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MICE: a New Active Combination for Non-small Cell Lung Cancer

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We have treated 38 patients with stage III/IV non-small cell lung cancer with the following regimen: mitomycin-C = 6 mg/m², ifosfamide = 3 g/m², cisplatin = 75 mg/m², vindesine = 3 mg/m² (MICE), intravenously (i.v.) on day 1, every 3 weeks. Among 26 patients with stage IV disease, 15 obtained a partial remission (PR) (response rate = 57%, 95% confidence interval = 38–76), with a median time to disease progression and a median survival of 4.9 and 7.1 months, respectively. 6 out 7 patients with stage IIIA disease were documented as PR and 5 of them underwent radical surgery with two pathologically confirmed complete remissions. Overall toxicity was substantial but manageable: 3 patients had grade III/IV leucopenia (although 5 patients had neutropenic fever) whereas 13 patients experienced grade II/III anaemia. In conclusion we believe that MICE regimen is an interesting combination and warrants further evaluations both for palliation and in a neoadjuvant setting.
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INTRODUCTION

THE HIGH incidence, the elevated mortality rate and the low curability of non-small cell lung cancer (NSCLC) represent a frustrating challenge for the oncologist.

A number of cytotoxic drugs have been studied alone or in combination to improve the results, but at present the response rate for this tumour ranges between 5 and 50% and median survival approximates 20–30 weeks in stage IV patients [1].

In an attempt to contribute to this challenge, we began a phase II study using the four most active drugs in NSCLC: mitomycin C, ifosfamide, cisplatin and vindesine (MICE) [2]. We based our experience on the Cullen's MIC regimen [3] by increasing the cisplatin dose and adding vindesine.

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PATIENTS AND METHODS

Patients

Between September 1989 and January 1992, 38 consecutive patients (36 males, 2 females) with advanced histologically proven NSCLC entered into the study according to the following elegibility criteria: performance status (ECOG) 0–3; age less than 70 years; histologically confirmed NSCLC; measurable disease; no prior chemotherapy; total white blood cell count $> 4000/mm^3$; platelet count $> 100000/mm^3$; bilirubin < 1.5 mg/dl; creatinine < 1.2 mg/dl; oral informed consent. 15 patients had adenocarcinomas, 21 squamous cell carcinomas, 2 large cell carcinomas. 5 patients had been previously resected for primary tumour and then they relapsed before entering into this study. All patients were chemo-naive. There were 26 stage IV, 7 stage III A and 5 stage III B patients. Sites of disease

included lung (33 patients), pleura (4 patients), nodes (19 patients), bone (12 patients), other sites (4 patients). The mean age was 55.5 years (range 34–70). Performance status (ECOG) ranged between 0 and 3: 6 patients = 0; 22 patients = 1; 8 patients = 2; 2 patients = 3. 13 patients had a weight loss > 5% before starting chemotherapy (Table 1). Staging investigations were performed as follows at start of treatment and every two to three cycles: physical examination; blood chemistry (using SMAC 12); routine chest roentgenography and/or whole lung computed tomography; fiberoptic bronchoscopy; computed tomography scan of the brain and abdomen; bone scintigraphy. A chest roentgenography was performed after each cycle if thoracic disease was present.

Treatment

Our combination consisted of mitomycin C = 6 mg/m^2 intravenously (i.v.); ifosfamide 3 g/m^2 i.v. with mesna 1000/mg/m^2 i.v. simultaneously, 500 mg/m^2 after 4 h and then 1000 mg/m^2 orally after 8 h; cisplatin 75 mg/m^2 i.v.; vindesine 3 mg/m^2 i.v., on day 1 (schedule is reported in Table 2). Each cycle was repeated after 21 days for a maximum number of six treatment courses. No dose reduction was allowed. In case of white blood cells (WBC) < 4000/mm^3 and/or platelets (PLT) < 100 000/mm^3 therapy was delayed by 1 week. Radiotherapy on bone metastasis was allowed if necessary. This regimen was given on an outpatient basis. Response to treatment and toxicity were evaluated according to WHO criteria [13].

RESULTS

All 38 patients entered into the study were evaluable for response and toxicity. 36 patients received a median of four cycles (range two to six), in 2 patients treatment was discontinued after one cycle because of early progressive disease.

In stage III A, 1 patient had stable disease, 6 experienced partial response (PR) and 5 were taken to surgery, of these 2 were pathologically confirmed complete responses (CR) (both squamous cell carcinomas). In stage III B, 2 patients were PR, 2 no change (NC) and 1 progressive disease (PD). Finally, in stage IV 15 patients were documented as PR, 5 as NC and 6 as PD (response rate = 57%, 95% confidence interval = 38–76). In stage III A patients, time to disease progression and overall survival were 20.2 months (range 2– 32+) and 21 months (range 3–32+) (5 surgically treated patients) respectively, in stage III B 8.4 months (range 0–23) and 11.6 months (range 2–28 +), in stage IV 4.9 months (range 0–20) and 7.1 months (range 1–25 +) (Table 3). The mean time of duration of PR in stage IV patients was 7.1 months (range 2–20). Weight gain (> 5%) was experienced by 6 responder patients and an improvement in performance status by 17 responders.

Responses according to histological type were: 7 PR, 5 NC and 3 PD in adenocarcinoma; 14 PR, 4 NC and 3 PD in squamous cell; 1 PR and 1 PD in large cell.

Toxicity

168 cycles were administered totally. Main toxicity was myelosuppression, with 1 case of grade 4 leucopenia and 2 of grade 3

Table 1. Patients' characteristics

Entered / evaluable	38 / 38
Performance status	
0	6
1	22
2	8
3	2
Weight loss > 5%	13
Mean age	55.5 years (range 34–70)
Sex (M / F)	36/2
Histology	
Adenocarcinoma	15
Squamous cell	21
Large cell	2
Stage	
III A	7
III B	5
IV	26
Sites of disease	
Lung	33
Liver	1
Bone	12
Nodes	19
Adrenal gland	3
Pleura	4

M, male; F, female.

Table 2. Schedule

8.30 a.m.	Metoclopramide 1.5 mg/kg i.v. in 100 ml 0.9% saline over 30 min.
9.00 a.m.	Dexamethasone 20 mg i.v. in 100 ml 0.9% saline over 15 min.
9.15 a.m.	Mitomycin C 6 mg/m^2 i.v. bolus.
9.30 a.m.	Ifosfamide 3 g/m^2 i.v. in 1000 ml 0.9% saline + mesna 1 g/m^2 over 60 min.
10.30 a.m.	Furosemide 20 mg i.v. bolus then 1000 ml 0.9% saline + 20 mEq KCl + cisplatin 75 mg/m^2 over 90 min.
12.00 a.m.	Vindesine 2–3 mg/m^2 + 500 ml 5% DW + 500 ml 0.9% saline + 20 mEq KCl over 90 min.
1.30 p.m.	Mesna 500 mg/m^2 i.v. in 250 ml 0.9% saline over 30 min + metoclopramide 0.5 mg/kg in 250 ml 5% DW over 30 min.
6.30 p.m.	Mesna 1 g/m^2 orally at home.

Table 3. (a) Responses according to stage

No. patients	Stage	CR	PR	NC	PD	TDP/OS	RR
7	III A	—	6*	1	—	20.2+/21+	66.6%
5	III B	—	2	2	1	8.4 /11.6+	
26	IV	—	15	5	6	4.9+/ 7.1+	57%

*5 CR after surgery with 2 pathologically complete responses.

Table 3. (b) Responses according to sites of disease

Site	CR	PR	NC	PD
Lung	4/33	16/33	9/33	4/33
Liver	1/1	—	—	—
Bone	—	—	8/12	4/12
Nodes	3/19	10/19	5/19	1/19
Adrenal gland	—	—	3/3	—
Pleura	1/4	1/4	2/4	—

CR = complete response; PR = partial response; NC = no change (stable disease); PD = progressive disease; TDP/OS = Time to disease progression/overall survival; RR = response rate.

Table 4. Toxicity

	WHO grade (No. of patients; % in parentheses) I	II	III	IV
Thrombocytopenia	—	—	2(5)	—
Anaemia	16(42)	10(26)	3(7.8)	—
Leucopenia	2(5)	1(2.6)	2(5)	1(2.6)
Nausea/vomiting	8(21)	5(13)	—	—
Diarrhoea	—	1(2.6)	—	—
Alopecia	—	—	38(100)	—
Mucositis	—	2(5)	—	—
Neurotoxicity	—	1(2.6)	1(2.6)	—

leucopenia, 10 of grade 2 anaemia and 3 of grade 3 anaemia. We noted a cumulative effect on haemoglobin and red cell count with increasing courses of chemotherapy : after three cycles most of our patients developed anaemia. Neutropenic fever was experienced by 5 patients. Grade 3 alopecia was universal, nausea and vomiting were mild or moderate. No case of renal toxicity was seen, but 2 patients experienced an acute pulmonary oedema, probably related to a relative intravenous fluids overload.

Vindesine-related paralytic ileus was developed by 1 patient (Table 4). Neither pulmonary toxicity related to mitomycin nor neurological symptoms due to ifosfamide administration were encountered in this study.

DISCUSSION

NSCLC is generally considered one of the most chemoresistant tumours, but there is an arising interest in its medical treatment [4, 5], although none of the most active drug combinations may be recommended for standard use. At present, one of the most controversial points is the use of chemotherapy or best supportive care in advanced NSCLC, because medical treatment has failed to provide a statistically significant survival advantage [6–8] and it has often caused worsening in quality of life [9].

In our experience, MICE had a reasonable tolerability and it was feasible on an outpatient basis. At the end of the treatment some of our responder patients had an improvement of performance status and experienced a weight gain. However, we could not do a critical evaluation of patients' quality of life with an appropriate questionnaire [10, 14] because of social and cultural characteristics and differences of our patients population.

The response rate of our regimen compared with Cullen *et al.* [3] in stage III NSCLC was 66.6 vs. 67% and in stage IV 57.7 vs. 35%; the difference between the two studies may be that MICE seems to be more active in extensive disease without an increased toxicity. Nonetheless, this difference may be related to the sites of disease of our stage IV patients: most of them had soft tissue metastasis and only 1 patient had liver disease.

Furthermore, we tested MICE in a neoadjuvant setting [11, 12] with some interesting results: 6 stage III A patients underwent surgery; 1 with stable disease died in 3 months and 5 partial responders before operation are all still alive without evidence of disease 17+, 22+, 26+, 26+ and 29+ months from surgery. 2 of these were pathologically confirmed complete responders.

The question of survival advantage conferred by chemotherapy in stage III and IV NSCLC can only be answered in a large randomised trial with a control arm. We think that MICE may be safely utilised in a treatment arm, by further enhancing its tolerability with growth factors and new antiemetic drugs.

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