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An EORTC Phase II Study of Vindesine in Advanced Prostate Cancer

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Abstract—*In a phase II study of vindesine in patients with bi-dimensionally measurable primary or metastatic prostate cancer, 27 patients (given 3 mg/m² weekly for at least 4 treatment cycles) were evaluable for response 6 weeks from the start of treatment. Dose escalation to 4 mg/m² weekly was attempted. Five patients (19%) achieved a partial remission of short duration, 11 patients (41%) showed no change and 11 patients (41%) showed progression. Thirty-one patients were evaluable for toxicity. Neurotoxicity occurred in 58% (severe in 23%) and was apparently cumulative dose-dependent, although there was variable individual sensitivity. Haematological toxicity was evidenced by lack of dose escalation in 32% of patients, dose delay in 71% and some degree of anaemia in 48%. Alopecia occurred in 55%. Other toxicities were few and minor. Vindesine shows marginal activity in prostatic cancer but at this dose schedule causes appreciable toxicity.*

INTRODUCTION

FEW CYTOTOXIC drugs have been evaluated on a phase II basis in advanced prostate cancer [1]. Cytotoxic chemotherapy is the only form of systemic treatment of potential value for patients resistant to or unresponsive to current forms of endocrine therapy. It is suggested that the role of combination and adjuvant chemotherapy in prostate cancer cannot be properly determined until the order of response for single agents is known from scientific studies.

In 1979 vindesine, a chemically derived structural analogue of vinblastine, was released to the EORTC Urological Group for use in a phase II study by Lilly Research, U.K. A report of a patient with advanced prostate cancer responding well to this treatment prompted the formulation of this study [2]. The objectives were to determine the response rate in patients in whom objective tumour response could be recorded, to estimate the duration of any response and to determine the incidence and severity of any toxic effects.

MATERIALS AND METHODS

It was agreed that the lowest limit of therapeutic activity of interest was an objective response rate of 20%, and that initially 29 patients would be entered. The study would be stopped if 3 or fewer responses were seen or if no responses were seen in the first 19 patients. This plan ensures that if the drug has a response rate of at least 25% the probability of rejecting it prematurely from further study is <0.05 [3].

Only patients for whom no other appropriate systemic treatment was available were studied. They were free to withdraw from the study at any time, for any reason. Patient entry required a histologically proven diagnosis of advanced prostatic carcinoma with bi-dimentionally measurable metastatic disease progressing despite continuing hormone therapy for patients with histopathological category G1/G2 lesions [4]. Patients with grade G3 tumours could be entered at diagnosis. Additive hormone therapy was

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‡‡See Table 2 for details.

stopped 4 weeks before the start of vindesine therapy in all but one patient. Previous chemotherapy (other than vindesine) did not disqualify, provided the last treatment was more than 4 weeks earlier.

In order to assess objective response rates lesions at the following sites were used, provided they were measurable in two dimensions: lung, subcutaneous deposits, lymph nodes, liver (scan) and osteolytic bone metastases. Sclerosis rather than shrinkage at the latter site would be the expected measurable response. Initially it was decided that the prostate itself could not be used as a marker lesion, but during the course of the study centres with experience in the use of intra-rectal ultrasound were allowed to enter patients with unmeasurable metastatic disease and to use the primary lesion as the marker lesion. However, brain metastases, serous effusions and osteoblastic bone metastases were not accepted as evaluable lesions because of difficulty of measurement. Similarly, serum acid phosphatase and other biochemical parameters were not used in the assessment of response.

Patients of any age were acceptable, but they had to have an estimated survival time of at least 90 days, an initial white cell count $> 3.0 \times 10^9/l$ and a platelet count $> 100 \times 10^9/l$. Patients who had been treated for another neoplasm were excluded from the study, as were patients who, in the opinion of the investigator, had other medically untreatable life-threatening diseases preventing adherence to the treatment schedule or where there was likely to be difficulty with follow-up. Patients with neurological conditions which would interfere with the evaluation of neurological toxicity were also excluded since this was an expected side-effect.

Pre-treatment evaluation included history and physical examination, height, weight, blood count, standard biochemical screen, serum acid phosphatase, chest X-ray, bone scan and liver scan if indicated, together with any other investigation thought necessary. Follow-up studies included blood counts and routine biochemistry before each course of treatment. Investigations necessary for the assessment of indicator lesions were repeated at the 6th week and provided that a response or no change category existed, these investigations were repeated at 6-weekly intervals (less if progression was suspected).

The initial dose of vindesine was 3.0 mg/m^2 per week, increasing by 0.5 mg/m^2 weekly to a maximum dose of 4.0 mg/m^2, providing toxicity allowed. Vindesine was given either directly into a vein by bolus injection or into the tubing of a fast-running intravenous infusion. Dose modification was not allowed, but if depression of the blood (WBC $< 3 \times 10^9/l$ or platelet counts $< 100 \times 10^9/l$) occurred a halt in dose escalation was allowed and/or the weekly dose was omitted. Treatment was to be given on a weekly basis up to 12 weeks, after which it was left to the individual investigator to continue treatment at increased intervals, with a maximum of 3 weeks between injections. Treatment was only continued as long as tolerance and patient compliance allowed, and provided that a response or no change category existed. If progression of disease was observed at or after 6 weeks of treatment the treatment was stopped and the patient went off-study.

Response criteria were: complete remission (CR): complete disappearance of all objective parameters; partial remission (PR): more than a 50% reduction in the sum of the products of the two largest perpendicular diameters of all measurable lesions, with no new lesion appearing; no change (NC): less than 50% reduction or less than 25% increase in the sum of the products of the two largest perpendicular diameters, with no new lesion appearing; progression (P): increase greater than 25% of the sum of the products of the two largest perpendicular diameters or the appearance of any new lesion; early death (ED): death occurring during the first 6 weeks due to tumour progression. Patients were considered evaluable for response if they had received a minimum of 4 cycles of treatment in the first 6 weeks. Patients who received less treatment and who otherwise fulfilled the study criteria were considered evaluable for toxicity only. An extra mural review of the case notes of the partial responders was undertaken by the study co-ordinator.

RESULTS

The study was started in October 1979 and closed to recruitment in December 1981. Forty patients were entered (Table 1) of whom nine

Table 1. Patient's evaluability

	No. of patients (%)
Evaluable for toxicity	31 (78%)
Evaluable for response	27 (68%)
Inevaluable for response	4 (10%)
Early death	2
Refused further treatment	2
Ineligible	9 (22%)
No marker lesion	4
No histology	1
G2 non-pretreated	1
No forms	1
Wrongly entered	2
Total patients entered	40 (100%)

Table 2. Evaluable patients by institute/investigator

Institute	Investigator	No. of patients
Amsterdam, Netherlands,		
Free University Hospital	G. Stoter	1
Ankara, Turkey,		
Hacettepe University Hospital	A. Akdas	4
Antwerp, Belgium,		
A. Z. Stuivenberg	K. Van Camp	2
Antwerp, Belgium,		
Middleheim Ziekenhuis	L. Denis	4
Huddersfield, U.K.,		
Huddersfield Royal Infirmary	R. W. Glashan	3
Leeds, U.K.,		
Regional Radiotherapy Centre,	L. Campbell-Robson	1
Cookridge Hospital	W. G. Jones	4
Leeds, U.K.,		
St. James's University Hospital	P. H. Smith	1
Oslo, Norway,		
Norwegian Radium Hospital	S. Fosså	5
Pontefract, U.K.,		
Pontefract General Infirmary	M. R. G. Robinson	1
Reims, France,		
Centre Jean Godinot	P. Coninx	3
Rotterdam, Netherlands,		
Radio-Therapeutisch Institute	J. Alexieva-Figusch	1
York, U.K.,		
York District Hospital	B. Richards	1

Table 3. Patient characteristics by response groups (at 6 weeks)—27 evaluable patients

	Response*		
	Partial response	No change	Progression
No. of patients	5 (19%)	11 (41%)	11 (41%)
Average age (yr)	53.2	67.4	62.3
Histology			
GX	0	1	1
G1	1	1	1
G2	2	6	1
G3	2	3	8
Previous treatment			
None†	1	0	0
Radiotherapy‡	4	5	4
Orchidectomy	0	9	9
Oestrogens	4	5	8
Progestogens	0	1	0
Estracyt®	2	2	4
Single-agent chemotherapy	0	0	4
Combination chemotherapy	1	1	3
Marker lesions§			
Lung (CXR)‖	2	3	3
Subcutaneous	1	1	1
Superaclavicular lymph node(s)	2	0	2
Inguinal lymph node(s)	1	1	1
Bone (lytic)	0	4	6
Mediastinal mass	0	2	1
Retroperitoneal nodes (CT)¶	0	0	1
Prostate (U/S)**	0	0	1
Liver	1	0	0

*No complete responses seen.
†Including no androgen deprivation.
‡None to indicator lesions.
§In some patients > 1 lesion was assessed.
‖Chest X-ray.
¶Computerised tomography.
**Ultrasound.

(22%) were ineligible. Clinicians and institutions entering evaluable patients are listed in Table 2. Thirty-one (78%) were evaluable for toxicity (mean age 63.6 yr, range 40–82 yr) among whom 27 (68%) were evaluable for response at 6 weeks. Of the 4 patients who were not evaluable for response, 2 (from the same centre) suffered non-drug-related early death and 2 refused further therapy after 2 courses (one because of neurotoxicity; the other did not wish to attend hospital).

Response

In the 27 patients evaluable for response, 211 courses of treatment were given (minimum 4, maximum 19, average 7.8).

The responses seen at the 6-week assessment are detailed in Table 3. No complete responses were observed. There were 5 partial responses, 11 patients in a no change state and 11 had progressed. No patient improved response category with continued treatment.

On the whole responses were of short duration. (Fig. 1). The median time to progression (from day 1 of treatment) for the response groups was: PR, 16 weeks; NC, 11 weeks; and P, 6 weeks.

The response by site of marker lesion is also presented in Table 3. Occasionally more than one marker lesion site was evaluated in the same patient. The table shows patient characteristics of age, histology grade and previous treatments in the response groups. It was noted that none of the 5 patients in the PR group had previously undergone orchidectomy compared with 18 of the 22 patients in the no change and progression groups. Using the Fisher exact test for small frequencies in a 2×2 contingency table, there was a significant difference between these groups ($P = 0.01$). No other significant difference between the patients in the response categories was discovered, including an analysis of the time from first diagnosis of prostate cancer to entry into this study. The serum acid phosphatase did not appear helpful as a tumour marker.

Toxicity

Toxicity was recorded in almost all 31 patients to some degree (Table 4). The principal side-effects were haematological and neurological. Other toxicities, apart from alopecia, were mild and few in number.

Thrombocytopenia was seen only in the one patient with bone marrow infiltration by tumour. The effect of vindesine on the white blood count prevented dose escalation in 32% of patients, and resulted in dose delay of one or more courses in 71%. Progressive anaemia was encountered in 48% of patients, often requiring blood transfusion for correction.

Neurotoxicity was by far the most significant toxicity occurring in 59% of patients. The severity of this side-effect was to some extent cumulative dose-dependent, although there was considerable individual variation and sensitivity. The effects are reversible with time. Neurotoxicity was

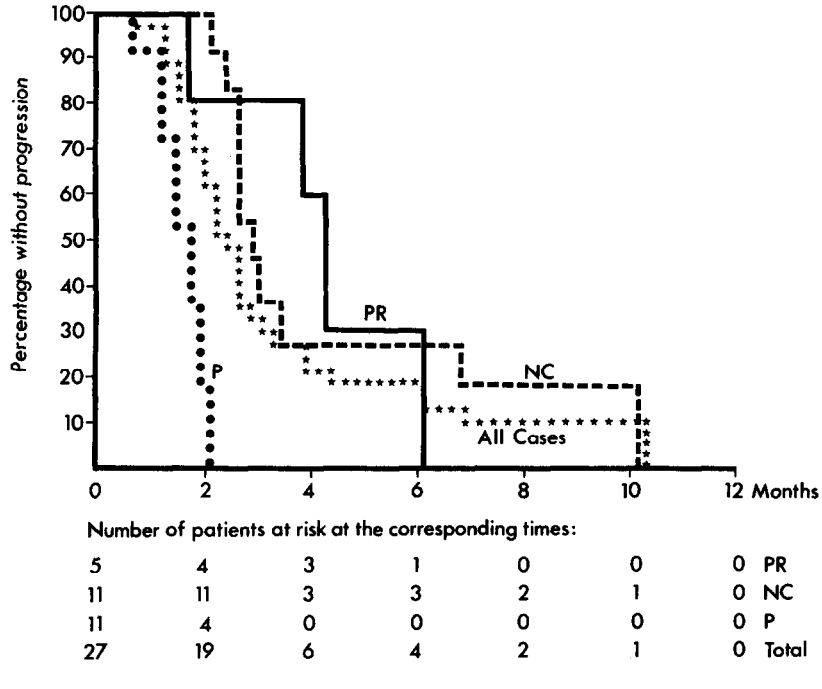

Fig. 1. Vindesine in prostate cancer—time to progression from day 1 of treatment by response groups (27 evaluable patients).

Table 4. Toxicity

	Patients (%)
Haematological toxicity	
No dose escalation	10 (32)
Dose delay (low WBC)	
1 course	6 (19)
2 courses	6 (19)
3 courses	6 (19)
4 courses	2 (6)
5 courses	2 (6)
None	9 (29)
Anaemia	15 (48)
Thrombocytopenia*	0 (0)
Neurotoxicity	
None	13 (42)
Mild	8 (26)
Moderate	3 (10)
Severe	7 (23)
Symptoms/signs	
Constipation	6 (19)
Paraesthesia	16 (52)
Depressed reflexes	10 (32)
Motor/sensory neuropathy	5 (16)
Myalgia	6 (19)
Muscle weakness	8 (26)
Muscle fasiculation	2 (6)
Cramps	3 (10)
Balance disturbance	2 (6)
Blurring of vision	1 (3)
Other toxicities	
Alopecia†	17 (55)
Nausea/vomiting	4 (13)
Diarrhoea	3 (10)
Fever	2 (6)
Tachycardia	1 (3)
Renal	0 (0)
Liver	0 (0)
Total	31 (100)

*Excepting one patient with bone marrow infiltration.

†Three patients had previous chemotherapy.

similar to that of the other vinca alkaloids, but in seven patients (23%) this progressed to a severe mixed motor and sensory neuropathy of sudden onset resulting in the discontinuation of vindesine.

DISCUSSION

Anecdotal reports of the use of vindesine in prostate cancer have been encouraging [2, 5, 6]. This is the first phase II study of this drug in advanced prostate cancer and reveals only marginal activity of the drug. Responses were of short duration and toxicity was considerable, but comparable to that described elsewhere [7–10]. Prostate cancer is a difficult disease in which to undertake phase II chemotherapy studies since the primary disease and the predominent metastatic lesions (osteoblastic bone metastases) are impossible to measure routinely for the assessment of response. Intra-rectal ultrasound can now be used to assess the primary lesion [11]. Only approximately 10% of patients have measurable soft tissue disease [12], although newer diagnostic tools (e.g. CT scan and ultrasound) will increase this percentage. Osteolytic lesions were acceptable for response measurement for this study, but it is debatable whether this is correct, and in the present EORTC Urological Group phase II study (30804—mitomycin-C) in advanced prostate cancer they are not accepted. In a phase II study additional medication which is likely to affect the response or influence the disease must not be given. Therefore additive hormone therapy was stopped one month before vindesine was started to avoid this complication. Some clinicians dislike this approach for fear of an accelerated relapse. In this study one patient was restarted on additive oestrogens before chemotherapy started. He was shown to have progressive disease at the 4th week on study despite vindesine and continuing hormone therapy.

The hormonal effects of an orchidectomy cannot be withdrawn like those of additive oestrogens. There was a statistically significant difference in the numbers of patients who had had an orchidectomy in the response groups, there being no orchidectomised patients in the PR group. This difference was just significant and should be confirmed in subsequent studies before conclusions are drawn. It seems unlikely that a withdrawal effect of endocrine treatment is responsible for the remissions observed. However, other factors may be operating in a combined fashion, including differences in 'G' category and greater numbers of previously applied treatments, possibly indicating a more aggressive or more advanced disease, especially in the progression group.

It is suggested that the incidence of toxicity could be lowered considerably by increasing the interval between doses, not escalating the dose above 3 mg/m^2 and considering infusion instead of bolus injection [13]. If no response is seen after 3–4 doses further treatment is unlikely to produce one.

In conclusion, an objective response rate of 19% has been determined in this study of vindesine in prostate cancer. This compares with rates of 24% for *cis*-platinum and 23% for adriamycin quoted in a review article by Smith [1]. In view of this low figure and the toxicity observed, it is unlikely that vindesine has any role in the management of prostate cancer.

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