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Vinblastine in Metastatic Renal Cell Carcinoma: EORTC Phase II Trial 30882

Sophie D. Fosså, Jean-Pierre Droz, Michele M. Pavone-Macaluso, Frans J.J. Debruyne, Karine Vermeylen, Richard Sylvester and the members of the EORTC Genitourinary Group.

32 patients with metastatic renal cell carcinoma (MRCC) who had had no prior chemotherapy received vinblastine 0.15 mg/kg intravenously once weekly for 6 weeks, thereafter every second week, provided no major toxicity. Dose modifications were based on haematological and neurological side-effects. Only one complete response was observed among 26 evaluable patients (response rate: 4%; 95% confidence interval: 0–20%). 4 out of 29 patients developed grade 3 leukopenia. Grade 3 peripheral neurotoxicity was recorded in 2 patients. 2 patients had grade 3 alopecia. Vinblastine has no major significance on the clinical management of MRCC.
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INTRODUCTION

THE EFFICACY of chemotherapy in metastatic renal cell carcinoma (MRCC) has been limited [1, 2]. Vinblastine has been reported to be the most active drug [3] with claimed response rates up to 25% [4]. However, not all older trials meet the strict criteria of a phase II study. Therefore the EORTC Genitourinary Group decided to re-evaluate the efficacy of weekly bolus injections of vinblastine in MRCC.

PATIENTS AND METHODS

From 1988 to 1990 eight institutions entered 32 patients with measurable MRCC into the EORTC phase II trial 30882 (Table 1).

Patients were eligible for the trial if they had shown progression of bidimensionally measurable metastases from renal cell carcinoma during the 2 months preceding the trial entry. Other eligibility criteria were: age below 65 years, performance status (WHO): 0 or 1, adequate renal and liver function, no previous chemotherapy, whereas prior hormone treatment and immuno-modulating therapy was allowed provided that all treatment had been stopped for at least 4 weeks before trial entry. Informed consent was obtained from all the patients.

Treatment

Vinblastine 0.15 mg/kg was injected into a line of a running normal saline infusion, once every week for 6 weeks. Thereafter

Table 1. Patients' characteristics

No. of eligible patients	31
No. of patients evaluable for response	26
Male/female	23/8
Age (years)	53* (37–64)†
Performance status (WHO)	
0	10
1	21
Weight loss prior to trial entry	
≤ 5%	21
6–10%	4
11–20%	3
unknown	3
Time from initial diagnosis to treatment start (weeks)	51* (0–513)†
Pre-trial treatment	
Surgery	28
Radiotherapy	7
Hormone treatment	4
Interferon	9
Sites of indicator lesions	
Lung	17
Lymph nodes	11
Liver	5
Skin	2
Other	3

* Median, † range.

treatment was continued by one intravenous injection of vinblastine 0.15 mg/kg given every second week until development of progressive disease or unacceptable toxicity.

Dose modification

The weekly vinblastine injections were postponed for 1 week if the leucocyte count fell below 3.0×10^9/l or platelets below 120×10^9/l. In such cases the subsequent vinblastine dose was to be reduced by 25%. If no haematological recovery was observed after 1 week's postponement, treatment was to be delayed for a further week. If treatment had to be delayed for more than 2 weeks, the patient went off study. A 25% reduction of the single dose was also recommended in case of grade II peripheral neurotoxicity. Treatment had to be discontinued in case of grade III peripheral neurotoxicity, but could (on the discretion of the investigator) be restarted with a 25% dose reduction after improvement of the neurological symptoms.

Response evaluation

The response rate was evaluated according to the WHO criteria [5] after a minimum treatment time of 6 weeks. Patients progressing before the end of the 6 weeks' treatment were included in the category 'progressive disease'.

RESULTS

1 of the 32 patients entered was subsequently deemed to be ineligible. Of the remaining 31 patients 2 were not evaluable for response or toxicity (incomplete data: 1; treatment not given according to the protocol: 1) and 3 patients were only evaluable for toxicity, leaving 26 completely evaluable patients.

A median of 5.5 cycles (range: 1–9) was given to the 29 evaluable patients. All treatment was given on an out-patient basis.

Only 1 complete response (liver metastases evaluated by ultrasound) was seen in the 26 completely evaluable patients. (response duration: 28+ months). 8 patients had stable disease and 17 patients had progressed at the first response evaluation.

The main toxicities were leukopenia (grade 1: 8; grade 2: 8; grade 3: 4), nausea/vomiting (grade 1: 2; grade 2: 4; grade 3: 1) and peripheral neuropathy (grade 1: 3; grade 2: 1; grade 3: 2). 5 patients developed alopecia (grade 1: 2; grade 2: 1; grade 3: 2). The vinblastine dose was reduced at least once in 9 patients and delayed in 10, mainly due to leukopenia and/or peripheral neuropathy.

DISCUSSION

Our series comprises mainly 'good risk' patients (good performance status, lung metastases only in 12 patients), who received relatively high doses of vinblastine. However, 9 patients had progressed on prior interferon therapy, which might represent a negative selection criterion.

Our response rate of only 4% [95% confidence interval (CI): 0–20%] is in disagreement with results from older *in vitro* [3] and clinical [4] studies. The present results compare, however, favourably with recent studies demonstrating a ≤ 10% response rate when using intravenous continuous 5 days infusions of vinblastine [6, 7], and support observations on inefficacy of combination treatment containing vinblastine [8].

Though the overall toxicity of vinblastine is mild, certain safety rules should be considered when vinblastine is given to patients with MRCC: The white blood cells must be monitored regularly and vinblastine doses have to be delayed and/or reduced according to leucopenia. Peripheral neuropathy represents the most important non-haematological toxicity and may necessitate discontinuation of the drug.

Patients with measurable MRCC should principally be entered into clinical trials evaluating experimental treatment. The most actual therapeutic approaches today comprise immunomodulating therapies with interferon [9] and/or interleukin-2 [10], achieving a 15–30% response rate. If this is not possible and the patient and/or the doctor considers systemic treatment, a 6–8 week trial with weekly intravenous vinblastine does not seem to be a completely unreasonable therapeutic alternative, not at least on the background of the inefficacy and toxicity of other cytostatics in MRCC [8]. In spite of occasionally impressive responses during treatment with vinblastine, the drug, however, has no major significance in the clinical management of MRCC.

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Prolonged Chemotherapy for Localised Squamous Carcinoma of the Oesophagus

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We evaluated the feasibility of six courses of chemotherapy in 34 consecutive patients with localised squamous cell carcinoma of the oesophagus. All 32 evaluable patients first received at least two courses of chemotherapy. There were 18 patients with resectable carcinomas who underwent surgery and 14 patients with unresectable carcinomas who received definitive chemoradiotherapy. After two courses of 5-fluorouracil and cisplatin 21 (66%) of 32 patients had either a complete or major response. A median of five courses (range, 1–6 courses) was administered. 17 out of 18 (94%) patients with resectable carcinoma had a 'curative' resection (negative proximal, distal, and radial margins by histopathology in an en-block resection specimen) and 2 patients had a complete pathological response. The median survival duration of all patients was 28 months (range, 2–46+ months). The median survival duration of 14 patients with unresectable carcinoma was 23 months (range, 8–36+ months), and the median survival duration of 18 patients with resectable carcinoma has not been reached at a median follow-up of 24+ months (range, 10+ to 46+ months). No deaths occurred because of chemotherapy or chemoradiation therapy. Our data suggest that prolonged chemotherapy is feasible in patients with locoregional squamous carcinoma of the oesophagus. An ongoing controlled trial will determine the contribution of chemotherapy to patients' survival.
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INTRODUCTION

CARCINOMA OF the oesophagus results in 5-year survival rates less than 6% which have not changed over the past 4 decades [1]. At the time of diagnosis, only 48% of patients have carcinoma confined to the oesophagus or regional lymph nodes [1]. Unless adequately controlled, the primary carcinoma is the common cause of morbidity and mortality.

The results of treatments to control the primary carcinoma have been dismal producing median survival rates well below 18 months [2, 3]. The 5-year survival rates following surgery have ranged from 1% to less than 20%, and the median survival duration has been 12 months or less [2, 4–6]. Similarly, treatments with definitive or palliative radiotherapy have resulted in poor 5-year survival rates as well [3, 7, 8]. The increased sensitivity with potential radiocurability of squamous cell carcinoma of the oesophagus to radiotherapy has long been known [9]; similarly, its sensitivity to many chemotherapy agents has been noted [10, 11]. More recently, the introduction of chemotherapy in the treatment of localised carcinoma has led to several newer approaches.

Chemotherapy has been employed in two common strategies. First, one or two courses of combination chemotherapy have been administered before surgery [12–14]. Second, combination chemotherapy and concurrent radiotherapy (chemoradiation therapy) have been administered [15–19] prior to surgery or chemoradiation therapy has been used as a definite method to eradicate localised carcinoma [20–22].

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