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Short communication

Phase II study of teniposide in adenocarcinoma of the lung

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Summary. A total of 26 evaluable patients with previously untreated, non-resectable adenocarcinoma of the lung were given 80 mg/m^2 i.v. teniposide daily for 5 days every 3 weeks. Three partial responses (11%) were obtained that lasted for 12, 11 and 32 weeks, respectively. Leucopenia was the dose-limiting side effect, with WBC counts of $<2 \times 10^9$/l being observed in 42% of patients, resulting in one septic death. At the dose and schedule used in the present study, teniposide showed only limited activity in adenocarcinoma of the lung.

Introduction

Adenocarcinoma of the lung (ACL) has lately attracted increasing interest because several centers have reported that the incidence of this disease is rising faster than that of other histologic types of lung cancer, and some reports even suggest that ACL is the most frequently occurring histologic type [13]. ACL is usually grouped together with squamous-cell and large-cell lung cancer to form the disease entity of non small-cell lung cancer (NSCLC), which is treated as one disease. However, both response to chemotherapy [3] and survival [3, 4, 8] may vary among the histological types, although this is not a universal finding.

The majority of patients with ACL have non-resectable tumors at the time of diagnosis and the prognosis for this patient group is dismal [12]. Systemic therapy with cytostatic agents is thus the rational treatment for this patient group but, due to the dismal results, remains experimental [10, 11]. High priority should therefore be given to the identification of new compounds with significant activity against ACL.

The activity of teniposide (VM-26) in ACL remains uncertain despite its introduction into clinical use in the early 1970s. Some studies have reported overall negative results, obtaining response rates ranging from 0 to 5% using doses not exceeding 300 mg/m^2 over 3 weeks [1, 2, 8]. In contrast, response rates of $\geq 50\%$ in patients with NSCLC and brain metastases, including several complete responses have also been observed [6, 7].

As the effectiveness of the congener etoposide (VP-16) is likely to be dose-related, higher doses of VM-26 may prove to be more effective. This suggestion held true in a study by Giaccone et al. [5], who used doses ranging from 360 to 540 mg/m^2 over 3 weeks and observed a response rate of 17% among 42 patients with all histologic types of NSCLC. The response rate among patients who had not previously received chemotherapy was 21%. The response status among 18 patients with ACL was not reported. Based on these results, the aim of the present study was to evaluate VM-26 given at moderately high doses to patients with unresectable ACL.

Patients and methods

A total of 27 consecutive patients with unresectable ACL were entered in the study between August 1988 and July 1989. The criteria for entry included histologically or cytologically verified non-resectable ACL, no previous chemotherapy or irradiation, the presence of uni- or bi-dimensionally measurable disease, a WHO performance status of ≤ 2, an age of ≤ 75 years, no previous or concurrent malignancies and no active uncontrolled infection. Pretherapeutic values for hemoglobin (≥ 6.5 mmol/l), WBC counts ($\geq 3 \times 10^9$/l) and plateletcounts ($\geq 100 \times 10^9$/l) were also required. Informed content was obtained and the study was approved by the regional ethical committee.

VM-26 was given at a dose of 80 mg/m^2 as an i.v. infusion over 1 h daily for 5 days at 3-week intervals. Blood pressure was controlled before, during and after infusion. Nadir WBC counts of $1-2 \times 10^9$/l and nadir platelet counts of $50-75 \times 10^9$/l were intended and doses of VM-26 were adjusted accordingly. WHO criteria were used in response assessment and evaluation of toxicity [14], and the duration of response was calculated from the date of the first observation of response until disease progression. Treatment with VM-26 was discontinued when there was definitive evidence of progressive disease (PD), whereas findings of no change (NC) or tumor regression, i.e. partial (PR) or complete (CR) response, indicated continuation of therapy. Treatment was discontinued if no PR or CR was obtained after six cycles of treatment. The maximal duration of therapy was 1 year.

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Table 1. Patients' characteristics and results[a]

Characteristic	Patients (*n*)
Entered/evaluable[b]	27/26
Male/female	12/15
Median age (range)	57 (36–67) years
WHO performance status:	
0	5
1	16
2	5
Responses to teniposide:	
CR	0
PR	3
NC	9
PD	12
Early death	2

[a] A total of 167 cycles of teniposide were given (median, 6/patient)
[b] 1 patient was lost to follow-up

Table 2. Hematologic nadir values

	WHO grade				
	0	1	2	3	4
WBCs (number of patients)	3	5	7	6	5
Platelets (number of patients)	16	2	1	3	4

Results

Patients' characteristics and treatment outcome are summarized in Table 1. One patient was lost to follow-up and was thus not evaluable. Three patients showed PRs (11%; 95% confidence limits, 2.4%–29.2%) that lasted 11, 12 and 32 weeks, respectively. The median survival was 18 weeks (range, 2–69+ weeks). Two patients represented early deaths, as they died after 16 and 20 days on study, respectively; one died of sepsis in the presence of leucopenia.

The dose-limiting toxicity was leucopenia (Table 2). In all, 18 subjects (67%) had leucopenia of WHO grade 2 or more, whereas 5 patients (19%) had grade 4 leucopenia and septic episodes requiring antibiotic therapy. Platelet suppression of WHO grade 2 or more was seen in 8 cases (31%), and 15% of our patients had grade 4 thrombocytopenia. There were no severe bleeding episodes, and other toxicity was not pronounced. None of our patients experienced hypotension, and no cardiac, renal or hepatic toxic effects were encountered.

Discussion

The 11% response rate obtained in the present study is inferior to the 21% response rate reported for previously untreated patients by Giaccone et al. [5]. The latter study involved the administration of VM-26 on days 1, 3 and 5 every 3 weeks at doses ranging from 120 to 180 mg/m^2, resulting in a cumulative dose of 360–540 mg/m^2 given over a period of 3 weeks. The dose intensity in the current study was 400 mg/m^2 every 3 weeks. However, the difference in response rates was not statistically significant. No conclusion can be drawn as to whether this difference is attributable to the lower single dose given in this study, a generally lower dose intensity, to differences in sensitivity among the histologic subtypes of NSCLC, or to stocastic variations alone, as the 95% confidence limits were 2.4%–29.2% as opposed to 8.3%–41%.

The toxicity of VM-26 given on this schedule was considerable, with 19% of the patients experiencing episodes of leucopenia and fever, 42% showing WBC counts of $<2 \times 10^9$/l, and 27% exhibiting platelet counts of $<50 \times 10^9$/l. Given these findings, it is noteworthy that an increase in the present dose does not apear to be practicable. In conclusion, VM-26 showed only modest activity in patients with non-resectable ACL in the present study. This finding, together with the pronounced toxicity observed, renders VM-26 unsuitable for further investigation in such patients using the present dose and schedule.

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