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Vindesine in Advanced Renal Cancer. A Study of the EORTC Genito-urinary Tract Cancer Cooperative Group*

SOPHIE D. FOSSÅ,† LOUIS DENIS,‡ ALLAN T. VAN OOSTEROM,§ MARLEEN DE PAUW‖ and GERRIT STOTER¶**

†*General Department, The Norwegian Radiumhospital, Oslo, Norway,* §*Department of Urology, University Hospital, Middelheim, Antwerpen, Belgium,* §*Department of Clinical Oncology, University Hospital, Leiden, The Netherlands,* ‖*EORTC Data Center, rue Heger-Bordet,* 1, 1000 *Bruxelles, Belgium and* ¶*Oncological Department, University Hospital, Amsterdam, The Netherlands*

Abstract—*Vindesine at a dose of* 3 mg/m^2 *i.v. once a week failed to produce responses in* 24 *adequately treated patients with measurable advanced renal carcinoma. Leukopenia and peripheral neurotoxicity were the most often observed side-effects. On the basis of the negative result, the application of vindesine in this disease is not recommended.*

INTRODUCTION

THE RESULTS of chemotherapy and hormone treatment in renal cell carcinoma (RCC) are disappointing [1]. However, vinblastine has been reported to yield a remission rate of 25% [2], but when these data are examined carefully it is more likely that the true remission rate seems to be between 10 and 15%.

Recently the EORTC Genito-urinary Tract Cancer Cooperative Group has initiated a series of single-agent phase II studies in measurable advanced RCC. Methylglyoxal-bis-guanylhydrazone, the first drug tested, showed minimal anti-cancer activity (10% partial remissions) and had significant toxicity [3]. The next cytotoxic drug to be studied was vindesine. The results of this phase II study are reported here.

Vindesine is a vinca alkaloid derivate with a wide spectrum of anti-tumour activity in animal test systems [4] and in a number of human tumours [5–9]. In renal cell cancer the drug's cytotoxic activity has been proven by minor regression or stabilisation of the disease [10, 11]. Bone marrow suppression and neurotoxicity have been reported to be the main side-effects [6, 8, 10].

MATERIAL AND METHODS

Twenty-seven patients (18 males, 9 females) with histologically proven measurable advanced RCC were entered into a phase II study using vindesine (3 mg/m^2 i.v. every week for 6 weeks, and every 2 weeks thereafter). All patients were under 75 years of age (mean 56.8) and had a WHO performance status ≤ 2. Only 3 patients had received prior systemic therapy by cytotoxic or hormonal drugs. Patients with severe hepatic dysfunction (serum bilirubin > 75 μmol/l), white blood cell count below 3×10^9/l, platelet count below 100×10^9/l, previous treatment with vinca alkaloids or brain metastases were ineligible. Three patients were not evaluable for response: one patient refused treatment after randomisation prior to the first injection; a second patient denied further injections after the first vindesine application; and for the third patient sufficient information about the treatment with vindesine was lacking. In 13 of the remaining 24 patients the disease had progressed during the last 2 months prior to trial entry. Further patient characteristics are shown in Table 1. Pretreatment studies included physical examination, with evaluation of the neurological status, blood cell counts, serume creatinine analysis, liver function tests

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Table 1. Patient characteristics

	No. of patients
Registered patients	27
Non-evaluable patients	3
Evaluable patients	24
Prior treatment:	
No treatment	2
Surgery only	16
Surgery + chemotherapy	1
Surgery + radiotherapy	3
Surgery + chemotherapy + radiotherapy	1
Surgery + hormone therapy	1
Marker lesions:	
Lung	15
Metastatic lymph nodes	4
Subcutaneous nodules	2
Primary tumour*	1
Metastatic lymph nodes + lung	1
Liver metastases* + primary tumour*	1

*Measurable by computer tomography.

and chest X-ray. Blood cell counts and the evaluation of the neurological status were repeated weekly prior to each dose of vindesine.

To be evaluable for response the patient should have received vindesine for at least 4 weeks. The evaluation of response was performed prior to the 5th vindesine injection and thereafter every month using the WHO criteria for response [12]. Computerised tomography and ultrasound echography were accepted as means of measuring indicator lesions. The weekly dose of vindesine was decreased by 50% in case of leukopenia ($2.0–3.0 \times 10^9/l$), thrombocytopenia ($50–100 \times 10^9/l$), paresthesias or hepatic dysfunction (serum bilirubin 25–50 μmol/l). If more severe toxicity was observed, treatment was delayed for 1 week. The degree of side-effects was graded according to the WHO criteria [12] (Table 2).

RESULTS

Response to treatment

The 24 evaluable patients received between 4 and 17 vindesine injections (median, 6). No complete or partial remissions were observed. In 10 patients the disease remained stable and in 14 progression was reported. Of the 10 patients with stable disease 5 had been reported to have progressive disease during the last 2 months prior to treatment.

Toxicity

Dose reductions or treatment delay due to leukocytopenia (grade 1–2) had to be applied 16 times in 15 patients. Neurotoxicity was cumulative and was observed in 10 patients, the symptoms starting after 3–4 injections. (Grade 1, 8 pts; grade 2, 1 pt; grade 3, 1 pt.) The neurological side-effects were the main reason why vindesine was discontinued after 6–8 weeks of treatment. Nausea, vomiting (10 patients) and diarrhoea (4 patients) were mainly of grade 1–2. Alopecia was observed in 6 patients but was wig-requiring in only 1. In 3 patients grade 1 hepatic dysfunction and in 1 patient grade 1 renal toxicity were observed during vindesine treatment.

DISCUSSION

This report does not confirm previous preliminary results showing some anti-tumour activity of vindesine (minor responses) in advanced renal cell cancer [10, 11]. No response to vindesine treatment was observed in the present study. 'Stable disease' or 'minimal regression' was

Table 2. Grading of toxicity

	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
Leukocytes ($\times 10^9/l$)	≥ 4.0	3–3.9	2–2.9	1–1.9	< 1.0
Platelets ($\times 10^9/l$)	≥ 100	75–99	50–74	25–49	< 25
Nausea/vomiting	none	nausea	transient vomiting	vomiting requiring therapy	intractable vomiting
Diarrhoea	none	transient, < 2 days	tolerable but < 2 days	intolerable requiring therapy	haemorrhagic dehydration
Hair loss	none	minimal hair loss	moderate, patchy alopecia	complete alopecia but reversible	non-reversible alopecia
Peripheral neurotoxicity	none	paresthesias and/or decreased tendon reflexes	severe paresthesias and/or mild weakness	intolerable paresthesias and/or marked motoric loss	paralysis

not considered to represent any beneficial effect of treatment, even in patients with progressing disease prior to registration. In renal cell cancer periods of progression may spontaneously alternate with intervals of stable disease. In about 1% of the patients spontaneous regression of metastases may be observed [13]. Therefore the cytotoxic activity of a chemotherapeutic agent in RCC can only be proven by documentation of a substantial complete and partial remission rate.

Due to the expected toxicity [6, 8–11] and the observed side-effects in a previous EORTC study with vindesine [14], the weekly dose in the present protocol was chosen to be 3 mg/m^2 rather than 4 mg/m^2 as recommended by other authors [7, 10, 11]. No dose increase was performed. However, the dose of vindesine used in the present study is now generally considered to be optimal. Cumulative peripheral neurotoxicity, though only rarely severe, was an unacceptable side-effect in 10 of 24 patients who were on vindesine treatment for more than 4 weeks. Due to these side-effects, the use of vindesine over longer periods seems to be limited. Haematological and other side-effects were minor and easily manageable. It remains uncertain whether the observed minor disturbances of the renal and liver function tests represented treatment-related side-effects or progressive metastatic disease. Toxicity-related change in hepatic (SGPT) and renal (serum creatinine) function tests due to vindesine was not reported by others [15].

In conclusion, vindesine has no role to play in the treatment of renal cell carcinoma.

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