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Short communication

Phase II study of fotemustine as second-line treatment after failure of immunotherapy in metastatic renal cell carcinoma

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Abstract. Sixteen patients who after prior systemic immunotherapy had progressing disease received fotemustine (100 mg/m^2) i.v. on days 1, 8, and 15 followed by a 5-week rest period. In responding or stabilized patients, maintenance therapy consisted of 100 mg/m^2 fotemustine given once every 3 weeks until progression on toxicity occurred. No objective response was observed. Four patients showed stable disease (median duration: 4 months; range: 3–19). The main toxicities were neutropenia (WHO grade 3 and 4: 27%) and thrombocytopenia (WHO grade 3 and 4: 27%). Fotemustine was administered on an outpatient basis and was generally well tolerated, but in our series of patients it had no antitumour activity in metastatic renal cell carcinoma after failure of immunotherapy.

Introduction

The efficacy of chemotherapy in metastatic renal cell carcinoma (MRCC) is very poor [2, 3]. Recently, interleukin-2 (IL2) alone or in combination with adoptive cellular therapy or alpha interferon (IFN) was reported as having produced a 15%–30% response rate in MRCC [8, 9]. Despite significant side effects, immunotherapy with IL2 represents the first-line treatment for MRCC at our institution. For patients whose disease progressed after treatment with biological response modifiers, another method of treatment was needed. Ideally, in this palliative situation, it should be given on an outpatient basis, with a low risk of toxicity.

Fotemustine is a new chloroethylnitrosourea with two main basic properties: easier intratumoral penetration and a greater ability to cross the blood-brain barrier. The activity of fotemustine has been clearly demonstrated in malignant melanoma [5, 6]. The drug is effective in cerebral metastases and is well tolerated and easy to use on an outpatient basis [5].

The preliminary results of a French multicentre phase II study in non-pretreated MRCC have shown a 19% response rate with fotemustine [4]. These findings prompted us to evaluate fotemustine when used as second-line single-agent chemotherapy in patients with MRCC that progressed after immunotherapy.

Patients and methods

Eligibility criteria. Sixteen patients who had progressive disease after prior systemic immunotherapy were entered into a phase II study between May 1989 and December 1989. Patients were eligible if they had histologically or cytologically proven MRCC; evidence of progressive measurable disease; age over 18 and under 75; WHO performance status of 0, 1, or 2; life expectancy greater than 3 months; normal renal, liver, and bone marrow functions; and no prior chemotherapy. Prior systemic immunotherapy was allowed provided that all treatment had been discontinued at least 4 weeks before trial entry. All patients gave written informed consent.

Patients' characteristics are outlined in Table 1. All 16 had received previous immunotherapy, mainly with IL2: 10 of them received two consecutive lines of such treatment, and partial responses were observed in 2. On study entry, patients were classified according to the prognostic subgroups defined by Elson [3], which are based on initial WHO performance status, time from initial diagnosis, number of metastatic sites, prior cytotoxic chemotherapy, and recent weight loss. All but 1 patient belonged to the poor prognostic classes (3 patients in class 3, 10 in class 4, and 2 in class 5).

Treatment. For induction therapy in outpatients, fotemustine was given at a dose of 100 mg/m^2, diluted in 250 ml of 5% glucose as a 1-h i.v. infusion, on days 1, 8, and 15, followed by a 5-week rest period. In responding or stabilized patients, maintenance therapy consisted of 100 mg/m^2 fotemustine given once every 3 weeks until progression or toxicity occurred.

Dose adjustment. The dose was decreased by 25% or 50% in the case of grade 1 or 2 neutrophil or platelet toxicity, and drug administration was delayed by 1 week in the event of grade 3 or 4 neutrophil or platelet toxicity at the scheduled treatment time.

If no haematological recovery was observed after a 1-week postponement, treatment was delayed for a further week. If treatment had delayed

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Table 1. Patient characteristics

No. of eligible patients	16
No. of patients evaluable for response	14
No. of men/No. of women	12/4
Median age (range)	54 (33–74)
Performance status (WHO)	
0	3
1	10
2	3
No. of patients with time from diagnosis to metastasis <12 months	12
No. of metastatic sites	
1	3
2	4
>2	9
Site of involvement	
Lung	10
Liver	4
Bone	7
Brain	4
Other[a]	14
Local relapse	1
Prior nephrectomy	16
Prior systemic treatment for metastatic disease	
No. of therapy modalities received	
1	5
2	9
3	2
Immunotherapy protocols given	
IL2+LAK	1
IL2+IFN	11
IL2 alone	3
IL2+TNF	7
IFN alone	2
IFN+vinblastine	4

IL2, Interleukin-2; LAK, lymphokine-activated killer cells; TNF, tumour necrosis factor; IFN, interferon alpha

[a] Other sites of involvement included lymph nodes (8), contralateral kidney (3), and skin (1)

for more than 2 weeks, the patient was withdrawn from the study. With grade 2 hepatotoxicity, the treatment was also delayed until complete recovery. In the event of grade 3 or 4 hepatotoxicity, the patient was withdrawn from the study.

Tumour evaluation. The extent of measurable tumour mass was assessed by computer-assisted tomographic scan. Tumour response was evaluated on day 49, but patients progressing early after completing the induction treatment were also considered evaluable. Toxicity was evaluated weekly until day 49. Response and toxicity were classified according to standard WHO criteria [7]. Patients were continued on therapy until such time as disease progression could be observed and documented. After progression, no further therapy was offered, but palliative treatment and supportive care were given. Overall survival rates were calculated by the Kaplan-Meier method.

Results

Two patients were not evaluable for response, 1 because of early death (before day 15) due to disease progression and 1 because of suspected toxic death on day 48 (gastric haemorrhage associated with grade 1 thrombocytopenia 4 days before death). No patient responded to treatment. Four patients showed stable disease and received maintenance therapy. In these patients, sites of involvement were lymph nodes (3 patients), lung (2 patients), bone (2 patients), contralateral kidney (1 patient), brain (1 patient), and skin (1 patient). The Elson prognostic groups were 2 for 1 patient, 3 for 2, and 4 for 1. Among these 4 patients 3 had received two successive lines of prior immunotherapy and 1 had partially responded to IL2 plus IFN. The durations of stabilization were 3.5, 4, 4, and 19 months. Disease progression was observed at evaluation in 10 patients. The median overall survival for all patients was 4 months.

There were 15 patients evaluable for toxicity after induction therapy. The main toxicities were delayed neutropenia (grade 3 and 4: 27%; nadir on day 42 or day 49) and delayed thrombocytopenia (grade 3 and 4: 27%, nadir on day 35). Haematological toxicity was manageable and reversible except in the 1 presumed case of thrombocytopenia already described. No febrile neutropenia occurred, and in only 1 patient was prophylactic platelet transfusion required. Moderate nausea/vomiting (grade 1 and 2) was observed in 50% of the patients, with no 5HT3 antagonists being used as antiemetic agents. Two patients had grade 2 liver toxicity (liver enzymes) which was reversible and had no clinical symptoms.

Discussion

Our series consisted mainly of poor prognosis patients: 3 presented with a low performance status (WHO score: 2); 12 had a period from diagnosis to metastasis of under 1 year; 13 had more than one site of metastasis; all had progressed after prior immunotherapy; 11 received at least two lines of systemic treatment before being included in the present study. All patients but 1 belonged to the Elson poor prognosis groups for which the theoretical median survival is under 5 months [3].

No objective response occurred, but 4 patients whose disease had progressed after previous immunotherapy benefited from treatment, experiencing stabilization of their disease. The results of the present study are in agreement with the disappointing final report of the French multicentre study group who evaluated the same schedule of treatment [1]: a 4% response rate in the 24 pre-treated patients and an 8% response rate in the 38 non-pre-treated patients.

The observed toxicity was acceptable and is also in agreement with that in previous reports [1, 5, 6]. The main problem was the delayed thrombocytopenia (only one transfusion was necessary), which required prolonged platelet monitoring for 4 weeks after the end of therapy.

Fotemustine was generally well tolerated and could be administered on an outpatient basis, but it was essentially ineffective in patients with MRCC after immunotherapy. Those patients with measurable progressive disease after immunotherapy will primarily be entered into clinical trials

evaluating new experimental drugs. If one of these products demonstrates any antitumour activity, the next step will be to evaluate this compound with interleukin-2 as first-line treatment in MRCC.

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References

1. Chevallier B, Toussaint C, Kerbrat P, Bonneterre J, Mousseau M, Audhuy B, Droz JP, Vignoud J, Coste M, Benoliel C, Berille J (1991) Final report: phase II study of fotemustine in advanced renal cell carcinoma; and assessment of Elson pronostic factors (abstract). Proc Am Soc Clin Oncol 10: 583
2. Droz JP, Theodore C, Ghosn M, Lupera M, Piot H, De Forges G, Klink A, Rouesse M, Amiel JL (1988) Twelve-year experience with chemotherapy in adult metastatic renal cell carcinoma at the Institut Gustave Roussy. Semin Surg Oncol 4: 97
3. Elson PJ, Witter S, Trump DL (1988) Prognostic factors for survival in patients with recurrent or metastatic renal cell carcinoma. Cancer Res 48: 7310
4. Kerbrat P, Toussaint C, Bonneterre J, Berille J (1989) Preliminary results: a phase II study of the nitrosourea fotemustine in non pretreated metastatic renal cell carcinoma (abstract). Proc ECCO 5: 0837
5. Khayat D, Bizzari JP, Frenay M, Naman H, Weil M, Goupil A, Namer M, Rouesse J, Banzet P, Jacquillat C (1988) Interim report of a phase II study of a new nitrosourea S 10036 in disseminated malignant melanoma. J Natl Cancer Inst 80: 1407
6. Khayat D, Lokiec F, Bizzari JP, Weil M, Meeus L, Sellami M, Rouesse J, Banzet P, Jacquillat C (1987) Phase I clinical study of a new amino-acid-linked nitrosourea, S 10036, administered on a weekly schedule. Cancer Res 47: 6782
7. Miller AB, Hoogstraten B, Staquet M, Winkler A (1981) Reporting results of cancer treatment. Cancer 47: 207
8. Negrier S, Philip T, Stoter G, Fossa SD, Janssen S, Iacone A, Cleton FS, Eremin O, Israel L, Jasmin C, Rugarli C, Masse HVD, Thatcher N, Symann M, Bartsch HH, Bergmann L, Bijman JT, Palmer PA, Franks CR (1990) Interleukin-2 with or without LAK cells in metastatic renal cell carcinoma: a report of a European multicenter study. Eur J Cancer Clin Oncol 25: 21
9. Rosenberg SA, Lotze MT, Muul LM, Chang AE, Avis FP, Leitman S, Linehan WM, Robertson CN, Lee RE, Rubin JT, Seipp LA, Simpson CG, White DE (1987) A progress report in the treatment of 157 patients with advanced cancer using lymphokine-activated killer cells and interleukin-2 or high-dose interleukin-2 alone. N Engl J Med 316: 889