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Short Communication

Sequential Chemoimmunotherapy for Advanced Non-small Cell Lung Cancer Using Cisplatin, Etoposide, Thymosin-α1 and Interferon-α2a

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A phase II study was performed to evaluate the clinical and immunological effects of a regimen of cisplatin (DDP) and etoposide (VP-16) combined with thymosin-α1 (TA1) and low-dose interferon-α2a (IFN) in the treatment of patients with advanced non-small cell lung cancer (NSCLC). Chemoimmunotherapy cycles were repeated every 3 weeks. There were 24 responses (two complete, 22 partial) among 56 assessable patients. Median survival was 12.6 months. Overall, treatment was well tolerated. Natural killer cell activity and lymphocyte subtypes were depressed by chemotherapy, but this effect was less prominent in patients receiving TA1 and IFN in comparison with a concomitant group of patients treated with DDP and VP-16 only. The combination of DDP and VP-16 and TA1 and IFN is effective in advanced NSCLC with acceptable toxicity. However, the results of this study need to be confirmed in a randomised trial.

Key words: thymosin-α1, chemotherapy, NSCLC, interferon-α2a
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INTRODUCTION

CISPLATIN-CONTAINING COMBINATIONS have been the most commonly used regimens in advanced non-small cell lung cancer (NSCLC), but response rates average only 30% and their impact on patient survival is far from being firmly established. Numerous attempts to improve upon these results have generally been inconclusive [1].

Biological response modifiers (BRM) have received little attention in NSCLC. Interferons (IFN) are known to stimulate natural killer (NK) cell activity, and patients with lung cancer have been reported to have diminished NK activity [2]. Although these agents did not effectively improve the outcome of patients with this disease, they were generally used at doses higher than those required to elicit a beneficial immunomodulatory effect. High doses of IFN were reported to be immunodepressive [3], whereas low doses were found to increase the cytotoxicity of cisplatin (DDP) and ifosfamide in human NSCLC xenografts [4].

In recent years, there has been an increasing body of evidence suggesting that thymic hormones may induce a great variety of biological effects, including stimulation of NK activity [5]. Therefore, it was reasonable to hypothesise a co-operation between these agents and IFN. Support for this hypothesis came from a series of experiments in which thymosin-α1 (TA1), a synthetic polypeptide of thymic origin [6], and low-dose IFN, singly or in combination with cytotoxic agents, were injected into normal and immunosuppressed mice [7], resulting in a high percentage of cure in mice bearing Lewis lung carcinoma receiving combined treatment [8].

This phase II study was undertaken in order to verify whether TA1 and low-dose IFNα could potentiate the activity of cytotoxic chemotherapy in the treatment of patients with advanced NSCLC.

PATIENTS AND METHODS

Eligible patients were required to have a histologically or cytologically confirmed diagnosis of advanced NSCLC, measurable or evaluable lesions, age ≤75 years, WHO performance status (PS) ≤2, no evidence of brain metastases, and good renal, hepatic and haematological functions. Patients previously treated with chemotherapy were excluded, as were those with a history of active cardiac disease. All patients provided informed consent.

Chemotherapy consisted of DDP 100 mg/m^2 administered on day 1 as a 2 h intravenous (i.v.) infusion with fluid loading,

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etoposide (VP-16) 120 mg/m^2 i.v. on days 1–3, TA1 1 mg subcutaneously (s.c.) on days 8–11 and 15–18, and recombinant IFN-α2a 3 MU s.c. on days 11 and 18, 1 h after the injection of TA1. TA1 was kindly provided by Sclavo (Siena, Italy) in lyophilised vials containing 2 mg/vial.

No specific anti-emetic treatment was recommended in the protocol. Courses were repeated every 3 weeks, according to haematological and renal status. Tumour response was assessed after two courses. If there was disease progression, treatment was discontinued. Patients with stable disease or objective response were given a maximum of six courses or until progression or major toxicity.

Lymphocyte phenotype (CD4, CD8) was examined on fresh samples, obtained on days 1, 4, 8, 12, 15 and 19 of each course, by FACS analysis, using commercially available monoclonal antibodies (Becton Dickinson, Mountain View, U.S.A.). NK activity was determined as reported elsewhere [7].

Response and toxicity were evaluated according to WHO criteria [9]. Survival from the first day of treatment to death was calculated by the method of Kaplan and Meier.

RESULTS

60 patients (Table 1) were entered into the study, and 4 were considered not evaluable for response (lost to follow-up, 1; treatment refusal, 2; excessive toxicity, 1). All patients were assessable for toxicity. The average total follow-up was 21 months.

Among the 56 patients evaluable for response, 2 had a complete response (CR) and 22 a partial response (PR) for an overall response rate of 43% (95% confidence interval, 30–56%). No statistical difference in response rate was found with regard to the stage of disease (stage III versus stage IV), the clinical evaluability of the disease (measurable versus evaluable), performance status (0–1 versus 2), or cell type (squamous cell carcinoma versus adenocarcinoma). 24 (43%) patients experienced stable disease. The median progression-free survival was 7.9 months (range 3–29) in responding patients, and 6.6 months (range 3–16) in patients with stable disease. Median survival of patients was 12.6 months, 15.7 months in responding and 10 months in non-responding patients ($P = 0.05$).

Table 1. Patients' characteristics

Entered/evaluable	60/56
Male/female	54/6
Median age, years (range)	60 (36–75)
Performance status (WHO)	
0	4
1	50
2	6
Weight loss	
<10%	53
⩾10%	7
Histology	
Squamous cell carcinoma	26
Adenocarcinoma	20
Other non-small cell	14
Stage	
III A	6
III B	27
IV	27
Prior treatment	
None	46
Prior surgery	12
Prior irradiation	5

The WHO grade toxic effects and the number are reported in Table 2. Myelosuppression, the most commonly observed toxicity, was substantial, with grade 3–4 leucopenia encountered in 37% of the patients. Most patients experienced grade 2–3 nausea and vomiting. Serum creatinine elevation was recorded in 32% of the patients, but it was transient. Apart from moderate fever and minimal flu-like symptoms, no other toxic reactions were related to IFN administration. No toxic effects could be related to the use of TA1.

Overall, the treatment was reasonably well tolerated. Dosage of chemotherapy was reduced in 8 patients (13%); courses were postponed by 1 week in 5 patients.

NK activity and lymphocyte subtypes were evaluated in 20 patients who received combined treatment, and were compared with those observed in a concomitant group of 7 patients treated with DDP and VP-16 alone.

NK activity was depressed by chemotherapy in both groups. However, while this effect persisted for several days in the chemotherapy group, recovery was significantly shortened in the chemoimmunotherapy group. Furthermore, this latter group benefited from an increase in NK activity from basal values. In both groups, NK activity reached basal values by day 21. CD4 and CD8 cells were also depressed by chemotherapy. Values decreased until day 19 in the chemotherapy group, whereas in the chemoimmunotherapy group there was an increase in CD4 cells concomitantly with the administration of TA1 and IFN, complete recovery being observed by day 15.

DISCUSSION

The overall response rate in 56 assessable patients with NSCLC treated in this study is at least comparable with, if not better than that observed in several randomised and non-randomised trials using a combination of DDP and VP-16. Three randomised trials tested VP-16 with DDP administered at a dose of 100 mg/m^2 [10–12]. The pooled response rate was 21% and median survival ranged from 5.3 to 7.0 months. Median survival in our trial was 12.6 months. In this regard, it is of interest that 43% of our patients benefited from a long-lasting stable disease. This may suggest that BRM may result in a longer survival even in patients achieving less than an objective response.

The toxicity patterns observed in this study were similar to

Table 2. Treatment toxicity in 60 patients

	No. of patients with toxic effects of WHO grade			
Toxic effect	1	2	3	4
Nausea and vomiting	5	37	16	0
Mucositis	3	1	0	0
Alopecia	0	10	49	0
Leucopenia	11	13	15	7
Thrombocytopenia	13	3	4	3
Anaemia	22	20	6	0
Creatinine	12	3	3	1
Transaminases	5	0	1	0
Peripheral neuropathy	7	1	0	0

those reported by other investigators using DDP and VP-16 or low-dose IFN. Tolerance was not a major problem. Although NK activity was depressed by chemotherapy, this effect persisted longer in patients given chemotherapy only in comparison with those receiving combined treatment. A similar pattern was observed for absolute numbers of CD4 and CD8 cells. This immunoenhancing effect of TA1 and low doses of IFN is consistent with previous reports demonstrating a regulatory role of TA1 in several immune responses [7, 8, 13]. The effectiveness of this combination therapy in these experimental studies was the result of the stimulating action on cytotoxic cells and the high level of tumour infiltrating lymphocytes associated with the treatment, probably due to the chemotherapy-related release of chemotactic or stimulating molecules at the tumour level. In colorectal cancer patients [14], combined treatment with low doses of IFN and 5-fluorouracil (5-FU) produced a short-term increase of NK activity and antagonised the inhibitory effect observed with 5-FU alone on CD8 cells. It is conceivable that TA1 and low-dose IFN may potentiate the activity of antiproliferative drugs. This potentiating effect was not observed when higher doses of IFN alone were added to chemotherapy. In several trials of chemoimmunotherapy in advanced NSCLC, response rates were low when IFN was added to cisplatin-containing regimens [15].

In conclusion, the results of this study indicate that TA1 and low-dose IFN may increase the response to DDP and VP-16 and survival in NSCLC patients. Nevertheless, although promising, these results warrant further evaluation in a prospective randomised trial of DDP and VP-16 with or without TA1 and IFN. This study is now in progress.

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