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Vindesine Therapy in Melphalan-Resistant Multiple Myeloma*

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Abstract—*Vindesine, a new vinca alkaloid, was administered in thirteen patients with advanced multiple myeloma (stages IIIA and IIIB), resistant to alkylating agents. Eleven patients received two complete courses and could be evaluated. Six patients (55%) showed objective improvement. This was indicated by a decrease of greater than 50% of pretreatment myeloma protein serum levels, normalization of elevated serum calcium levels, and improvement of haemoglobin concentration and renal function. Neutropenia of short duration, mild paraesthesias and alopecia were noted as side effects.*

INTRODUCTION

MULTIPLE myeloma can be treated initially with melphalan and prednisone, resulting in the majority of patients in objective regression of symptoms and of tumour cell mass as well as in a significant increase in survival time [1]. In the later stages, however, the disease frequently becomes resistant against melphalan though not necessarily against other alkylating agents [2].

Cell cycle specific agents such as vincristine have also been effective in multiple myeloma, especially when used in combination with alkylating agents [3, 4]. In a small number of patients we observed objective responses with vincristine in combination with prednisone [5]. The rapid onset of disabling neurotoxicity appeared to be the major side effect, sometimes even after a single dose. This is in contrast with other observations [3] and could possibly be related to the poor condition and the relatively advanced age of the myeloma patients we have treated. It was this side effect which was responsible for withdrawal of vincristine in most of our patients, and which has led us to consider a new vinca alkaloid: vindesine.

Vindesine (desacetyl vinblastine amide sulphate) is held to be more or less the intermediate between vincristine and vinblastine as far as pharmacokinetics and neurotoxicity are concerned [6]. The clinical value and anti-tumour effects of vindesine are still under study, while responses have been reported in acute lymphoblastic leukemia and in some types of non-Hodgkin lymphoma [7], in solid tumours such as breast carcinoma [8] and in non-small cell carcinoma of the lung [9].

In patients with advanced multiple myeloma who were no longer responsive to alkylating agents a short term study was started to test the clinical effects of vindesine.

A regimen of two cycles, each consisting of three injections of vindesine at weekly intervals combined with oral prednisone, was chosen on grounds relating to cell cycle kinetics of advanced multiple myeloma [10], as well as to the pharmacokinetics of vindesine [6, 11].

The responses to this vindesine–prednisone regimen in thirteen patients will be reported.

MATERIALS AND METHODS

Patients

Thirteen consecutive patients with advanced multiple myeloma who were no longer responsive to melphalan or to high dose cyclophosphamide, or who developed severe pancytopenia without a significant tumour response to this therapy, entered the study. Informed consent was obtained from every patient.

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Pancytopenia was defined as follows: leukocyte count below 1.5×10^9/l, platelet count below 50×10^9/l, and haemoglobin less than 100 g/l.

Vindesine was given as an intravenous bolus injection at weekly intervals for 3 consecutive weeks (initially at a dosage of 3 mg/m^2 body surface) followed by a therapy-free interval of 3 weeks. After the third patient had entered the study this dosage was reduced to 2 mg/m^2 because of neurotoxicity and leukopenia. Prednisone was given orally in daily doses of 100 mg for 5 days following each vindesine injection.

The following dosage modifications were used. In cases of severe neurotoxicity and bone marrow toxicity the next injection was withheld until the signs of toxicity had improved or until peripheral blood cell counts had returned to pretreatment values. In patients who were on the regimen using 3 mg/m^2 vindesine this dosage was reduced to 2 mg/m^2 after toxicity had occurred.

Patients were considered evaluable after having completed at least one course of 3 weekly injections of vindesine. Where possible the patients were evaluated 12 weeks after the first vindesine injection, e.g. after 2 courses of 3 weekly vindesine injections, each course followed by a 3-week therapy-free interval.

All patients were evaluated upon entry in the study and were staged [12]. Stage I disease patients had a low myeloma cell mass, and fulfilled all of the following criteria: haemoglobin >100 g/l, serum calcium <3.0 mmol/l, myeloma protein serum level for IgG <50 g/l, IgA <30 g/l, urine light chain excretion <4 g/24 hr. Stage II disease patients were intermediate, fitting neither stage I or III. Stage III disease patients fulfilled any of the following criteria: haemoglobin <85 g/l, serum calcium >3.0 mmol/l, advanced lytic bone lesions, myeloma protein level for IgG >70 g/l, IgA >50 g/l, urine light chain excretion >12 g/24 hr. Patients were subclassified A and B according to normal or abnormal renal function, respectively. Routine laboratory tests, including serum immunoglobulin levels, were performed at the time of the weekly vindesine injections. A skeletal X-ray survey was carried out at the start of the study and after 3 months. Tumour cell mass was calculated using myeloma protein levels, haemoglobin concentration, serum calcium levels and the extent of bone lesions as parameters [13]. Performance was scored to the Karnofsky scale [14].

The criteria of the South Western Oncology Group (SWOG) were used to define response, improvement and progression [15].

Response. A patient was considered to respond to therapy if all of the following criteria were met: (a) a sustained decrease of the production rate of myeloma protein to less than 25% of the pretreatment value; (b) the disappearance of Bence–Jones proteinuria; (c) anemia must have been corrected (haematocrit >27%) and serum calcium must have been normalised if these abnormalities were considered to be caused by myeloma; (d) lytic skeletal lesions must not have increased.

Improvement. A decrease in myeloma protein serum levels to less than 50% of the pretreatment level. Those patients who showed a decrease of myeloma protein to levels greater than 50% of the pretreatment values and who showed no progression were considered unresponsive.

Progression. Increased myeloma protein serum level, or increased Bence–Jones proteinuria; development of hypercalcaemia; increase or occurrence of new lytic lesions.

RESULTS

The results of vindesine therapy are given in Table 1. With one exception the patients were staged as IIIA or IIIB. Eleven out of the thirteen patients who entered the study could be evaluated. Six patients were considered to react favourably to the vindesine–prednisone combination (55%): two patients showed an objective response while four patients improved. With one exception (HdeJ) all patients could be evaluated according to the SWOG criteria. Median follow-up so far has been 5 months (range 1/2–8+ months). Of the five patients who died two had received incomplete courses and could not be evaluated. The other three patients who died developed bronchopneumonia (J-W, JS) or progressed to plasma cell leukemia (HW).

The regimen for the first three patients in which 3 mg/m^2 vindesine was used appeared to be too toxic: profound neurotoxicity, consisting of muscle weakness (HdeJ) and paraesthesias (deJ-B), was experienced as a serious and disabling side effect. One patient (H-O) also developed complete alopecia. Leukopenia (nadir 0.8×10^9/l after 7 days, patient H-O) and mild thrombocytopenia (nadir 72×10^9/l after 11 days, patient HdeJ) developed when this dosage was used. In patient H-O the leukocyte count improved to greater than 1.5

Table 1. *Patient characteristics*

Patients	Sex	Age	Type	Stage	Serum myeloma protein levels (g/l) or Bence–Jones excretion (g/24 hr) before and at the end of the treatment period	Karnofsky score	Treatment result	Follow-up period in months
W-L	F	65	IgG κ	IIIB	104–37	30–80	I	4 alive
N-B	F	70	IgG κ	IIA	47–23	60–90	I	6 alive
J-W	F	77	IgG κ	IIIA	83–40	60–60	I	$2\frac{1}{2}$ (†)
HW	M	57	IgG λ	IIIA	86–57	80–50	P	5 (†)
H-O	F	59	IgG λ	IIIB	71–54	30–80	NR	8 alive
JS	M	79	IgG λ	IIIA	133–54	50–70	R	5 (†)
K-M	F	79	IgA κ	IIIA	105–82	90–90	NR	7 alive
M-V	F	63	IgA λ	IIIA	31–26	60–60	NR	5 alive
vdL-S	F	38	BJ κ	IIIA	7.4–3.5	50–70	NR	5 alive
HdeJ	M	80	BJ κ	IIIA	<1.0–<1.0	60–80	I	8 alive
JK	M	56	BJ λ	IIIB	5.8–0.1	60–90	R	5 alive
deJ-B	F	60	IgG λ	IIIB	23–n.a.	70–0	NE	2 (†)
H-B	F	58	IgA λ	IIIB	30–n.a.	20–0	NE	$\frac{1}{2}$ (†)

R, Responded;
I, improved;
NR, non-responder;
P, progressive;
NE, not evaluable;
n.a., not available;
(†), died during the study.

$\times 10^9$/l in 2 weeks, and therapy was resumed at a dosage of 2 mg/m^2. In patient HdeJ neurotoxicity made it necessary to postpone vindesine administration for 5 weeks. The patients' thrombocytopenia gradually improved, and after 4 weeks values greater than 100×10^9/l were observed. In both patients subsequent treatment at the reduced dosage of 2 mg/m^2 did not lead to further complications. In the next ten patients the dosage of vindesine therefore was reduced to 2 mg/m^2, in other respects the same protocol was used. The results further mentioned in this study are related to this dosage, unless stated otherwise. This regimen was tolerated well with only mild and transient neurotoxicity in six patients, mainly consisting of paraesthesias, and with rapidly developing alopecia, which was almost total in four patients. Nausea of short duration occurred in three patients, while other possible side effects of vindesine such as vomiting, paralytic ileus and stomatitis were not observed. In two patients vindesine administration had to be postponed for one week during the second cycle, due to leukopenia (nadir 1.1×10^9/l and 1.2×10^9/l).

Vindesine treatment did not result in thrombocytopenia or in aggravation of preexisting thrombocytopenia. In one patient (K-M) severe thrombocytopenia with bleeding tendency even slightly improved after vindesine was started.

A few patients will be discussed in more detail. Patient H-B entered the study in a very poor condition, demonstrated by extensive skeletal destruction and renal as well as bone marrow insufficiency. This patient died of bronchopneumonia 17 days after vindesine was started with slight improvement of hypercalcaemia and skeletal pains. The other patient who could not be evaluated (deJ-B) refused any further treatment because of the alopecia which developed several days after the first injection of vindesine. She died two months later due to renal insufficiency and cardiomyopathy caused by the combination of multiple myeloma and amyloidosis. Patient H-O is recorded non-responsive, since the decrease in serum myeloma protein was less than 50%. However, this patient showed nearly complete disappearance of skeletal pains and improved bone marrow function, while she was able to resume her daily activities as a housewife, while living on her own, 8 months after vindesine therapy was started. Her Karnofsky score improved from 30 to 80%. Patient JK was on melphalan–prednisone treatment when his renal function deteriorated till he was considered as having terminal renal insufficiency. His creatinine clearance at that time was 6 ml/min, despite hydration and other conservative measures. After two courses of vindesine–prednisone his massive Bence–Jones proteinuria had dropped to less than 0.1 g/24 hr and his creatinine clearance had improved to 30 ml/min. Patient W-L had been treated with two cycles of melphalan–prednisone for a recently discovered multiple myeloma. She was referred with progressive severe hypercalcaemia, for

which she needed daily calcitonin injections, and with severe diffuse skeletal pains and impairment of both renal and bone marrow function. The myeloma protein serum level had remained unchanged during the melphalan–prednisone treatment. After the first vindesine injection serum calcium returned to normal within 24 hr, while after two courses she was able to walk with support. Renal function had normalised and bone marrow function had improved. The decreases in myeloma protein serum level and calculated tumour cell mass are shown in Fig. 1. This

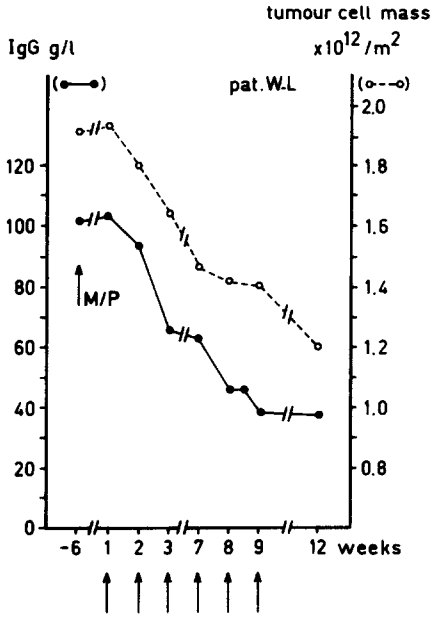

Fig. 1. Effect of vindesine–prednisone on myeloma protein level and tumour cell mass. (●—●) indicates IgG level, (○--○) indicates tumour cell mass. M/P indicates the last course of melphalan–prednisone, while the arrows at the bottom indicate the vindesine injections. (patient W-L).

patient was given vindesine–prednisone during the first 3 weeks, while she received vindesine only during the second course of 3 weeks. Patient JS was severely disabled by progressive skeletal pains while on melphalan–prednisone. He had improved impressively on vindesine but during maintenance treatment he developed bronchopneumonia, refused any further treatment and died subsequently. Leukocyte counts one week prior to this terminal illness were normal. The data on the changes of this patient's myeloma protein serum level and calculated tumour cell mass are given in Fig. 2. The low levels of urine Bence–Jones protein excretion in patient HdeJ did not allow evaluation by the SWOG criteria. This patient was considered as having improved because of a decrease in calculated tumour cell mass, disappearance of skeletal pains and an improved performance status, compared with progressive disease prior to vindesine treatment.

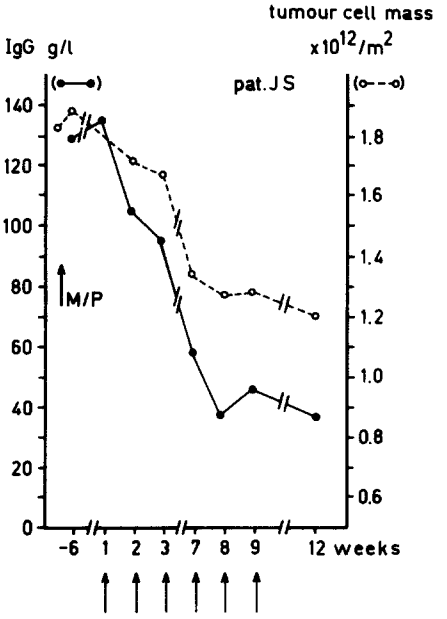

Fig. 2. Effect of vindesine–prednisone on myeloma protein level and tumour cell mass. (●—●) indicates IgG level, (○--○) indicates tumour cell mass. M/P indicates the last course of melphalan–prednisone, while the arrows at the bottom indicate the vindesine injections (patient J-S).

DISCUSSION

Treatment of multiple myeloma in patients with a poor prognosis or in advanced stages with melphalan-resistance is still a matter of discussion [3]. Therapy regimens which include vincristine have been advocated for early stages [3] and for poor risk patients [16], but have so far not been documented in advanced, melphalan-resistant myeloma. Based on our earlier experience with vincristine in myeloma where clinical improvement was accompanied by rapid onset of disabling neurotoxicity we started a pilot study with a different vinca alkaloid: vindesine. Although it is difficult to determine anti-tumour effects of a new drug without a controlled trial, the data presented strongly suggest anti-tumour effects of vindesine on multiple myeloma with only mild neurotoxicity. Part of the anti-tumour effects may have been caused by prednisone which was administered simultaneously, although the same dosage used previously in combination with melphalan or cyclophosphamide had been without demonstrable effect in these patients. This makes it highly probable that

vindesine was mainly responsible for the results obtained, a hypothesis strengthened by the observations in patient W-L (Fig. 1) when prednisone was not administered during the second course of vindesine injections and myeloma protein serum levels still continued to drop.

Vindesine as it was used in the present study exhibited rather mild side effects when the dosage had been reduced from 3 mg/m^2 to 2 mg/m^2 body surface per week. Bone marrow depression was slight at this dosage, occurred in two patients and appeared to be rapidly reversible. The overall effect of vindesine on thrombocytes seemed to be platelet sparing. In no case, not even in patients with preexisting pancytopenia, did aggravated thrombocytopenia occur. The incidence and severity of neurological side effects could also be reduced by decreasing the dosage of vindesine to 2 mg/m^2. The major side effect consisted of alopecia, which developed in four patients at this reduced dosage and was unacceptable for one patient, who refused any further treatment for this reason. The absence of severe bone marrow depression enabled the continuation of an effective cytotoxic therapy without prolonged therapy-free intervals at a stage where progression of the disease may be very rapid.

Tumour reaction in responsive patients was apparent soon after the first injection and generally a period of 3–6 weeks appeared to be sufficient to evaluate therapy response. The rapid fall in myeloma protein serum levels in responding patients resembled the normal T1/2 of serum immunoglobulins, and it seemed that production of myeloma proteins was effectively halted by vindesine. The absence of rebound production during the 3-week therapy-free interval indicated that vindesine also had another, more permanent effect on myeloma cells. This is supported by the rapid improvement in skeletal pain, the normalization of elevated serum calcium within 24–48 hr after injection and by the decrease in calculated tumour cell mass. Moreover, it appears that this effect can be maintained and in some patients even enhanced by a maintenance regimen, which also includes vindesine (to be reported elsewhere).

The results of this study strongly suggest anti-tumour activity of vindesine in melphalan-resistant multiple myeloma. The observed response rate of 6 out of 11 patients (55%) was clearly above expectations, and although only two patients fulfilled the SWOG criteria for response, four more patients showed definite improvement.

We conclude from these results that a trial in multiple myeloma including vindesine and starting at an earlier stage of the disease is justified. The absence of apparent cross-resistance with alkylating agents may also be a favourable factor in this respect.

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