treatment protocol consisted of two cycles of 4 weeks on/4 weeks off followed by two shorter cycles of 3 weeks on/3 weeks off, in the absence of life-threatening toxicity or progressive disease. All patients were evaluable for toxicity. The main treatment-limiting side-effects were digestive intolerance (nausea, vomiting) and severe asthenia. Antitumoral efficacy was not increased (ORR = 27%). Haematological and neurological toxicities were moderate and manageable. The antitumoral activity of the CDDP–α-IFN combination with higher doses of the latter is similar to our previous experience, but tolerance issues make it a poorer choice for eventual comparative trials, or as a standard therapeutic indication. © **1997 Published by Elsevier Science Ltd.**

Key words: cisplatin–α-interferon, malignant mesothelioma
Eur J Cancer, Vol. 33, No. 11, pp. 1900–1902, 1997

INTRODUCTION

MALIGNANT MESOTHELIOMA (MM) remains an uncommon aggressive tumour with acknowledged poor chemosensitivity. We have reported previously encouraging antitumoral activity (response rate = 36%) with the systemic CDDP–α-IFN combination, given weekly [1]. The protocol design was based on preclinical data in MM culture cell lines suggesting synergy between α-IFN and cisplatin. Recombinant α-IFN has been studied extensively in two solid tumours (renal cancer and melanoma). During those clinical trials, a large range of dosage (2–50 MUI/m²) was evaluated and no clear dose–response relationship was suggested [2]. In all these studies α-IFN toxicities were directly related to its administered dose intensity. A dose in the range of 5–10 MUI given s.c. 3–5 times a week would seem to be the choice in terms of therapeutic index.

These considerations led us to start a second consecutive phase I–II study. While keeping the same dose and weekly schedule of cisplatin, the α-IFN doses were doubled (6 MUI instead of 3 MUI/s.c. injection), trying to explore an incrementalist hypothesis of efficacy.

We present here the final report from this experience, while comparing it to the former study.

Correspondence to E. Cvitkovic.
Received 29 Jan. 1997; accepted 7 Apr. 1997.

PATIENTS AND METHODS

From March 1993 to May 1994, 33 consecutive patients with a diagnosis of advanced pleural malignant mesothelioma were referred to us for first-line systemic treatment. All of them had measurable (bidimensional) or evaluable disease by CT scan.

Eligibility criteria included no previous chemo- or immunotherapy for MM, performance status (ECOG) < 2, age < 75 years, normal renal, hepatic and bone marrow functions (> 3000 WBC/w/m^3, > 100 000 platelets/w/m^3) and informed consent. Histological diagnosis was confirmed in collaboration with the French Mesothelioma Registry Panel pathologists.

From the 33 patients, 2 patients refused the proposed treatment, while another was excluded from the analysis after histological review (adenocarcinoma). The 30 patients with confirmed MM treated with the combination are the subject of the present report.

Antitumoral activity was evaluated before each treatment course according to WHO criteria. All responses were independently reviewed by at least 2 observers. Complete response was defined as the disappearance of all measurable lesions for at least a month, partial response was defined as reduction of greater than 50% compared with pretreatment values in the sum of the products of perpendicular diameters in measurable lesions, lasting longer than 4 weeks. Stable disease was defined as < 50% reduction or < 25 increase in measurable/evaluable lesions for at least 12 weeks.

The treatment schedule was the same as previously reported from our first phase I–II study [1] and the only modification was the daily α-IFN dosage (6 MUI instead of 3 MUI). The treatment was CDDP 60 mg/m^2 (day 2) and α-IFN 6 MUI m^2/day (d1–d4) given s.c., weekly for 4 consecutive weeks followed by 4 weeks rest (one cycle = 8 weeks) for the first two cycles. Treatment duration was reduced to 3 weeks (one cycle = 6 weeks) for the last two cycles.

Oral paracetamol was given for α-IFN side-effects. The antiemetic regimen was kept unchanged from the previous experience. It was started immediately before the weekly CDDP infusion, and included intravenous $5HT_3$ antagonists (Ondansetron) and Lorazepam on the day of CDDP administration, followed by metoclopramide (1 mg/kg i.v. every 6 h for 24 h). Corticosteroids were added after the first course if the association $5HT_3$ antagonist–lorazepam was deemed ineffective. Delayed nausea was prevented by metoclopramide and benzodiazepines. If protracted nausea was severe, parenteral nutrition was given to prevent major weight loss.

RESULTS

Patients characteristics are listed in Table 1. There were 27 men and 3 women, and 18 of them had known asbestos exposure in their medical history. Median performance status was 1 (range 0–3), while 11 (37%) patients had recent > 5% weight loss. Five patients presented a thrombocytosis (> 400 000 platelet/m^3). All results from both our first study

Table 1. Two-cisplatin α interferon comparative studies

Patient characteristics	Previous study [1]	Present study
Number of pts	23	30
Women/men	4/19	3/27
Median age	56 (31–69)	58 (44–67)
Asbestos exposure	14 (61%)	18 (60%)
Weight loss > 5%	5 (22%)	11 (37%)
Thrombocytosis	8 (35%)	5 (17%)
Staging (UICC)		
Stage II-III-IV	9/12/2	14/15/1
Histological subtype		
Epithelial	12	17
Mixed	8	10
Fusiform	3	1
Not known	0	2
Toxicity		
Evaluable patients	23	30
Asthenia grade > 2	21 (91%)	30 (100%)
Nausea–vomiting grade III–IV	7 (30%)	16 (53%)
Median weight loss	6.2% (0–18)	6.8% (1–19.8)
Increased creatininaemia grade II		1 (3%)
Neurotoxicity grade III	2 (9%)	4 (13%)
Neutropenia grade III	5 (22%)	8 (27%)
Thrombopenia grade III	5 (22%)	8 (27%)
Thrombopenia grade IV*	0	1* (3%)
Efficacy		
Evaluable patients	22	30
Overall response	8 (36%)	8 (27%)
Complete response	0	1 (3%)
Partial response	8 (36%)	7 (23%)
Stable disease	3 (14%)	13 (43%)
Progressive disease	11 (50%)	8 (27%)
Median overall survival (months)	12 (5–32)	15 (5–32)
Survival of responders (months)	25 (9–32)	19 (7–34)
Survival of non-responders (months)	8 (5–24)	10 (4-24)

*One patient with previous chemotherapy for Hodgkin's disease.

and the present one are summarised in Table 1. While aware that sequential phase II experiences lack the comparative validity of prospectively controlled trials, we consider the intrinsic value of such exploratory experiences as clinically relevant.

Toxicity was evaluable for all patients. A total of 103 cycles were given, with a median number of cycles per patient of 2 (1–4). One patient died during the second week of the first cycle. Severe fatigue and nausea–vomiting were the limiting toxicities of this combination. Maximal toxicities per patient are reported in Table 1. Digestive intolerance was the main side-effect. Protracted nausea–vomiting was prevalent despite our intensive antiemetic treatment (anti-HT_3 + metoclopramides, benzodiazepine and corticosteroids). Fifty-three per cent of patients complained of severe (grade III–IV) nausea and vomiting, with delayed onset after the CDDP infusion (observed several days after treatment). Its intensity increased from week 1 to week 4 in each given cycle. The median weight loss while on treatment was 6.8% (1–19.8) from baseline related mainly to reduced food intake. In one case the treatment was stopped after the first cycle on account of reversible renal toxicity (grade II increasing creatininemia). The second main toxicity observed in this trial was a severe cumulative asthenia.

Four patients (13%) developed grade III peripheral neuropathy during or after the last treatment course. One patient had neurotoxicity, grade III at the moment of inclusion resulting from previous chemotherapy for Hodgkin's disease, approximately 10 years before MM diagnosis, which did not worsen during the four cycles of CDDP–α-IFN treatment—this was not considered a side-effect of the current treatment. Despite the higher dose of α-IFN, haematological toxicity was manageable. We failed to observe any episodes of grade 4 neutropenia or thrombopenia, except in the above-mentioned patient (pretreated with MOPP and radiotherapy).

Efficacy

Twenty-nine patients were evaluated for antitumoral activity. One patient was excluded from the efficacy analysis, since he died during the first treatment cycle and his early death was not clearly related to the treatment given or to disease progression.

The overall response rate was 27%, with one CR and 7 PR, all of them validated by third-party radiological reviews. The median time to treatment failure (TTP) was 7 months (5–12). As of December 1995, all patients had died of their disease, with 18 (69%) having received a second-line treatment for disease progression. With a median follow-up (March 1993–December 1995) of 17 months (5–33), median overall survival was 15 months (5–26).

DISCUSSION

The aim of the present study was to evaluate the therapeutic effect and the toxicity of increased doses of α-IFN in combination with CDDP for the treatment of MM. This association with lower doses (3 MUI) of α-interferon had been already tried with acceptable tolerance and encouraging results [1]. The limiting treatment toxicities were nausea–vomiting and cumulative severe fatigue. Grade 3–4 nausea/vomiting have been shown in several previously published phase I–II studies with the same combination [3, 4]. Acute and delayed nausea were evaluated separately in a phase I study with CDDP in protracted infusion associated with α-IFN, and the incidence of both increased with dose escalation of CDDP [3]. The same study correlated digestive intolerance to higher AUC (area under the curve) of free platinum. A phase II study with the same immunochemotherapy combination in non-small cell lung cancer has shown a similar incidence of this side-effect for the same CDDP dose levels and two different dose levels of α-IFN [5]. The severe asthenia leading to a decrease in patient performance status was another side-effect commonly found. We also observed a low incidence of peripheral neuropathy [4]. Compared to other published phase I–II studies, our haematological toxicity experience was minimal, manageable and was never a dose-limiting toxicity [6, 7]. Minor transient increase in serum creatinine was observed in many cases, but only one grade 2 and two grade 1 [3–5].

We confirm that the combined α-IFN–CDDP regimen is active in patients with advanced malignant mesothelioma. The antitumoral efficacy results of the present study are superposable with our previous experience with lower doses of interferon, be it in terms of objective response rate or in time-related natural history of disease parameters [1]. It seems clear to us that no therapeutic enhancement was obtained by the increase of the α-IFN dose. The mechanism and clinical relevance of an eventual CDDP activity potentiation by α-IFN remains unclear.

In conclusion, we do not recommend increased doses of α-IFN when used with weekly CDDP for the treatment of malignant mesothelioma. Our former experience with the same schedule [1] is our group's internal reference for comparative prospective studies in this disease.

1. Soulie P, Ruffie P, Trandafir L, *et al.* Combined systemic chemo-immunotherapy in advanced diffuse malignant mesothelioma: report of a phase I-II study of weekly cisplatin/interferon alpha 2a. *J Clin Oncol* 1996, **14**(3), 878–885.
2. Amato R, Meyers C, Ellerhorst J, *et al.* A phase I trial of intermittent high-dose α-interferon and dexamethasone in metastatic renal cell carcinoma. *Ann Oncol* 1995, **6**, 911–914.
3. Gosland MP, Goodin S, Yokel RA, Smith M, John WJ. A phase I trial of 5-day continuous infusion cisplatin and interferon α. *Cancer Chemother Pharmacol* 1995, **37**, 39–46.
4. Dhingra K, Talpaz M, Dhingra HM, *et al.* A phase I trial of recombinant alpha-2a interferon (Roferon A) with weekly cisplatinum. *Invest New Drugs* 1991, **9**, 37–39.
5. Bowman A, Fergusson RJ, Allan SG, *et al.* Potentiation of cisplatin by alpha-interferon in advanced non-small cell lung cancer (NSCLC): a phase II study. *Ann Oncol* 1990, **1**, 351–353.
6. Richner J, Joss RA, Goldhirsch A, Brunner KW. Phase II study of continuous subcutaneous interferon-alfa combined with cisplatin in advanced malignant melanoma. *Eur J Cancer* 1992, **28A**, 1044–1047.
7. Ardizzoni A, Salvato F, Rosso R, *et al.* Combination of chemotherapy and recombinant alpha-interferon in advanced non-small cell lung cancer. *Cancer* 1993, **72**, 2929–2935.

Acknowledgements—The authors thank Marie-José Ferreira for excellent secretarial assistance in preparing this paper.