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Combination of Cisplatin and Interferon-α2a (Roferon®-A) in Patients with Non-small Cell Lung Cancer (NSCLC). An Open Phase II Multicentre Study

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Preclinical and preliminary clinical data suggested a potentiation of the cytotoxic activity of cisplatin (CDDP) by interferon-α (IFN-α) in non-small cell lung cancer (NSCLC). This open, non-randomised, phase II study was set up to determine the response rate, duration of response, survival, safety and tolerability following treatment with the combination of recombinant IFN-α2a and CDDP in NSCLC. 100 previously untreated patients with unresectable, measurable or evaluable stage III/IV NSCLC were enrolled for treatment with a combination of IFN-α2a (9 MIU three times weekly) and CDDP (100 mg/m² every 28 days). Patients were stratified according to histology, i.e. squamous cell carcinoma versus non-squamous cell carcinoma. The planned maximum treatment duration was 6 months or until disease progression. Responding patients could be treated with IFN-α2a as maintenance for an additional 6 months. To be evaluable, the patients must have received at least 2 weeks of treatment with IFN-α2a and at least one dose of CDDP. There were 75% male and 25% female patients with a mean age of 59 years (range 34–74). An overall response rate of 33% (95% confidence interval (C.I.) = 23–44) was achieved among the 84 evaluable patients. There was one complete responder and 27 partial responders, while 32 patients had stable disease. The duration of partial response ranged from 3 to 12 months. The median survival was 6.4 (95% C.I. = 5.7–8) months. The response rate in patients with stage IIIa disease (45%) was significantly higher ($P = 0.047$) than in patients with stage IV disease (22%). The median survival in patients with stage IIIa disease (9.3 months) was significantly longer ($P = 0.025$) than patients with either stage IIIb (6.3 months) or stage IV disease (6.2 months). The major forms of toxicity were gastrointestinal and constitutional symptoms of mild to moderate severity. The main severe adverse events (WHO grade 3–4) were nausea and vomiting (32%), anorexia (16%) and fever (11%). The most frequent severe haematological toxicities (WHO grade 3–4) were neutropenia (27%), anaemia (18%) and thrombocytopenia (10%). 13 patients experienced WHO grade 3–4 renal toxicity. This study confirms the antitumour activity of the combination of IFN-α2a and CDDP in NSCLC. Further study of this combination is warranted.

Key words: interferon-α2a, cisplatin, non-small cell lung cancer, phase II
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INTRODUCTION

NON-SMALL cell lung cancer (NSCLC) is the leading cause of death from malignant diseases in the Western world, and the available therapeutic options for patients with advanced disease are limited. Disease palliation is usually obtained by combination chemotherapy [1]. The most active single agent so far identified is cisplatin (CDDP).

In 1986, Carmichael and colleagues [2] demonstrated that interferon-α (IFN-α) potentiated the activity of CDDP *in vitro* and *in vivo* against NSCLC. This observation led to clinical studies with combination chemotherapy in NSCLC patients. The first published study by Smyth and associates [3], in 33 previously untreated but inoperable NSCLC patients, reported a 21% response rate in 28 evaluable patients. A higher response rate was seen in patients with squamous cell carcinoma (SCC) (5/12, 42%) than in non-SCC (1/16, 6%). The dosage regimen used was 3 MIU IFN-α three times weekly subcutaneously, in combination with 100 mg/m² CDDP intravenously on day 8 repeated every 4 weeks. Haematological, renal and neurological toxicities were predictable and non-significant. In the follow-up phase II study by the same author [3], using an increased dose of IFN-α (5 MIU) and CDDP (100 mg/m²) on day 1 repeated every 3 weeks, a preliminary report on 6 evaluable patients showed a partial response (PR) in 3 patients.

In a study of patients with various solid tumours, Martinelli and colleagues [4] demonstrated that IFN-α2 can be given three times a week at a dose of 5 MIU/m² in combination with a 5-day infusion of CDDP (20 mg/m²/day). Neutropenia was the most troublesome side-effect following the 5-day CDDP infusion. However, there were no responses among the 3 NSCLC patients in this study. In a further phase I study by Walsh and colleagues [5], in 26 patients with various advanced refractory solid tumours (including 8 NSCLC patients), it was shown that IFN-α2b, given at a dose of 5 MIU/m² three times weekly, with

weekly CDDP in escalating doses (5–30 mg/m^2) for 3 weeks, followed by 2 weeks rest, could be repeated up to five times with only mild haematological toxicities. Malaise and fatigue were the only dose-limiting toxicities leading to a decrease in performance status. There was no response among the 8 NSCLC patients.

On the basis of the preclinical findings of Carmichael and colleagues [2] and the encouraging preliminary clinical results of Smyth and associates [3] and the other authors, a multicentre, open, non-comparative study, to assess the efficacy and safety profile of the combination of CDDP and IFN-α2a in advanced previously untreated NSCLC patients, was performed.

PATIENTS AND METHODS

Eligibility criteria

Patients who were 18–75 years of age with unresectable, histologically confirmed stage III or IV non-small cell carcinoma of the lung, which had not been previously treated systemically, were included in the study. Patients had to have at least one measurable or evaluable lesion. Patients were stratified according to histology, with an accrual of at least 25 evaluable patients in each histological group of SCC and non-SCC which included adenocarcinoma or large cell undifferentiated carcinoma of the lung. Patients were expected to have a Karnofsky performance status [6] (KPS) $\geq$ 60 and a life expectancy of more than 3 months. Patients were also required to have a good haematological status (total white blood cell count $\geq 4.0 \times 10^9$/l, granulocytes $\geq 2.0 \times 10^9$/l, platelets $\geq 100 \times 10^9$/l, haemoglobin $\geq$ 9.5 g/dl), and to have normal renal function (serum creatinine $\leq$ 120 μmol/l, creatinine clearance $\geq$ 65 ml/min) and hepatic function (serum bilirubin $\leq$ 35 μmol/l, and aspartate aminotransferase, alanine aminotransferase and alkaline phosphatase $\leq$ 1.25 times the upper laboratory range).

Patients were excluded if they had symptoms or signs of central nervous system or leptomeningeal metastases or signs of cardiovascular involvement by tumour. Patients were also excluded if they had congestive cardiac failure, angina, myocardial infarction or arrhythmia which was not responsive to conventional therapy, uncontrolled hypertension by anti-hypertensive drugs, uncontrolled infection or an additional malignancy (other than basal cell carcinoma of the skin and cervical intra-epithelial neoplasia grade III).

Informed consent was obtained from all patients prior to commencing treatment, and the study was approved by the Ethics Committees of the 12 participating institutions.

Drug therapy

IFN-α2a (Roferon®-A, F. Hoffmann La-Roche, Basel, Switzerland) was administered subcutaneously or intramuscularly at a dose of 9 MIU given three times a week. CDDP was administered intravenously at a dose of 100 mg/m^2 (maximum dose, 200 mg) given every 28 days, starting 8 days after the first IFN dose. The CDDP treatment was repeated with a maximum of six cycles. Treatment was either reduced or halted if either haematological, renal toxicities, peripheral neuropathy or any other WHO grade 4 toxicity occurred during the study, and resumed at full or reduced dose if recovery was less than 2 weeks. Treatment was stopped if progressive disease was observed. Responding patients were allowed maintenance therapy with IFN-α2a alone for 6 months after completing the CDDP therapy.

Prophylactic anti-emetics were administered according to standard schedules for each participating centre, and concomitant radiotherapy was allowed for bone pain, provided the irradiated lesion was not an indicator lesion. Additional antineoplastic agents, including agents which modulate the endocrine and/or immunological response to cancer or steroid therapy, except as anti-emetics, were not permitted.

Response criteria

Response to treatment was assessed according to standard criteria [7–9]. X-rays and/or CT scans were taken at baseline and every 4 weeks. Radiological investigations from all patients showing objective responses were reviewed independently by the investigators and the sponsor. When there was a difference in opinion, the films were referred to a panel comprising expert radiologists and oncologists, who were not involved in the treatment of the patients. The final assessment was agreed upon with the principal investigator. Patients who did not receive at least 2 weeks of treatment with IFN-α2a and at least one dose of CDDP were not considered evaluable for response, but were included in the "intent-to-treat" analysis as treatment failures. The frequency of responders and the 95% confidence interval (95% C.I.), defined by the Pearson-Clopper limit, were calculated. The survival of the patients was analysed using the Kaplan–Meier method [10]. Subgroup analyses of differences in proportion of responders were performed with the χ^2 test. The effect of prognostic factors on survival was analysed with the Cox regression method.

The TNM classification of lung cancer [11] was used for baseline assessment of the disease status of the patients. Body weight measurements and assessments of KPS [6] were made at baseline and before each cycle of treatment with CDDP.

Toxicity criteria

Adverse events (AE) were recorded and graded according to the WHO criteria [9]. Audiograms were performed in all patients who reported subjective ototoxicity.

Blood samples for routine haematology and biochemistry were collected at baseline and at regular intervals during the study to record haematological nadirs. Creatinine clearance was either measured directly or calculated using the Cockroft and Gault formula [12]. Additional blood samples were drawn prior to treatment and at monthly intervals for determination of IFN-α2a antibodies using an enzyme immunoassay (ELISA) procedure [13] in the screening for binding antibodies and an anti-viral biological assay for the determination of neutralising antibodies [14].

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RESULTS

Study population

From May 1989 to January 1991 (20 months), a total of 100 patients with locally advanced NSCLC entered the study from 12 centres worldwide. There were 75 males and 25 females. The median age was 59 years (range 34–74) and the median KPS was 80 (range 60–100). There were 45 patients with SCC and 55 with non-SCC. The non-SCC group consisted of 44 adenocarcinomas and 11 large cell carcinomas. One patient had stage I disease, while 20 had stage IIIa, 12 had stage IIIb and 67 had stage IV disease.

Of the 100 patients in the intent-to-treat analysis, 16 patients were considered not evaluable for response (7 patients received less than 2 weeks of IFN-α2a treatment and/or no CDDP, 6 patients had no postbaseline tumour asssessment for comparison, 1 patient had irradiation to the primary tumour, another had pneumothorax and 1 had stage I disease). There were no differences in the demographic data between the 100 patients in the intent-to-treat analysis and the 84 evaluable patients (Table 1).

23 patients completed the scheduled treatment of 24 weeks of IFN-α2a and six doses of CDDP. 77 patients left the study before completing the scheduled treatment (26 due to adverse events, 27 due to progressive disease, 7 refused further treatment, 6 for multiple reasons and 11 died before completing the scheduled treatment). 10 of the 23 patients who completed the scheduled treatment also received maintenance therapy. 2 patients completed the 6 months maintenance therapy, while 8 patients withdrew (4 due to adverse events and 4 due to progressive disease).

Treatment schedules

Dose reduction in IFN-α2a and CDDP (for toxicity) occurred in 29 and 24% of the patients, respectively, while dose delay (for any reason) occurred in 27 and 18% of the patients, respectively.

Table 1. Comparison of patients' characteristics

	All patients (n = 100)	Evaluable patients (n = 84)
Sex (male/female)	75/25	62/22
Age (years)		
Median (range)	59 (34–74)	58.5 (34–74)
Weight (kg)		
Median (range)	64.9 (36–110)	64.7 (36–110)
Height (cm)		
Median (range)	170 (143–188)	170 (143–188)
Body surface (m^2)		
Median (range)	1.73 (1.24–2.32)	1.74 (1.24–2.32)
Race		
Caucasian	89	73
Oriental	9	9
Black	2	2
Stage of disease		
I	1 (1%)	0 (0%)
IIIa	20 (20%)	19 (23%)
IIIb	12 (12%)	10 (12%)
IV	67 (67%)	55 (65%)
Histology		
Squamous cell carcinoma	45 (45%)	38 (45%)
Adenocarcinoma	44 (44%)	35 (42%)
Large cell	11 (11%)	11 (13%)

Table 2. Response evaluations

Responses	All patients (n = 100)	Evaluable patients (n = 84)
Complete response (CR)	1	1 (1%)
Partial response (PR)	27	27 (32%)
No change (NC)	32	32 (38%)
Progressive disease (PD)	26	24 (29%)
Non-assessable (NA)	14	0 (0%)
Overall response, % (95% C.I.)	28 (19–38)	33 (23–44)

A reduction in both IFN-α2a and CDDP doses occurred in 15% patients, while 10% patients had a delay in treatment with both drugs.

Response to therapy

The efficacy evaluation is summarised in Table 2. There was an overall response rate of 33% among the 84 evaluable patients. Table 3 summarises the responses in different stages of the disease and the two histological subtypes. There was a significantly higher (P = 0.047) overall response rate with stage IIIa patients (45%) compared with stage IV patients (22%).

However, there was no significant difference (P = 0.86) in overall response rates between patients with SCC (29%) and non-SCC patients (27%).

Duration of response and survival

The onset of PR was usually observed after 1–2 months treatment. The duration of response ranged from 3 to 12 months. Since progressive disease (PD) was reported for only 7 of the 27 PRs, a reliable median duration of response could not be calculated.

A survival analysis was performed approximately 10 months after the last patient completed the maintenance treatment. At that point, 9 patients were still alive. A summary of the survival data is presented in Table 4 and the Kaplan–Meier [10] survival plots are as shown in Figure 1 (for all patients) and Figure 2 (by stage of disease). The overall median survival was 6.4 months. The median survival in patients with stage IIIa disease was significantly longer (P = 0.025) than in patients with either stage IIIb or stage IV disease whereas age, sex and histological differences did not affect survival.

Performance status

After 2 months of treatment, a performance status assessment (changes in weight and KPS) was carried out. A weight loss of greater than 10% occurred in 17/57 patients, i.e. 30% of cases where weight was recorded. In responders, a weight loss of greater than 10% in weight was limited to 2 of the 28 (7%) patients. A decrease in KPS of more than 20 units occurred in 11/55 patients i.e. 20% of cases where KPS was recorded. In responders, only 2 patients had a decrease in KPS of more than 20 units.

Toxicity

Clinical AEs occurred in nearly all patients. The most common AEs, which occurred in 10% or more patients are summarised in Table 5, only the worst incidence of each event being reported. Most patients suffered more than one AE on more than one occasion. The majority of these events were mild to moderate

Table 3. Response to therapy according to stage and histological subtypes

	Response				
	CR	PR	NC	PD	NA
Stage					
I (n=1)	0	0	0	0	1
IIIa (n=20)[a]	1 (5%)	8 (40%)	4 (20%)	6 (30%)	1 (5%)
IIIb (n=12)[b]	0 (0%)	4 (33%)	3 (25%)	3 (25%)	2 (17%)
IV (n=67)[c]	0 (0%)	15 (22%)	25 (37%)	17 (25%)	10 (15%)
Histology					
Squamous (n=45)[d]	1 (2%)	12 (27%)	12 (27%)	13 (29%)	7 (15%)
Non-squamous (n=55)[e]	0 (0%)	15 (27%)	20 (36%)	13 (24%)	7 (13%)

χ^2 test: a vs. b+c; P = 0.063 (CR + PR). a vs. c; P = 0.047 (CR + PR). d vs. e; P = 0.86 (CR + PR). See Table 2 for abbreviations.

Table 4. Median survival according to stage and histological subtypes

	Median survival (months)*	95% C.I.
Stage of disease		
I (n=1)	—	—
IIIa (n=20)[a]	9.3	5.4–16.5
IIIb (n=12)[b]	6.3	4.1– 8.5
IV (n=67)[c]	6.2	5.1– 7.2
Histology		
Squamous (n=45)[d]	7.3	5.7–12.8
Non-squamous (n=55)[e]	6.2	4.1– 7.6
All patients (n=100)	6.4	5.7– 8.0

*Time from start of therapy: a vs. b+c; P = 0.025. d vs. e; $P > 0.05$.

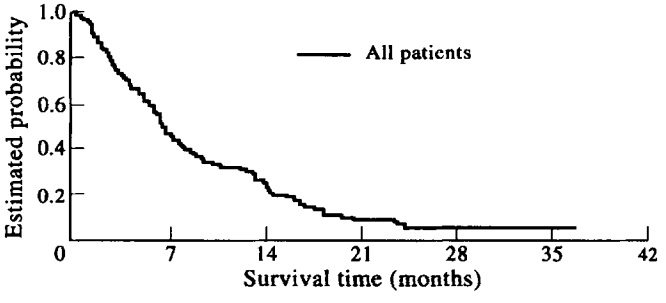

Figure 1. Survival curves on all patients.

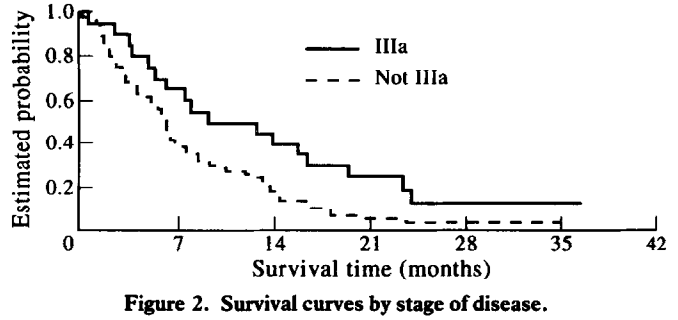

Figure 2. Survival curves by stage of disease.

(WHO grade 1/2), but in 18 cases the severity was rated as serious (WHO grade 4). Apart from the 6 cases reported in Table 5, there were 2 cases of pneumonia and 1 case each of the following: cardiovascular attack, oesophagus obstruction, pancytopenia, electrolyte abnormality, hypokalaemia, dyspnoea, haemoptysis, pulmonary oedema, and 1 of acute and 1 of chronic renal failure.

The most common haematological toxicities were anaemia, leucopenia and thrombocytopenia (Table 6). There was a clear trend for a decrease in the values of laboratory parameters during therapy, but in most cases these parameters returned to their baseline values after the end of therapy. Blood transfusions were given to 41 patients, which included transfusion of platelets to 5 patients. 7 patients terminated the study due to grade 3–4 haematological toxicity. In 3 cases, this was the primary reason for withdrawal while in the other 4 cases, this was one of multiple AEs causing termination of treatment.

Renal toxicities, as measured by serum creatinine or creatinine clearance, were mostly less than grade 3 (Table 6). 10 patients were withdrawn from the study due to renal toxicity, 5 solely due to renal toxicity while the other 5 were due to multiple AEs which included renal toxicity. Excluding patients with liver metastases, 1 patient experienced WHO grade 4 liver toxicity (alkaline phosphatase) during treatment.

Table 5. Main clinical events (occurred in ≥ 10% patients)

	No. of patients	Severity (WHO grades)			
		1	2	3	4
Nausea/vomiting	90	10	48	29	3
Fever	57	13	33	10	1
Anorexia	46	9	21	14	2
Fatigue	24	5	13	6	0
Diarrhoea	22	10	6	6	0
Chills	16	9	5	2	0
Constipation	15	11	4	0	0
Weight loss	14	0	9	5	0
Headache	11	7	3	1	0
Asthenia	10	0	3	7	0
Myalgia	10	6	2	2	0
Depression	10	5	4	1	0

Table 6. Haematological, renal and liver toxicities during treatment

	No. of patients	Severity (WHO grades) 0	1	2	3	4
Haematology						
Haemoglobin	96	24	24	31	15	2
Leucocytes	96	27	28	27	12	2
Neutrophils	93	35	9	23	21	5
Platelets	96	57	16	13	7	3
Renal						
Serum creatinine	96	63	28	3	2	0
Creatinine clearance	95	50	15	17	8	5
Liver						
Alkaline phosphatase	93	52	31	8	1	1
ALAT	81	54	22	4	1	0
ASAT	86	68	10	4	4	0
Bilirubin	93	89	4	0	0	0

ALAT, aspartate aminotransferase; ASAT, alanine aminotransferase.

Anti-IFN antibody

Neutralising antibodies to IFN-α2a were detected in 11 of 94 patients screened for antibody levels. 3 of these positive patients were responders (1 complete responder (CR) and 2 PRs). The small number of patients who developed neutralising antibodies did not allow any correlation to be made between the antibody titres and response.

DISCUSSION

Several phase I/II and phase II studies recently published have suggested that the combination of CDDP and IFN-α is active in treating patients with advanced NSCLC [15–19]. A summary of the studies performed by Smyth's group [3] was reported by Bowman and colleagues [15]. An overall response rate of 30% in 60 evaluable patients was reported in this open phase II study, using IFN-α2b (3–5 MIU) and CDDP (100 mg/m^2). Although, as with the present study, they could find no difference in response rate between limited and extensive disease, they found that the response rate in patients with SCC (11/24, 46%) was greater than in non-SCC patients (7/36, 19%). However, other authors reported a less favourable response rate with a similar treatment regimen. For example, Rosell and associates [16], in a phase II study in 30 patients with mostly advanced stage IV disease, using IFN-α2b (5 MIU) and CDDP (2 × 50 mg/m^2, on days 1 and 8), reported a response in only 4 (13%) patients (1 CR and 3 PRs), 3 of whom were SCC and 1 was non-SCC. In another phase II study, in a mixed group of patients which included 11 patients with NSCLC, Silverman and colleagues [17] obtained a response in only 1 patient. These authors adminstered IFN-α2b (5 MIU/m^2) concomitantly with CDDP (20 mg/m^2) in 4-day cycles. It is of interest that their only responding patient achieved a CR.

Unlike most of the reported phase II studies, the present study was a multicentre international study which is more representative of the type of situation found in phase III studies. Thus, population bias due to centre effects may be balanced out, to some extent. It might, therefore, be expected that a lower response rate than is usually seen in single centre phase II studies would be achieved. However, when all these results are summarised (Table 7), there appears to be no major difference in response rate between the present study and those published earlier, the calculated 95% C.I. overlapping each other.

The optimal dose and schedule of this combination remains unclear and the magnitude of their possible potentiation can only be achieved by a randomised study against CDDP alone. However, based on what is known about the activity of single-agent cisplatin in NSCLC [18], the combination appears to be superior in terms of response rate. In addition, the median survival in patients with stage IIIa disease compared favourably with treatment using radiotherapy alone [19], although patients wth stage IIIa disease tend to have an inherently better survival than patients with stage IIIb and stage IV diseases [11].

In terms of the amount of CDDP and IFN, calculated on a weekly basis, that can be delivered with acceptable toxicity, doses of 25–30 mg/m^2/week of CDDP combined with 3–5 MIU/m^2 IFN-α2 (a or b) three times weekly have been recommended for phase II studies [20, 21]. The toxicity of the combination, according to our data as well as the published data, is manageable, with the previously known spectrum of toxicity of the two drugs clearly defined. The typical side-effects specifically associated with each drug do not appear to be potentiated with the combined use of CDDP and IFN-α2a.

Few authors have combined CDDP and IFN with other cytotoxics in the treatment of NSCLC. Rosso and the Italian Collaborative Oncological Group for Lung Cancer (FONICAP) performed a phase II study with a platinum-containing regimen plus IFN-α2 [22]. They used cyclophosphamide 400 mg/m^2, epidoxorubicin 50 mg/m^2 and CDDP 40 mg/m^2 plus IFN-α2b (5 MIU three times weekly), and showed a 19% overall response rate in 32 eligible patients. Following this, they tested the same chemotherapeutic regimen with or without IFN-α2b, in a larger phase III trial [23], showing an advantage in response rate for the IFN arm (22 versus 11%), but no difference in survival, with a slightly worse toxicity profile for the IFN combination arm. Some authors have tried even more complex combinations with cytotoxics and cytokines. Mattson and associates [24] performed a randomised phase II trial consisting of three treatment arms: arm I, CDDP (60 mg/m^2) and VP16 (100 mg/

Table 7. Response rates in published studies using CDDP and IFN-α in NSCLC

Reference	Total evaluable patients	No. of responders	Response rate (%)	95% C.I.
Smyth *et al.*, 1988 [3]	28	6	21	11–52
Bowman *et al.*, 1990 [15]	60	18	30	19–43
Rosell *et al.*, 1991 [16]	30	4	13	4–31
Silverman *et al.*, 1991 [17]	11	1	9	0–41
Valone *et al.*, 1992 [21]	7	2	29	4–71
Present paper, 1995	84	28	33	23–44
Total	220	59	27	21–33

m^2) arm II, chemotherapy plus IFN-γ (0.2 mg/m^2); arm III, chemotherapy plus IFN-γ plus IFN-α (6 MIU). Their preliminary report in 32 patients shows no difference in response rate between the three arms: 4 PR/13 in arm I; 3 PR/12 in arm II; 2 PR/7 in arm III, but the sample size was too small to detect any significant difference.

In conclusion, our data support the concept of IFN-α2a as a potentiator of the activity of CDDP in NSCLC. The toxicity of the combination is manageable, although most of the patients suffered from AEs that were related to either drug. This regimen should be considered for further clinical testing either in combination with radiotherapy in patients with limited disease or with either mitomycin [18] or etoposide [25] in patients with disseminated disease.

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