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Letter to the Editor

Phase One Study of Twice-weekly Vindesine

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In view of the prolonged tertiary half-life of vindesine [1], it was expected that twice-weekly administration of this drug might lead to a prolonged but relatively low drug concentration that could result in ameliorated toxicity while preserving antitumor activity [2–4], without requiring prolonged hospitalization. We therefore determined the optimal dose level of vindesine in that schedule in a phase I study.

Nineteen patients, 12 male and nine female, were entered into the study. Mean age was 56.5 yr, range 22–73 yr. Five patients had non-small cell lung cancer, four small cell lung cancer, gastric cancer was present six times, and breast cancer, disseminated melanoma, testicular cancer and cancer of the uterine cervix once each. Twelve patients were evaluable for response.

Vindesine was given twice weekly, on Tuesday and Friday. The first dose step was 1.5 mg/m^2 per injection. After four injections a 2-week therapy-free interval was kept. Therapy was discontinued in the case of tumor progression or excessive toxicity. As excessive were considered neurotoxicity $\geq$ grade 2, leucopenia grade 3 or above [5].

In the first dose step (1.5 mg/m^2 per injection) five patients were entered. Three patients received 16 injections each; in these patients treatment was terminated because of tumor progression. One of these patients had slight sensory polyneuropathy grade 1 after nine injections; this disappeared in the therapy-free intervals and reappeared after the fourth injection of the subsequent cycles. Two of the patients developed anemia grade 1 after 12 and 16 courses respectively. One other patient in this dose step received four injections, without toxicity, and one only three injections, leading to leucopenia grade 4. None of the patients experienced any other toxicity. One patient with gastric cancer experienced a partial remission of an evaluable abdominal mass, lasting for 2 months, after four injections. This partial remission was consistent with substantially improved findings on endoscopy.

In the second dose step (1.75 mg/m^2 per injection) nine patients were treated. No leucopenia or neurotoxicity above grade 1 was detected. One patient had grade 1 neurotoxicity that was reversible in the therapy-free interval between courses. The highest number of injections in this dose step was 36, in a patient who experienced a partial remission of a non-small cell lung cancer, after eight injections and lasting for 6 months. Anemia, grade 1, probably related to treatment, occurred in two patients after three and 12 injections respectively.

In the third dose step 2 mg/m^2 was given twice weekly in the same way. Six patients were entered. Severe leucopenia occurred in three patients (grade 4), after two, four and four injections. Two patients had severe neurotoxicity, one had difficulty in walking because of motor nerve toxicity and another experienced paralytic ileus. In both cases the syndrome occurred after the second injection and was reversible. In one patient no toxicity was evident after six injections. In one patient a complete response of a lung metastasis from a malignant melanoma occurred, lasting for 5 months. In another patient a partial remission of a small cell lung cancer was seen after two injections.

Other forms of toxicity, specifically alopecia or thrombocytopenia, were not seen in any of the dose steps.

The regimen described in this study does not permit a substantially higher dose of vindesine to be delivered, and the spectrum of toxicity remains the same as with bolus injections. Of 12 patients evaluable for response, three had partial and one a complete remission in this phase I trial of twice-weekly vindesine (Table 1). In the highest dose step of 2 mg/m^2 unacceptable neurotoxicity was the main reason for termination of treatment,

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Table 1. Characteristics of patients responding to twice-weekly vindesine

Diagnosis	Time of response (no injections)	Duration of response (weeks)	Location of response
Gastric cancer	4	8	abdominal mass
Melanoma (no prior therapy)	3	20	lung
Adenocarcinoma lung (no prior therapy)	8	24	lung
Small cell lung.cancer	2	6	lung

Table 2. Toxicity of twice-weekly vindesine in three dose steps

Dose step (mg/m^2/injection)	Patients (No.)	Injections (No.)	Remission		Toxicity	
			Partial	Complete	Neuro > 2*	Leuco ≥ 3*
1.5	5	55	1	0	0	1
1.75	9	110	1	0	0	0
2.00	6	23	1	1	2	3

*WHO grading (10).

despite the responses seen. Although leucopenia also occurred, it was rapidly reversible and did not lead to complications. At the lower dose levels activity was also seen, without severe toxicity (Table 2). Prolonged treatment was usually possible.

We conclude that a phase II study of this regimen at a dose level of 1.75 mg/m^2 might be interesting, especially in patients with lung cancer, and possibly also in malignant melanoma and gastric cancer.

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