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Phase II study of vinflunine in patients with metastatic renal cell carcinoma

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Summary *Purpose:* An open-label, multicentre, non-comparative phase II trial to determine the response rate of intravenous vinflunine as first line chemotherapy in patients with metastatic renal cell carcinoma (RCC). *Patients and methods:* Patients with metastatic RCC were treated with vinflunine 350 mg/m^2 ($n = 11$) or 320 mg/m^2 ($n = 22$) administered intravenously every 21 days. *Results:* Out of 33 patients included in this study, one partial response was observed in the group treated at 350 mg/m^2 and none in the group receiving 320 mg/m^2 resulting in a response rate in this population of 9.1% (95% CI: 0.2–41.3). Median progression free survival was 5.6 months (95% CI: 2.8–14.4) for patients treated at 350 mg/m^2, and 3.3 months (95% CI: 1.6–6.4) for those treated at 320 mg/m^2.The median survival time was 10.4 months (95% CI: 6.8–12.4) for the whole study population. The principal toxicities were grade 3/4 neutropaenia —90.9% at 350 mg/m^2 and 68.1% at 320 mg/m^2, febrile neutropaenia was recorded in 3 patients (27.3%) at 350 mg/m^2 and in 5 patients (22.7%) at 320 mg/m^2. One episode of thromboembolic event was reported in 1 patient at each dose level. *Conclusion:* Vinflunine given intravenously once every 3 weeks has not shown any clinically relevant activity in the management of patients with metastatic renal cell carcinoma; tolerance of the treatment was better at a dose of 320 mg/m^2 than at 350 mg/m^2.

Keywords Vinflunine · Renal cell carcinoma

Introduction

Metastatic renal cell carcinoma is characteristically unresponsive to chemotherapy [1]. Although modest progress has been made with immunotherapy [2] and more recently with angiogenesis inhibitors [3–5], identification of other active agents remains a priority. Vinblastine has been found

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to be one of the few consistently active agents identified, inducing objective responses in 7 to 15% of patients [6].

Vinflunine is a novel third generation vinca alkaloid with superior antitumor activity compared to its parent compound vinblastine. It has demonstrated *in vivo* activity against seven of the eleven xenografts studied exhibiting a high level of activity against RXF944LX experimental renal cell carcinoma [7]. Moreover, in the initial Phase I trials, one patient with RCC achieved a partial response and another achieved prolonged disease stabilisation [8]. Therefore, this first bifluorinated antitubulin agent was a good candidate to be tested in patients with metastatic renal cell carcinoma as first line chemotherapy.

During the course of this study data emerged from 3 phase II studies ongoing at the time of commencement of the present trial, Preliminary phase II safety data available for 28/40 patients and for 52 cycles administered showed that six patients experienced eight episodes of febrile neutropenia and/or sepsis: three of them experienced a septic shock unresponsive to resuscitation (2 patients with a metastatic Renal Cell Carcinoma and one with a pretreated Transitional Cell carcinoma of the Bladder). This led to a reduction in the starting dose for the trial. Therefore we report the outcomes of this study in two separate cohorts

Patients and methods

This study was an open-label, multicentre, non-comparative phase II trial. It was designed to determine the efficacy of vinflunine in patients with advanced metastatic renal cell carcinoma, previously untreated by chemotherapy. The primary objective was to assess efficacy in terms of response rate. The secondary objectives were to assess the duration of response, progression free survival (PFS) and overall survival (OS), and to evaluate the toxicity associated with this treatment. The protocol and its amendments were submitted to Independent Ethics Committees (IEC) according to local requirements. The study was conducted in accordance with the ethical principles set forth in the Declaration of Helsinki (Somerset West 1996) and in compliance with Good Clinical and Laboratory Practices. Written informed consent was obtained from each participating patient prior to entry into the study.

Patient selection

Patients were recruited from eight active centres between December 2000 and January 2002. Patients eligible for the study were required to (i) have a histological diagnosis of metastatic renal cell carcinoma with documented evidence of progressive disease and (ii) have been previously untreated by chemotherapy. Patients were eligible if they had received immunotherapy, and either failed or progressed, providing they had recovered from all side effects. The presence of at least one bidimensionally measurable lesion, assessed by CT-scan performed less than 28 days before first day of study drug administration, was required. Patients were required to be aged ≥ 18 years with Karnofsky Performance Status (KPS) $\geq 80\%$ and an estimated life expectancy of at least 12 weeks. Evidence of adequate bone marrow function (Absolute Neutrophil Count $\geq 2.0 \times 10^9$/L, Platelets $\geq 100 \times 10^9$/L), hepatic function (Bilirubin $\leq 1.5 \times$ upper normal limit (UNL), Transaminases $\leq 2.5 \times$ UNL, unless due to liver involvement), renal function [defined as calculated creatinine clearance >/= 40 mls/min using the Cockroft and Gault formula] and a normal ECG was required. Patients with CNS metastases were excluded.

Treatment schedule

Vinflunine was administered every three weeks in normal saline as a 10-min intravenous infusion. Tolerance was assessed throughout the treatment period and before each administration according to the NCI Common Toxicity Criteria (Version 2.0). All patients who received at least one cycle of treatment were considered as evaluable for safety. The use of hematopoietic growth factors (G-CSF) was allowed for patients with febrile neutropenia or neutropenic infections according to local practice.

Vinflunine scheduled on Day 1 every 3 weeks had to be delayed by 1 or 2 weeks in the case of hematological or non-hematological toxicity (grade >2 toxicity impacting a major organ, except for alopecia). The dose was to be reduced to 280 mg/m^2 from the next cycle if febrile neutropenia and/or grade 4 neutropenia ($<0.5 \times 10^9$/L) lasting 7 days or more was observed between two consecutive administrations of vinflunine. If this toxicity was observed again after a dose reduction, the dose was to be further reduced to 250 mg/m^2. If the same event recurred at this reduced dose level, the treatment was to be stopped. Blood counts were to be performed every two days until recovery of ANC $\geq 1.0 \times 10^9$/L. No dose re-escalation was allowed after dose reduction. In case of grade 2 mucositis and/or constipation lasting more than five days, or grade ≥ 3 mucositis, and/or constipation of any duration, the vinflunine dose was to be reduced to 280 mg/m^2 from the next cycle on. If one of these toxicities was seen again after dose reduction, the dose was to be reduced further to 250 mg/m^2. The treatment was to be discontinued if the event recurred at this reduced dose. Each patient had to receive at least two cycles of treatment unless treatment was discontinued due to any of the following reasons: (i) early progression, (ii) unacceptable toxicity, (iii) serious intercurrent illness, (iv) other reactions that could affect the clinical status of the patient to a significant degree

requiring discontinuation of the drug, (v) request by the patient to withdraw consent.

After the initial two cycles, tumor response was assessed. The treatment had to be discontinued for patients showing progressive disease (PD). Patients showing Stable Disease (SD) received two further cycles of vinflunine, followed by a second assessment; and the treatment was to be continued according to the Investigator's opinion. Patients presenting with a Complete or a Partial Response (CR, PR) could continue treatment either until PD, toxicity or patient preference precluded further therapy..

Baseline and treatment evaluation

Pre-registration assessments included a detailed medical history; CT-scan or physical examination (in case of superficial lymph node or skin nodule) for tumor assessment. All positive imaging procedures at study entry had to be repeated every six weeks. An assessment of symptoms was made at study entry and then throughout treatment. Physical examination and vital signs were assessed on Day 1 of each cycle. A complete blood cell count (including a differential and platelet count) was taken at baseline (within a maximum of seven days prior to study drug administration) and, during treatment, before each cycle. Additional samplings were planned on Day 8 and Day 15 of each cycle: in case the ANC was $<1.0 \times 10^9$/L, counts were repeated every two days until recovery to ANC $\geq 1.0 \times 10^9$/L. Transaminases, alkaline phosphatases, total bilirubin, LDH, creatinine, electrolytes including Ca^{2+}, Na^+ and K^+ and total protein were assessed at every cycle. Electrocardiogram was to be performed and recorded prior to initial administration and repeated at every cycle.

Efficacy was assessed using the WHO criteria modified by SWOG [9, 10]. CR was defined as disappearance of all lesions clinically and radiologically assessed. Partial response (PR) was defined as $\geq 50\%$ reduction in the sum of the products of perpendicular diameters of all lesion measurements maintained for at least 4 weeks while no other type of lesion progressed or appeared. The time to treatment progression was calculated for patients with confirmed response (CR or PR) from the date of registrationuntil the date of documented progression, start of new anti-cancer therapy, date of death, lost follow-up or last news.

The progression free survival was defined as the time elapsed from registration until progression, death, lost to follow-up or last news. Survival was defined as the time elapsed from date of registration to death or lost to follow-up.

Statistical analysis

Sample size was based on the one-sample multiple testing procedure as described by Fleming [11]. With 55 evaluable patients, a null hypothesis for the true response rate of 5% and an alternative hypothesis of 15%, the type I error α was 5% and the type II error β was 15%.

Continuous data were summarized using median, minimum and maximum values. Categorical data were presented

Table 1 Demographic characteristics

Initial dose of vinflunine	350 mg/m^2	320 mg/m^2
Patients	11	22
Age (median/range) years	56.6 (43.9–75.5)	60.0 (24.8–76.7)
KPS		
100%	3 (27.3%)	4 (18.2%)
90%	4 (36.4%)	10 (45.5%)
80%	4 (36.4%)	8 (36.4%)
Female	3 (27.3)	6 (27.3)
Male	8 (72.7)	16 (72.7)
Histology		
Clear cell	18 (81.8)	8 (72.7)
Papillary	2 (9.1)	–
Chromophobe	–	1 (9.1)
NOS	2 (9.1)	2 (18.2)
Sites of metastases		
Lung	7	18
Liver	2	4
Lymph nodes	6	12
Bone	5	3
Multiple	4	6
Prior therapies		
Radiation	6 (27.3)	7 (22.7)
Immunotherapy (interferon)	3 (27.3)	3 (13.6%)

in contingency tables with frequencies and percentages. Confidence intervals were calculated at the 95% level. Time dependent parameters were analyzed using the Kaplan-Meier method and 95% confidence interval for the median was reported.

Efficacy analyses were performed on the intent-to-treat and evaluable population. The primary efficacy parameter was response rate and included only confirmed CR and PR. The other efficacy parameters were duration of response, progression-free survival and overall survival.

Safety analyses were performed on the population of patients having received at least one dose of study treatment. Worst NCI CTC grade for hematological and non-hematological adverse events were presented.

All statistical analyses were carried out with 8.2 version of SAS® (SAS Institute Inc., Cary, NC, USA) for Windows®.

Results

Thirty three patients with metastatic renal cell carcinoma were enrolled in this study; and 33 received treatment with vinflunine and 31 were eligible by the study criteria. Five patients were not evaluable for tumor response but were included in the intent-to-treat analysis for evaluation of efficacy. Demographic features of the patients subdivided by the planned dose of vinflunine are summarized in Table 1.

In the first step of Fleming's procedure, which required 20 evaluable patients at the initial dose of 350 mg/m^2, one response was seen (Partial Response = 1, Stable disease = 7, Progressive disease = 0, Not evaluable = 3). However, this dose was modified in the light of safety data emerging from other phase 2 studies before the required total accrual was achieved (see below). No responses were seen in the cohort treated at 320 mg/m^2 (Stable disease = 13, Disease Progression = 7, Not evaluable = 2). The five patients who were not evaluable all went off study after a single cycle of treatment because of toxicity. Median progression free survival was 5.6 months (95% CI: 2.8–14.4) for patients treated at 350 mg/m^2, and 3.3 months (95% CI: 1.6–6.4) for those treated at 320 mg/m^2 and 3.4 months (2.8–6.4) for the entire group. The median survival time was 10.4 months (95% CI: 6.8–12.4) for the whole study population.

Table 2 Toxicities

	350 mg/m^2 (n = 11%) Grade 3/4	320 mg/m^2 (n = 22) Grade 3/4
Abdominal pain	1 (9.1)	1 (4.5)
Myalgia	2 (18.2)	1 (4.5)
Stomatitis	1 (9.1)	3 (13.6%)
Dysphagia	1 (9.1)	1(4.5)
Dehydration	2 (18.2)	1 (4.5)
Anorexia	0	7(31.8%)/1(4.5)
Vomiting	0	1(4.5)
Constipation	0	3 (13.6)
Neutropenia	4 (36.4%)/6 (54.5)	3 (13.6)/12 (54.5) 3 (13.6)
Anaemia	6 (54.5%)/1 (9.1)	12 (54.5%)/3 (13.6)
Febrile neutropenia	3 27.3)	5 (22.7)
Fatigue	3 (27.3%)	3 (13.6)
Depression	3 (27.3%)/1 (9.1)	0
Seizures	1 (9.1%)/1 (9.1)	0
Thromboembolism	0/1 (9.1)	0

Safety evaluation

The total number of cycles administered at 350 mg/m^2 was 48; the median number of cycles given was four cycles (range 1 to 14); the median relative dose intensity was 99.0% of the theoretical dose scheduled. At 320 mg/m^2, 85 cycles were administered (median 3.5, range 1–14) with a relative dose intensity of 98.8%. On a per patient basis, the most frequent clinical adverse events without any grade 3 or 4 at 350 mg/m^2 were constipation (81.8%), nausea (72.7%), stomatitis (63.6%), injection site reactions (54.5%), anorexia (36.4%) and diarrhoea (36.4%). Three patients experienced abdominal pain and myalgia (27.3%), which were grade 3 in one case and two patients, respectively. Four patients had significant Grade 3 gastrointestinal toxicities, one each with stomatitis and dysphagia and two with dehydration. The incidence of vomiting was also 27.3%, without any grade 3 or 4; Hematological toxicity consisted of Grade 3 neutropenia in (36.4%, 4 patients) and grade 4 neutropenia (54.5%, 6 patients). Three episodes of uncomplicated febrile neutropenia were recorded in 3 patients (27.3%). One patient died on Day 9 following the first vinflunine dosing, possibly due to pulmonary embolism. Other important toxicities included grade 3 fatigue (27.3%, 3 patients) and grade 4 depression, seizures and thrombosis/embolism (9.1%, 1 patient each).

At 320 mg/m^2, 16 out of 22 patients experienced constipation (72.7%) with one grade 3 and two grade 4. The same number of patients had stomatitis, 3 (13.6%) of them having a grade 3, 50% of patients reported abdominal pain (1 patient with grade 3), myalgia was present in 40.9% of patients (one patient with grade 4), and anorexia in 31.8%. Hematological toxicity in the form of grade 3 neutropenia (13.6%, 3 patients) and grade 4 neutropenia (54.5%, 12 patients) was experienced in and grade 4 anemia occurred in two patients. Five patients (22.7%) developed five episodes of uncomplicated febrile neutropenia.

During the study, complete blood cell counts were performed at baseline and weekly (Day 1, Day 8, Day 15 of each cycle). Grade 3–4 neutropenia occurred in 37.5% of cycles given at 350 mg/m^2 and 37.6% for cycles given at

the lower dose. Grade 1 – 2 events were more frequent for neutropaenia and anaemia at 320 mg/m^2, thrombocytopaenia was less frequent at this lower dose level.

No clinically significant alterations in biochemical parameters were observed (creatinine, total bilirubin, SGOT/AST, SGPT/ALT and alkaline phosphatase). A number of grade 1/2 events occurred, mostly grade 1 for creatinine, bilirubin and liver function.

Discussion

This phase II study was designed to test the activity and safety of vinflunine given intravenously as first line treatment for metastatic renal cell carcinoma.

Overall, the adverse events observed were manageable. In this study, no unexpected adverse event was seen. Hematological toxicity was comparable at the two doses administered, although there was a higher incidence of grade 3/4 episodes at 350 mg/m^2 it did not translate into an increased incidence of febrile neutropaenia. The principal additional toxicities include fatigue, constipation, stomatitis and myalgia. At 320 mg/m^2, one thromboembolic event was recorded, and 5 patients (22.7%) discontinued for adverse events and there were no treatment related deaths. The febrile neutropenia rate of 23% is not excessive compared to other vinca alkaloids such as the parent compound vinorelbine used in breast cancer. In one study of 59 women as first line therapy [12], 80% had grade 3–4 neutropaenia and they reported this as manageable as we have. At the 350 mg/m^2 dose one grade 4 thromboembolic event occurred in this population with advanced disease. It is unclear whether this is a chance event due to disease or drug related. The typical gastrointestinal vinca alkaloid effects observed at the recommended dose of 320 mg/m^2 such as constipation (grade 3/4 in 13.6%), vomiting (grade 3 in 4.5%) and stomatitis (grade 3 in 13.6%) are well documented and anticipated and usually easily manageable. The breast cancer study had a similar incidence. Anorexia was slightly more common in our study (4%) than expected but did not result in any patient withdrawals.

Only one tumor response was seen at 350 mg/m^2 but disease stabilisation was demonstrated in 72.7% and 59.1% of patients treated with 350 mg/m^2 and 320 mg/m^2 of vinflunine, respectively. The median progression free survival was 3.4 months and the median overall survival was 10.4 months. The actual recommended dose of vinflunine being 320 mg/m^2, it is worth noting that the median progression-free survival of patients treated with that dose was 3.3 months (95% CI: 1.6–6.4) and the median overall survival reached 7.0 months (95% CI: 6.0—not reached).

Immunotherapy in the form of interferon and/or interleukin-2 has remained standard initial therapy, as some patients have prolonged benefit [2]. More recently impressive new data with angiogenesis inhibitors may suggest that targeted therapy may supplant it [3–5]. However the options for those who fail to respond or progress after such initial treatments remains blank. There remains a need to explore other therapies and two recent studies with gemcitabine and either continuous infusion 5 FU [13] or capecitabine [14], both showing responses of 17% and 15% respectively suggests that chemotherapy may yet have some role to play in this condition. Vinflunine as a single agent is of little benefit, however the high disease control rate seen (59% at 320 mg/m^2) is higher than reported in the randomised trial of vinblastine [6] (45%) as was the progression free survival (15 weeks vs 9). This may suggest that a combination with either of the above mentioned drugs may represent an avenue to explore in future studies of refractory patients.

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