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Influence of Pretreatment Clinical Characteristics on the Response Rate to Mitomycin/Vindesine/Cisplatin (MVP) in Unresectable Non-small Cell Lung Cancer

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The authors report their experience with the MVP (mitomycin/vindesine/cisplatin) regimen of the Memorial Sloan-Kettering Cancer Center (MSKCC) which showed the highest response rate in non-small cell lung cancer (NSCLC). The aim was to respect the original reported schedule to appreciate its activity, because the same drug combination with dose and schedule variations used by other investigators has failed to reproduce the original report results. 82 consecutive previously untreated patients with unresectable and/or metastatic NSCLC received mitomycin (8 mg/m^2 days 1, 29, 71), vindesine (3 mg/m^2, days 1, 8, 15, 22, 29, 43, 57, 71) and cisplatin (120 mg/m^2, days 1, 29, 71), with evaluation on day 71. 24 objective responses were noted (29%) (2 complete response/22 partial response) (95% CI 19%–39%), without differences according to histology. Differences in median survival were noted according to the performance status and type of response. Overall survival rates in responding patients were similar to those noted with the original schedules. Analysis of selection criteria showed that there were more patients with bone ($P < 0.01$) or liver metastases ($P < 0.05$), less women ($P < 0.001$) and less adenocarcinoma ($P < 0.001$) than the MSKCC trial. A dose intensity analysis showed only a minimal difference in the average weekly doses of vindesine (10% lower than MSKCC trial: 1.8 mg/m^2 vs. 2.25 mg/m^2). Disease improvement, a subjective response criterion used in the MSKCC trial, was probably underestimated in the current study. We conclude that the potential benefit of chemotherapy with a three-drug combination in NSCLC is greatest in patients with stage IIIa and IIIb disease or stage IV disease with a good performance status and a low metastatic volume.
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INTRODUCTION

THE ROLE of chemotherapy in inoperable non-small cell lung cancer (NSCLC) is still contested and many doubts have been raised about its usefulness. After initial positive reports, controlled trials have failed to confirm the response rate and an improvement in survival [1–4], but recent trials have proven some value, especially in low volume or non-metastatic disease [5].

The current most frequently reported combinations in NSCLC contain cisplatin and a vinca alkaloid, and yield response rates of around 25% [6, 7]. The addition of mitomycin to the cisplatin–vindesine regimen (MVP), was reported to signifi-

cantly increase the response rate [8, 9]. Several co-operative group experiences, without reproducing the same schedule or dose, have reported response rates in excess of 30% but have neither approached nor crossed the 50% response rate barrier [10–12].

Failure to achieve the same results in multicentric trials is a well-known phenomenon of clinical oncological research, which has been attributed to many factors. The most consistent finding in these trials is the modification of eligibility criteria, dose schedule and dose intensity.

We decided to use the original Memorial Sloan–Kettering Cancer Center (MSKCC) schedule to evaluate its feasability and activity in advanced NSCLC in an open phase II trial involving three institutions (the ATTIT trial).

PATIENTS AND METHODS

Patients' characteristics

From June 1987 to April 1989, 82 previously untreated patients with histologically or cytologically proven unresectable NSCLC entered the study.

There were 79 men and 3 women. Median age was 53 years (range 38–75). 54 (66%) had a performance status (Karnofsky index) of > 70%. Histology showed squamous cell (38 patients, 45%), adenocarcinoma (23, 27%), large cell (15, 18%) and unclassified (6, 7%) carcinomas (Table 1).

In addition to a full physical examination, all patients had the following staging procedures: chest radiography (posterior-anterior and lateral) and thoracic computed tomography (CT); bronchoscopy; isotopic bone scan, CT of the brain; abdominal ultrasound and/or a CT of the abdomen; and blood counts and standard biochemical parameters measurement.

Patients were classified using the system proposed by the American Joint Committee on Cancer [13]. Stages were: 19 patients, stage IIIa (23%), 10 IIIb (12%) and 53 IV (65%). 17 patients had more than one metastatic organ site involved. Bone involvement was the sole metastatic site in 20 patients and associated with other metastatic sites in 9 patients.

Table 1. Characteristics of 82 patients, compared with those of 87 patients treated at MSKCC

Characteristics	ATTIT (%)	MSKCC (%)	*P*
Median age (yr)	53	55	NS
Sex			
Male	79 (96)	63 (72)	<0.001
Female	3 (3)	24 (28)	<0.001
Karnofsky performance status			
60–70%	28 (34)	36 (41)	NS
80–100%	54 (66)	51 (59)	NS
Histological subtype			
Adenocarcinoma	23 (28)	54 (41)	<0.001
Epidermoid carcinoma	38 (46)	22 (25)	<0.01
Large cell carcinoma	15 (18)	11 (13)	NS
Not specified	6 (7)	—	
Prior treatment			
Radiotherapy	4 (5)	5 (6)	NS
Surgery	10 (12)	4 (5)	NS
Radiotherapy and surgery	3 (4)	3 (3)	NS
Stage			
IIIa	19 (23)	}23 (26)	NS
IIIb	10 (12)	}	
IV	53 (65)	59 (68)	NS
No. of metastatic sites			
1	36 (40)	31 (36)	NS
>1	17 (20)	28 (32)	<0.06
Type of metastatic sites			
Lung	7 (8)	19 (22)	<0.007
Bone	29 (35)	18 (21)	<0.01
Bone only	20 (24)		
Extrathoracic lymph nodes	4 (5)	18 (21)	<0.001
Liver	15 (18)	8 (9)	<0.05
Brain	10 (12)	6 (7)	<0.1
Adrenal glands	6 (7)	5 (6)	NS
Other	3 (3)	4 (5)	NS

NS = not significant.

Chemotherapy protocol

All patients received, before evaluation of antitumour response, mitomycin (8 mg/m^2, days 1, 29, 71), vindesine (3 mg/m^2, days 1, 8, 15, 22, 29, 43, 57, 71) and cisplatin (120 mg/m^2, days 1, 29, 71) with hydration and mannitol-induced diuresis [8].

Cisplatin was reduced by 50% if the creatinine clearance was between 45 and 54 ml/min, and withheld if it was less than 45 ml/min, if the leucocyte count fell below 2000/mm^3, or if there was evidence of marked neurotoxicity or ototoxicity > 2.

Vindesine was attenuated by 50% when leucocyte count was between 2000 and 2900/mm^3 and platelet count <140 000/mm^3, or if there was evidence of moderately symptomatic (WHO grade ≥ 2) neurotoxicity. Vindesine was withheld if the leucocyte count was < 2000/mm^3, platelet count < 100 000/mm^3, bilirubin > 2.5 mg/dl, or if there was evidence of marked neurotoxicity (≥ WHO 2). Mitomycin was withheld if the leucocyte count was < 3000/mm^3, platelet count < 100 000/mm^3 or if the creatinine clearance fell to below 45 ml/min.

Evaluation of response

Patients were evaluated at day 71 of chemotherapy, using Eagan's response criteria [14], and considered adequate for response assessment if they received at least one dose of cisplatin and mitomycin and three doses of vindesine. Response duration and survival were calculated from the first day of chemotherapy. All patients were evaluable for response, toxicity (both evaluated at day 71) and survival according to WHO criteria [15].

After response evaluation stage III responders underwent full dose radiotherapy or surgery. The regimen was continued up to six cycles in stage IV responders but was discontinued in non-responders.

Statistical methods

The duration of response and overall survival were criteria chosen together with the type of response for the construction of Kaplan–Meier plots. The calculation of *P* values was based on the two-tailed significance test.

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Table 2. Observed toxic effects in 82 patients treated with MVP

Type (WHO criteria)	0	1	2	3	4
Leucocytes*	381	60	37	11	—
Neutrophils*	380	62	32	13	2
Platelets*	43	6	—	—	—
Haemoglobin†	124	7	7	3	1
Constipation†	130	5	5	1	1
Peripheral neuropathy†	80	41	14	6	—
Renal†	136	3	1	2	—

*Evaluated at days 7, 14, 21, 29, 43, 57 and 71 for a total of 489 cycles.
†Evaluated at days 29 and 71 for a total of 142 cycles.

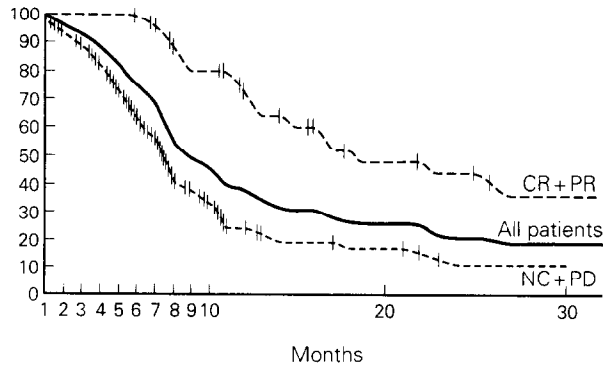

Fig. 1. Actuarial survival in 82 patients by response category. CR = complete response, PR = partial response, NC = no change and PD = progressive disease.

RESULTS

Dose intensity

Before evaluation after the third cycle, the 82 patients received in total 216 courses of mitomycin, 613 courses of vindesine and 216 courses of cisplatin. Mean doses for each patient per cycle were mitomycin 8 mg/m^2, vindesine 2.9 mg/m^2 and cisplatin 118 mg/m^2. The average number of cycles given for each drug was mitomycin 2.6, vindesine 6 and cisplatin 2.6. Mean weekly doses for each cycle were mitomycin 2 mg/m^2, vindesine 1.8 mg/m^2 and cisplatin 29.7 mg/m^2.

Treatment was stopped in 25 patients (3 patients after inclusion, 10 patients after first cycle, 12 patients after second cycle) due to toxicity in 2 patients, evolutive disease in 17, death unrelated to toxicity in 1 and refusal in 5 patients.

Toxicity

Haematological toxicity. (Evaluated at day 7, 14, 21, 28, 43, 57, 71 for a total of 489 weekly periods.) Leukopenia was grade 0 in 381 cycles, 1 in 60, 2 in 37 and 3 in 11. More frequent incidences of leukopenia were noted at days 14 and 21. Granulopenia was grade 0 in 380 cycles, 1 in 62, 2 in 32, 3 in 13 and 4 in 2. Thrombopenia was grade 0 in 483 and 1 in 6. One episode of febrile neutropenia was noted in 4 patients. Haemoglobin toxicity was grade 0 in 124, 1 in 7, 2 in 7, 3 in 3 and 4 in 1. 4 patients required blood transfusions (Table 2).

Non-haematological toxicity. (Evaluated at day 28 and 71, for a total of 142 cycles.) Peripheral neuropathy was 0 in 80, 1 in 41, 2 in 14, 3 in 6 and 4 in 1 patient.

Chemotherapy had to be discontinued in the patient with grade 4 peripheral neuropathy. Serum creatinine rose 120 μmol/l in six cycles. Permanent hypoacusia was noted in 4 patients after two cycles. No patient developed symptomatic renal dysfunction or required dialysis. In 142 evaluable cycles, constipation was WHO grade 0 in 130 cycles, 1 in 5, 2 in 5, 3 in 1 and 4 in 1. Alopecia (WHO grade 3) was seen in all patients.

Response

All patients except 1 were alive at day 71. 1 patient died before evaluation (Karnofsky index 60%, presence of brain metastases), and was considered in progression. 2 complete responses (CR, 2%) and 22 partial responses (PR, 27%) (95% CI 19%–39%) were noted in 82 patients. Minor responses were classified as no change (NC). According to the stage of disease, 1 CR (5%) and 7 PR (37%) were achieved in 19 stage IIIa patients, 1 CR (10%) and 3 PR (30%) in 10 stage IIIb patients and 12 PR (23%) in 53 stage IV patients (Table 3).

The median duration of response was 11 months for the patients who achieved a complete or a partial response.

Objective responses according to the different histological type were 3/15 in large cell carcinoma patients (20%), 13/39 in squamous cell carcinoma (33%), 8/23 in adenocarcinoma (34%) and 0/6 in unclassified NSCLC.

After day 71 of chemotherapy, 16 patients (6 PR, 10 NC) continued MVP and 31 patients (6 PR, 19 NC, 6 stage IIIA/IIIB progressive disease) were submitted to locoregional radiotherapy. 12 patients (2 CR, 7 PR, 3 NC) had radiotherapy followed by MVP. MVP was given at the same doses for a maximum of six cycles of mitomycin and cisplatin, both repeated every 6 weeks, with vindesine given every 2 weeks until the last doses of mitomycin and cisplatin.

Two pneumonectomies and two lobectomies were performed in 4 stage IIIa patients (3 PR, 1 NC). 3 patients (2 PR, 1 NC)

Table 3. Responses in 82 patients, compared to those in the MSKCC trial

Type	IIIa (n=19)	IIIb (n=10)	IV (n=53)	Total (n=82)	MSKCC (n=87)
CR	1 (5)	1 (10)	— (—)	2 (3)	6 (7)
PR	7 (37)	3 (30)	12 (23)	22 (26)	46 (53)
NC	10 (52)	5 (50)	21 (39)	36 (43)	26 (29)
PD	1 (5)	1 (10)	20 (38)	22 (27)	9 (11)

Percentages are shown in parentheses.
CR = complete response, PR = partial response, NC = no change and PD = progressive disease.

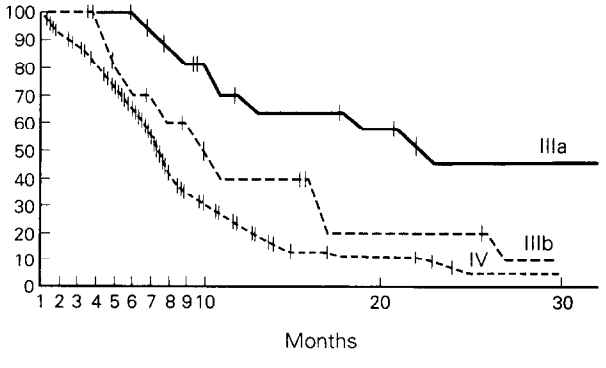

Fig. 2. Actuarial survival in 82 patients by disease stage.

completed day 71 of chemotherapy and the third 1 refused. 1 patient was submitted to a metastatectomy. He had a PR of a solitary metastasis in the left adrenal gland 2 years after a lobectomy for T3N0MO epidermoid lung cancer.

Survival

As of July 1990, with a median follow-up of 28 months, the median survival was 9 months for all 82 patients. In patients with an objective response the median survival was 18.5 months, and 7.5 months in non-responding patients ($P < 0.005$) (Fig. 1). There was a significant difference in the median survival of patients with stage IIIa disease (22 months) compared to those with stage IIIb (10 months) ($P < 0.01$) and stage IV (7.5 months) ($P < 0.001$) (Fig. 2).

Patients with a Karnofsky performance index of < 70% had a median survival of 5.5 months, and 12.5 months when the index was > 70% ($P < 0.01$) (Fig. 3).

DISCUSSION

The combination of a vinca alkaloid with cisplatin and mitomycin (the MVP protocol) is an active regimen in NSCLC patients. However, our results did not confirm the response rate of 60% (95% CI 50%–70%) reported by MSKCC (Table 3). Differences may be chiefly related to patient population characteristics, or to response evaluation criteria and methodology.

Differences in patients' characteristics compared to the MSKCC trial were noted in the sex ratio (3/82 women vs. 24/87) ($P < 0.001$), histology (23/82 adenocarcinoma vs. 54/87) ($P < 0.001$) and type of metastatic involvement; bone (29/54 patients vs. 18/59 patients) ($P < 0.01$) and liver (15/53 vs 8/59) ($P < 0.05$) (Table 1). These prognostic factors have been acknowledged as influencing both survival and response rates in chemotherapy trials in NSCLC [16, 17]. Patients with squamous cell carcinoma were more frequent in our study, as in other European series, in contrast to the increasing incidence of adenocarcinoma reported in the USA [18, 19].

When selection criteria were comparable, the MSKCC results were confirmed. Folmann and Rosman [20] reported a response rate of 73% in 56 NSCLC patients treated with the MVP regimen. In that study, the sex ratio, histological subtypes, stages and sites of distant metastases were similar to those of the MSKCC trial. Dose intensity may partially explain the differences noted in other MVP trials. In the ECOG trial [21], 20% response rate were achieved in stage IV patients (23% in our study) when cisplatin was administered at a weekly dose intensity of 13 mg/m^2. Similarly, a comparison of dose intensities of MVP in the non-randomised trials of Martini *et al.* at the

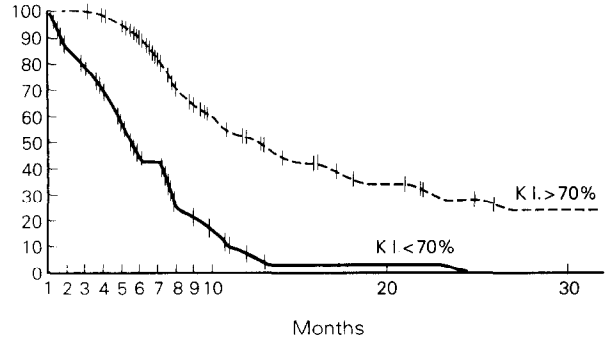

Fig. 3. Actuarial survival in 82 patients by performance status categories. KI = Karnofsky index.

Table 4. Cycles, mean doses and weekly dose intensity disparity compared for each drug over an 8-week period

	Total cycle	Cycle	Mean dose (mg/m^2)	Mean weekly dose (mg/m^2) ATTIT	MSKCC	% Weekly gap MSKCC doses
Mitomycin	216	2.6	8	2	2	0
Vindesine	613	6.0	2.9	1.8	2,25*	−10
Cisplatin	215	2.6	118	29.7	30	−1

*Vindesine or vinblastine.

MSKCC [22] and Burkes *et al.* [23] in stage III NSCLC patients shows that higher response rates were obtained when cisplatin was used at 30 mg/m^2 per week. The difference between our trial and the MSKCC trial in weekly doses administered, evaluated over an 8-week period of treatment, was −1% for cisplatin and −10% for vindesine. No difference was noted for mitomycin (Table 4).

The gap of 1% (29.7 mg/m^2) for cisplatin and 10% for vindesine (1.8 mg/m^2) in dose intensity of weekly doses between the current ATTIT trial and the MSKCC trial does not explain the differences noted in response rate.

Even if the response rates noted in this study are not as high as those reported by the original protocol, the median survival was very similar to the MSKCC trial for responding (18.5 vs. 16 months in MSKCC) and non-responding patients (7.5 vs. 6.5 months).

Differences in response rates may also be related to our response evaluation criteria. Disease improvement, a response category utilised in the MSKCC trial for patients with evaluable disease, was probably underestimated in our study. This type of response was defined at the MSKCC in a previous study by Kris *et al.* [24], in which the improvement category was based on a definite but subjective decrease in size agreed by three investigators, for all disease not fitting the definition of "measurable".

Although in our study such patients were frequent, we have chosen the orthodoxy of denoting minor responses as "no change". This standard of evaluation criteria methodology selected a smaller group of responding patients with better prognostic factors. This fact is reflected in a better duration of response of responding patients than in the MSKCC trial (11 vs. 6.5 months).

Another result reported with this regimen has been the use of the MVP regimen in stage IIIa patients before surgery. In our series, 4 patients were submitted to surgical resection (two lobectomies and two pneumonectomies). 1 patient submitted to a lobectomy died 15 months after the beginning of chemotherapy after 11 months of disease-free survival. 3 patients are alive, free of disease 17, 18 and 26 months after thoracotomy.

These results confirm that the potential benefit of combination chemotherapy may be at its greatest when used as initial therapy in locoregional advanced NSCLC [22–26]. However, evidence is still not sufficient to recommend neoadjuvant chemotherapy used in stage IIIa patients as a feature of standard practice for all patients. Controlled trials and more complete staging are needed to counteract the discrepancies in resection rates and survival actually reported [27–29]. Differences may be related to heterogeneity of lymph node involvement and primary tumour categories present in stage IIIa (T3NO-1, T1-3N2), the different

natural history of these stages and an underestimated preoperative evaluation of mediastinal node involvement [30].

The results of this study indicate that systemic chemotherapy should be investigated in patients with stage IV NSCLC. Since palliation is the main goal, a correct evaluation of the presence of unfavourable prognostic factors must be done before choosing the type of treatment.

Patients with metastatic disease are unlikely to respond if they have a poor performance status, weight loss of >10%, or extensive hepatic/bone disease. Survival benefit is a very elusive goal. The ECOG trial [16] showed that combination regimens in this type of patient give rise to more life-threatening and lethal toxicities than single agent treatment, with no gain in survival. These patients are eligible for symptomatic treatment or for phase II monochemotherapy trials, in order to maximise the chances of finding new and potentially useful agents in NSCLC treatments.

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