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Clinical report

Vinorelbine and interferon-α2c as second-line therapy in metastatic renal cell carcinoma

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Second-line treatment of patients with metastatic renal cell carcinoma (MRCC) progressing under therapy with biological response modifiers (BRM) is an unresolved issue. Thirty-seven patients with MRCC progressing under treatment with BRM received vinorelbine i.v. at a dose of 30 mg/m^2 q 22 days and 4 800 000 IU interferon (IFN)-α2c s.c. thrice weekly. Partial remission (PR) occurred in 8% of patients, stable disease (SD) (median duration 8, range 3–35+ months) was observed in 46% of patients. Median overall survival was 15 (range 1–49) months. No major toxicities occurred. Patients with MRCC who failed first-line treatment with BRM had a high chance to enter PR or SD under combined, low-toxic therapy with vinorelbine and IFN-α2c. [© 2000 Lippincott Williams & Wilkins.]

Key words: Interferon, renal cell carcinoma, second line, vinorelbine.

Introduction

Treatment of patients with metastatic renal cell carcinoma (MRCC) is still a disappointing endeavor. Neither cytotoxic agents, such as vinblastin and circadian floxuridine,[1–3] nor hormonal therapy[4–6] have produced response rates of more than 15%. Although response rates of up to 48% have been reported from the combined use of chemotherapy and biological response modifiers (BRM) including interleukin (IL)-2, interferon (IFN)-α with 5-fluorouracil[7] or IFN-α with vinblastin,[8,9] the use of such combinations was restricted due to their toxicity. Currently, the combined administration of i.v. IL-2 and s.c. IFN-α is considered standard first-line therapy in MRCC, although response rates of only up to 20% have been reported.[10] However, even less is known about the ideal second-line treatment of MRCC. Within the frame of a phase II study on the first-line consecutive use of s.c. IFN-γ and IL-2 in patients with MRCC,[11] we have also included a subsequent second-line protocol including the combination of i.v. vinorelbine with s.c. IFN-α2c for patients failing treatment under the first-line regimen. Based on the generally accepted superiority of vinorelbine over vinblastin,[12–14] which in turn represents the most efficacious cytotoxic agent in MRCC and on the potential synergistic effect of its simultaneous use with IFN-α, a combination of vinorelbine with IFN-α was chosen for the present phase II trial.

Patients and methods

Patients

Thirty-seven patients with MRCC were treated according to the protocol which had passed the institutional ethical board. All patients had progressed during the prior first-line treatment of MRCC with sequential s.c. IFN-γ and IL-2 BRM therapy.[11] Inclusion criteria consisted of measurable disease, a Karnofsky performance status of $\geqslant 60$ and a life expectancy of at least 12 weeks. Other eligibility criteria included a peripheral white blood cell (WBC) count of at least 3500/μl and a platelet (PLT) count of at least 100 000/μl, maximal bilirubin and creatinine serum concentrations of 1.25× upper limit of normal values, and no clinical signs of peripheral neuropathy.

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Diagnosis and treatment

After informed consent was given by the patient, pretreatment investigations included clinical history, physical examination, complete blood count, blood chemistry, chest X-ray, bone scan, liver sonography and additonal CT scan or ultrasound when indicated. Physical examination and complete blood count were repeated every week and radiographic studies for evaluation of response were performed q 3 chemotherapy courses.

Vinorelbine was given at a dose of 30 mg/m^2 diluted in normal saline as an i.v. infusion over 20 min q 22 days. Prophylactic antiemetic treatment consisted of 4 mg ondansetron given i.v. prior to chemotherapy and 8–16 mg ondansetron given orally from days 1 to 3 following chemotherapy.

Patients self-administered IFN-α2c (Berofor®; Bender, Vienna, Austria, licenced by Boehringer Ingelheim, Ingelheim, Germany) at a dose of 4 800 000 IU s.c. thrice weekly. To avoid influenza-like symptoms, paracetamol was given orally at a dose of 500 mg twice daily during the entire treatment period.

Encountered toxicities were classified according to the WHO grading system.[15] WHO criteria were used for evaluation of response.[15] Stable disease (SD) was defined corresponding to this definition and under the exclusion of criteria valid for complete remission (CR), partial remission (PR) or progressive disease (PD), respectively. The duration of survival was calculated from the beginning of second-line treatment described above.

Statistics

Survival curves were calculated and plotted according to the method of Kaplan and Meier. Statistical comparisons of survival curves were performed using Wilcoxon's test. p values below 0.05 were considered to be significant.

Results

Patients

Patients' characteristics are detailed in Table 1. From 1994 through 1998, 37 patients with MRCC progressing under first-line therapy with BRM were entered into the trial. The median time of observation was 43 (range 9–66) months. All patients were assessable for toxicity and response. The most frequent metastatic site was the lung, followed by regional lymph nodes and the skeleton with the majority of patients presenting with one or two metastatic sites. Median time from diagnosis of MRCC to the start of second-line treatment presented in this report was 6 (range 1–55) months.

Toxicity

Toxicity was evaluated following a total of 208 (median 5; range 1–20) courses of cytotoxic treatment. As shown in Table 2, no life-threatening

Table 1. Patient characteristics

Characteristic	No. of patients
Entered	37
evaluable toxicity	37
evaluable response	37
Age	59 (44–81)
Sex	
male	31
female	6
Metastatic sites	
liver	5
lung	23
bone	7
regionary lymph nodes	14
CNS	3
other	15
No. of metastatic sites	
1	13
2	14
3+	8
First-line therapy	
IL-2+IFN-γ	32
IL-2+GM-CSF+IFN-γ	1
IFN-γ	4

Table 2. Treatment-associated toxicities in 37 evaluable patients

Toxicity	WHO grade and percent of patients			
	WHO I	WHO II	WHO III	WHO IV
Fever	0	13.5	2.7	0
Edema	0	2.7	0	0
Headache	8.1	0	0	0
Leukopenia	13.5	13.5	2.7	0
Thrombopenia	2.7	0	0	0
Anemia	10.8	8.1	8.1	5.4
Peripheral neuropathy	2.7	0	0	0
Nausea/emesis	2.7	5.4	2.7	0
Cardiac	2.7	0	0	0
Alopecia	0	0	2.7	0
Other	8.1	0	0	0
stomatitis	2.7			
pulmonary	2.7			
diarrhea	2.7			

complications occurred and no patient had to be hospitalized on account of toxic side effects of treatment. The most common side effects were anemia and neutropenia in one-third of the patients. Other frequent toxicities were fever despite paracetamol administration and nausea despite antiemetic drugs applied in 16 and 10%, respectively. In one patient one episode of supraventricular tachycardia was observed and another patient suffered from mild dyspnea on exertion.

Response to treatment and survival

As shown in Table 3, three out of 37 patients (8%) presented with a PR of 4.2, 5.7 and 7.8 months duration, respectively. An additional 17 (46%) patients experienced SD with a median duration of 9 (range 4–37) months. The remaining 17 (46%) patients developed primary progression under treatment. Out of 17 patients who had experienced primary progression under prior BRM treatment, two (12%) reached PR and six (35%) SD under the reported second-line treatment. Median overall survival was 15 (range 1–49) months (Figure 1). The number of metastatic sites was not predictive for survival (Figure 2). A cumulative analysis of survival in patients with PR plus patients with SD or only in patients with SD showed that patients from either group showed significantly longer survival (23 and 21.5 months, respectively), as compared to patients with primary PD (11 months; p=0.006 and 0.02, respectively; Figure 3).

Table 3. Response to treatment for 37 evaluable patients

Response	n=37 (%)	Duration median
CR	0	NA
PR	3 (8%)	4.2/5.7/7.8 months
SD	17 (46%)	9 months (range 4–37)
PD	17 (46%)	

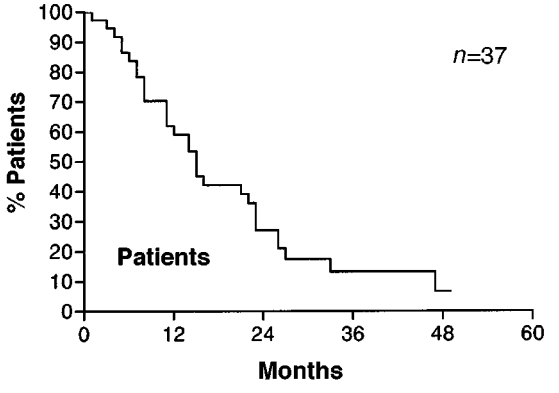

Figure 1. Overall survival.

Discussion

No ideal treatment modality has yet been developed for patients with MRCC, either primarily unresponsive to BRM treatment or developing disease progression following transient primary response to treatment.

Attempts have been made to identify such a procedure by testing for the efficacy of BRM,[16–18] cytotoxic drugs, and, finally, a combination of BRM with cytotoxic treatment.

While using IFN-α2c in the second-line setting, objective responses and disease stabilization were achieved in 9.7 and 25.8% of patients, respectively.[19] In another study, 31% of patients reached PR and 54% SD by using IL-2 after progression under treatment with IFN-2α.[17] Finally, retreatment with a different IL-2-based therapy than originally scheduled resulted in a response in 14% of patients.[16]

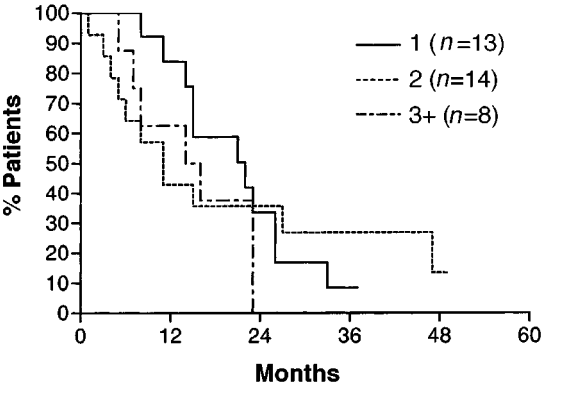

Figure 2. Survival depending on the number of metastatic sites.

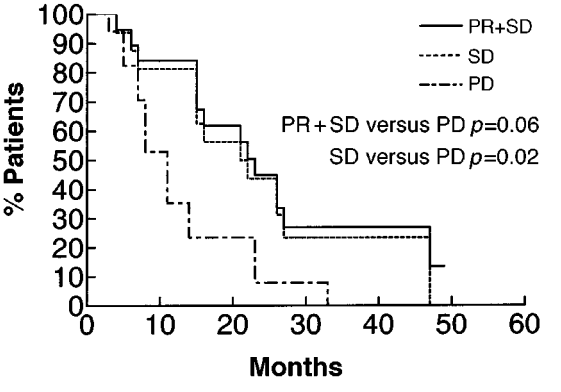

Figure 3. Survival depending on the response.

Only one study reported on the efficacy of second-line cytotoxic therapy. This showed that fotemustine had no antitumor activity when used as second-line agent in patients with MRCC.[20] In contrast to many first-line studies on combined chemo-immunotherapy, little is known of the value of combined chemo- and immunotherapy in the second-line setting: objective remissions in 15% and disease stabilization in 35% of patients were obtained using IFN-α and vinblastin[21] in a trial involving 14 patients.

With an overall response rate of 8%, our data failed to demonstrate a superiority of vinorelbine over historical experience with vinblastin in this disease and setting. Furthermore, since similar and even higher response rates up to 5–30% were obtained in the past with IFN-α alone, the question arises as to whether IFN-α2c alone was responsible for the results obtained in the present trial.

It is remarkable, however, that disease stabilization occurred in 46% of patients with a duration of a median of 9 (range 4–37) months which was associated with longer median survival of 21.5 months, as compared to 11 months in patients with PD (p=0.02). Our data are consistent with those of two other trials using vinorelbine and IFN-α[22,23] which have shown disease stabilization to occur in 55 and 46% of patients, respectively. Interestingly, however, the toxicity in the present trial was particularly low.

Since MRCC is a tumor showing very different patterns of and frequently slow progression, it remains undetermined whether patients could have reached disease stabilization with best supportive care alone and without any specific tumor therapy. To date, only one randomized trial comparing immunotherapy with best supportive care[24] shows no difference in terms of disease stabilization and median overall survival in patients treated with IFN-γ (12.2 months), as compared to patients receiving placebo (15.7 months). As IFN-γ was used, these data were not apt to be comparable to results from our trial which included IFN-α2c.

In conclusion, second-line treatment options in MRCC have not yet been well characterized, although the combined use of cytotoxic drugs and BRM seems to be most promising. Accordingly, the current protocol was pursued and produced modest activity, yet low toxicity. In view of the latter, use of the present protocol could be justified as a treatment arm in a necessary randomized study that would examine for the efficacy of second-line therapy compared with best supportive care.

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