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Short communication

Mitomycin C, teniposide, and cisplatin combination chemotherapy for advanced non-small-cell carcinoma of the lung

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Summary. A total of 45 patients with advanced non-small-cell lung carcinoma were treated with a combination of cisplatin, teniposide, and mitomycin C. Most subjects exhibited good prognostic factors (performance status, 0–1; minimal weight loss; locoregional disease). Toxicity consisted mainly of myelosuppression and nausea and vomiting. Four patients died of sepsis due to chemotherapy-induced leukopenia. The response rate was 39.5%, with no complete responses being observed; the median duration of partial responses was 231 days and median survival was 243 days. Although the response rate and durations of both response and survival were comparable with those obtained using other cisplating-containing regimens, myelotoxicity was rather pronounced in the present study. Further studies of teniposide in this type of combination are not warranted.

Introduction

Non-small-cell lung cancer (NSCLC) is relatively refractory to chemotherapy. Among the active drugs, cisplatin, mitomycin C, the two vinca alkaloids vinblastine and vindesine, etoposide (VP16), and ifosfamide have been used in combination regimens, with response rates in excess of 50% being observed in several studies [7]. In our experience, the MVP regimen (mitomycin C, vinblastine, and cisplatin) has achieved a 50% response rate, resulting in a median duration of response of 232 days and in median survival of 280 days [2]. Although this and other similarly aggressive regimens that include cisplatin are likely to prolong survival in responding patients, the side effects are nevertheless remarkable. Marrow toxicity and neurotoxicity were troublesome in the MVP study. Vinblastine-induced peripheral neurotoxicity was observed in 26% of patients and constipation, in 30% [2].

Teniposide (VM26), an epipodophyllotoxin derivative, as is VP16, produced a 21% response rate in untreated NSCLC patients when given at doses ranging from 120 to 180 mg/m^2 in a recent phase II trial at our institution [3]. VM26 had previously been inadequately tested using likely suboptimal dosing (not exceeding 300 mg/m^2 per cycle; see [3]). A response rate of 11% has very recently been reported in a group of untreated adenocarcinoma patients [9]. Moreover, VM26 appears to be one of the most active agents in small-cell lung cancer [1, 4]. In the present study, VM26 replaced vinblastine in an MVP-type regimen aimed at obtaining a higher response rate associated with a reduction in neurotoxicity.

Patients and methods

Patients with histo-cytologically documented NSCLC that was not amenable to radical surgery or irradiation were admitted to this phase II study. Additional eligibility requirements incluced an Eastern Cooperative Oncology Group (ECOG) performance status of <3, an age of <71 years, serum creatinine levels of <1.5 mg/dl, bilirubin values of <1.5 mg/dl, a WBC count of >4000/mm^3, a platelet count of >100,000/mm^3, and normal cardiac function. Patients who had undergone therapy within the 4 weeks prior to the start of treatment were excluded from the present study. Evaluable or measurable disease had to be present, and areas of prior radiation were not evaluable. Subjects were also required to have a life expectancy of $\geq$2 months and to give their informed consent to participate.

The treatment consisted of 10 mg/m^2 mitomycin C given as an i.v. bolus on days 1 and 43 and then every 12 weeks; 100 mg/m^2 VM26 given as an i.v. infusion in 500 ml saline over approx. 1 h on days 1, 3, and 5 every 3 weeks for three cycles and then every 6 weeks; and 100 mg/m^2 cisplatin, which was given according to usual hydration schedules with 2.5 l fluids and 250 ml 18% mannitol on day 1 every 3 weeks for three cycles and then every 6 weeks. A maximum of six cycles were given to responding or stable patients. Each cycle (consisting of cisplatin and VM26 with or without mitomycin C) was started only if the leukocyte count was >4,000/mm^3, the platelet count was >100,000/mm^3, and serum creatinine levels were <1.4 mg/ml. Dosing of drugs was modified according to marrow tolerance as follows: if a WBC count of <1,000/mm^3 or a platelet count of <75,000/mm^3 was observed at any time during therapy, VM26 and mitomycin C doses were reduced

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Table 1. Patients' characteristics

Total/evaluable patients		45/38
Median age (range)		56 (40–70) years
Sex: M/F		37/8
ECOG performance status:		
	0	6
	1	25
	2	14
Locoregional/metastatic disease		15/30
Prior treatment:		
	Chemotherapy	8
	Radiotherapy	4
	Surgery	5
Histology:		
	Squamous-cell carcinoma	20
	Adenocarcinoma	15
	Large-cell carcinoma	7
	Undifferentiated	3
Weight loss:		
	<5%	28
	5–10%	7
	>10%	10

to 75% of the initial level. No dose increment was allowed. A WBC, differential, and platelet counts as well as determinations of hemoglobin values and blood chemistry (liver enzymes, electrolytes, total protein, albumin, blood urea nitrogen, creatinine, glucose) were performed before the start of chemotherapy together with investigations aimed at defining the extent of disease. Routine extensive investigations were not done and only symptomatic patients underwent additional studies. Blood cell counts and renal function were checked before every cycle, and blood-cell nadirs were examined by weekly full blood counts during the initial two cycles. Locoregional disease included the primary tumor, hilar and mediastinal lymph nodes, ipsilateral pleural effusion and supraclavicular adenopathies.

Response and toxicity assessments were performed according to WHO recommendations [10]. The duration of response and of survival were estimated from the commencement of therapy. Survival curves were plotted using the Kaplan and Meier method [5] and compared using log-rank statistics [6].

Results

A total of 45 consecutive patients were entered in the present study between October 1986 and February 1988. The main characteristics of our subjects are summarized in Table 1. Approximately two-thirds of the patients showed a good performance status (0 or 1), a weight loss of <5%, or locoregional disease; 8 had previously received chemotherapy, which consisted of a single drug in 6 cases.

A total of 162 cycles of mitomycin C, teniposide, and cisplatin (MTP) were given. The main side effects encountered were myelosuppression and emesis; the overall toxicity is summarized in Table 2. In all, 48%, 33.3%, and 77.3% of our patients developed grade 3–4 leukopenia, thrombocytopenia, and nausea and vomiting, respectively. Four subjects died of sepsis induced by severe leukopenia during the first cycle of chemotherapy. Hair loss was total in 63.4% of patients and symptomatic ototoxicity was observed in two cases. In all, 7 patients could not be evaluated for response, leaving 38 evaluable subjects; reasons for nonevaluability included early toxic death due to leukopenia-induced sepsis in 4 cases, 2 refusals due to excessive nausea and vomiting, and 1 early death due to causes unrelated to toxicity or disease progression.

Table 2. Side effects expressed as percentages of exposed patients

Toxicity	WHO grade				
	0	1	2	3	4
Anemia	19	31	33.3	14.3	2.4
Leukopenia	9.5	9.5	33.3	28.7	19
Thrombocytopenia	31	16.7	19	11.9	21.4
Nausea/vomiting	0	4.5	18.2	50	27.3
Infection	80	4.4	6.7	0	8.9
Nephrotoxicity	92.9	7.1	0	0	0
Stomatitis	71.4	11.9	11.9	4.8	0
Diarrhea	72.7	6.7	15.6	0	0
Neurotoxicity	76.2	19	2.4	2.4	0
Alopecia	0	22	14.6	63.4	0

No complete responses were observed, although 15 patients showed a partial response (39.5%; 95% confidence interval; 31.5%–47.4%), 17 displayed no change (44.7%), and 6 (15.8%) exhibited disease progression. The median duration of partial responses was 231 days and the no-change status lasted a median of 150 days ($P < 0.05$). The overall median survival was 243 days. Patients showing an ECOG performance status of 0 or 1 survived significantly longer than did those whose score was 2 (338 vs 122 days; $P < 0.05$), and subjects who had shown a loss of <5% in body weight survived longer than those who had lost more weight before study entry (310 vs 181 days; $P < 0.05$). Patients with locoregional disease lived longer (median survival, 287 days) than those with metastatic disease (median survival, 181 days), although the difference was not significant.

Discussion

The MTP regimen achieved a response rate and median survival that were comparable with those previously obtained using other cisplatin-containing regimens [7]. Unfortunately, myelotoxicity, for which VM26 was responsible together with mitomycin C, was pronounced and caused four septic deaths. Other side effects were rather well tolerated and neurotoxicity, observed in 24% of patients, was usually mild and more likely attributable to cisplatin administration. Although this was not a randomized study, the substitution of VM26 for vinblastine in the MVP regimen did not appear to offer any advantage over our prior experience [2]. In fact, the response rate in the present study was lower, with no complete responses being observed, and was hampered by more profound myelosuppression.

Although the introduction of VM26 in the present combination regimen cannot be recommended due to its toxicity, the possibility cannot be ruled out that this drug might be valuable when given in combination with less myelo-

toxic drugs. An EORTC (European Organization for Research and Treatment of Cancer) study is currently comparing cisplatin combined with teniposide versus teniposide alone; the same study is evaluating a 1-day VM26 administration schedule vs treatment given on 3 alternate days. This trial will elucidate whether the single drug obtains better results than the combination regimen and provide information on the schedule dependency of VM26. A clear schedule dependency for VP16 has been demonstrated in small-cell lung cancer [8], and intermittent scheduling might possibly be advantageous in achieving higher activity against topoisomerase II, which is the target for both epipodophyllotoxins.

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