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Short communication

Phase II study of VP 16-213 (etoposide) in metastatic transitional cell urothelial cancer

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Summary. *Fifteen patients with measurable metastatic transitional cell bladder cancer were treated with VP 16-213 100 mg/m² IV daily for 4 days, repeated every 3 weeks. There were no complete or partial (greater than 50% reduction in area, maintained for 6 weeks) responses. Two patients showed transient reduction by 50% in the area of measurable lesions, and a further five patients showed brief stabilisation of previously progressive disease. The treatment was well tolerated. In two patients, total WBC at the nadir fell below 1.0 × 10⁹/l but without complications from infection.*

We conclude that VP 16-213 is inactive in metastatic transitional cell urothelial cancer.

Introduction

Chemotherapy of metastatic transitional cell carcinoma is far from satisfactory. Though in American publications *cis*-platinum, adriamycin, and cyclophosphamide are regarded as the most active drugs [15], in our hands methotrexate has been the most reliable, with rates of 26%, 38%, and 37% for responses lasting an average of 6 months in three separate studies [6, 10, 13]. *cis*-Platinum yielded a rate of 30% for responses lasting 3 months [9], but the toxicity made this drug less acceptable in this elderly group of patients. With adriamycin and bleomycin we have obtained response rates of less than 10% [14]. There is a need for information on other new drugs before attempts are made to develop combination therapy.

VP 16-213 (etoposide) has recently established itself as an important new drug in the treatment of testicular teratoma and oat cell carcinoma of the lung [1, 5, 7, 12]. Information on its activity in patients with metastatic bladder cancer is limited [2–4, 8, 11]. Many previous studies have used weekly or twice-weekly dose regimes which have not been optimal in teratoma or oat cell carcinoma, but even so responses have been reported. Panduro et al. [11] obtained one complete response in a series of 19 patients treated PO at a starting dose of 130 mg/m² daily for 5 days, repeated every 3 weeks. We report the results in a series of 15 patients treated IV with a starting dose of 100 mg/m² daily for 4 days, which is within what is currently regarded as the optimal dosage schedule [12]. The series is sufficiently large for us to conclude that the true response rate is unlikely to be greater than 20%.

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Materials and methods

The characteristics of the patients treated are summarised in Table 1. The primary site was bladder in 13, renal pelvis in one, and prostatic ducts in one. The diagnosis was confirmed by histology in every case: in two patients solitary lung metastases were also biopsied and confirmed to be transitional cell carcinoma. The patients with liver metastases also had measurable lung or local disease. Nine patients had had previous chemotherapy: all had received methotrexate IV; in addition one had received *cis*-platinum, one *cis*-platinum followed by cyclophosphamide, methotrexate, and 5-fluorouracil, and one multiple courses with different agents over 7 months. All had adequate bone marrow, judged by WBC greater than 3.0 × 10⁹/l and platelets greater than 150 × 10⁹/l. All patients had evidence of progression of lesions in the month before starting VP 16-213.

VP 16-213 was given as an IV infusion in normal saline over 30 min. The standard schedule was 100 mg/m² daily for 4 days, repeated every 3 weeks. Dose modifications were made initially on the basis of age and previous myelosuppressive treatment, and adjusted on subsequent courses from the previous nadir blood count (days 10–11): the course was reduced by 1 day if the nadir total WBC was less than 1.2 × 10⁹/l or the platelet count less than 80 × 10⁹/l, and increased if the WBC was greater than 2.5 × 10⁹/l and the platelet count greater than 200 × 10⁹/l.

Table 1. Characteristics of patients

Ages	44–77; mean 61 years
Performance status at start of treatment:	
ECOG 0:	2
1:	3
2:	8
3:	2
Previous treatment:	
Radiotherapy	13
Chemotherapy	9
Cystectomy	2
Sites of evaluable lesions:	
Local	4
Lung	7
Lymph nodes (CT scan)	4
Liver (CT scan)	2

Table 2. Doses of VP 16-213 administered

No. of courses per patient	1: 3
	2: 3
	3: 6
	4: 3
	15
No. of courses at	
100 mg/m^2 daily for 5 days	3
4 days	21
3 days	14[a]
2 days	1
	39

[a] Dosage reduced to 75 mg/m^2 in one case

Patients were treated for a minimum of three courses unless there was unequivocal disease progression before these had been administered. Complete response was defined as the disappearance of all evaluable lesions, and partial response as a shrinkage of the area of measurable lesions by at least 50%, sustained for a minimum of 6 weeks and without other evidence of disease progression.

Results

In all 39 courses were given: details are shown in Table 2. Six patients started treatment with a 3-day course because of advanced age (75 years and over: 3 patients) or extensive previous treatment (3 patients). In one of these, the dose was subsequently increased, and in one it was reduced further to 75 mg/m^2 for 3 days. Dose reduction was necessary because of haematological toxicity in three other patients.

No patient showed a complete or partial response according to the definitions given under *Methods*. In two patients measurable lesions diminished by 50% after one course. Although in one the response was sustained for 6 weeks, there was disease progression at other sites, and both patients died within 12 weeks of starting treatment. Five patients had transient relief of symptoms or stabilisation of previously progressive disease, but in no case was this sustained for more than 12 weeks (4 courses). In eight patients there was uninterrupted disease progression.

Side-effects were mild. Most patients experienced moderate alopecia. Nausea and vomiting was not a problem, but one patient complained of right-sided abdominal pains 1 week after treatment during two successive courses: the pains subsided spontaneously. One patient had transient jaundice after the first course. In three patients the nadir total WBC was below 2.0 × 10^9/l in two below 1.0 × 10^9/l: there was no haematological toxicity in subsequent courses after dosage reduction.

Discussion

The intermittent daily schedule and the doses of VP 16-213 we have used are within the range currently regarded as optimal. Schmoll [12] defines a dose range of 60 mg/m^2 to 120 mg/m^2 daily for up to 5 days. Because of the age of our patients and the previous treatment of the majority with pelvic radiotherapy, we decided on a starting dose below the maximum, with provision for increases in the absence of toxicity. Three of the patients who started at this dose in fact required dosage reduction for haematological toxicity (platelets less than 80 × 10^9/l or total WBC less than 1.2 × 10^9/l). In only two patients were we able to increase the dose to 100 mg/m^2 for 5 days.

Despite previous treatment with radiotherapy, most patients had not had extensive chemotherapy. Because of this, and their good average performance status (1.66), they were a fairly favourable group for chemotherapy. Even so, we failed to obtain either complete or partial response in any patient. The 95% confidence interval for the true response rate is 0 to 20%, and we must therefore conclude that in the doses and schedule used, VP 16-213 has little activity as a single agent in metastatic transitional cell carcinoma of the bladder.

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