Cancer Chemother Pharmacol (1998) 42: 415–417

CLINICAL TRIAL REPORT

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Phase II trial of titanocene dichloride in advanced renal-cell carcinoma

Received: 18 February 1998 / Accepted: 23 April 1998

Abstract Titanocene dichloride was capable of inhibiting the growth of different types of human tumors in vitro. A total of 14 patients with metastatic renal-cell carcinoma (RCC) received 270 mg/m^2 titanocene dichloride every 3 weeks for 6 weeks. Although the toxicities and side effects encountered were mild to moderate, no partial or complete response was detectable. In conclusion, titanocene dichloride has no advantage in the therapy of RCC.

Key words Titanocene dichloride · Chemotherapy · Renal-cell carcinoma

Introduction

At present there is no satisfying therapy for patients with metastatic renal-cell carcinoma (RCC). Titanocene dichloride is the best-characterized substance among a group of early-transition metal complexes with documented antineoplastic effects in vitro and in vivo. The in vitro activity of titanocene dichloride has been demonstrated in different types of tumors of murine and human origin, such as colon and lung cancer, respectively [2, 3]. Furthermore, titanocene dichloride has been tested against different drug-resistant tumor cell lines. One study has obviously shown that the compound is not cross-resistant to Adriamycin or cisplatin [1]. Kurbacher et al. [4] have recently reported a higher level of cytotoxicity for titanocene dichloride in primary RCC specimens as compared with antineoplastic agents such as cisplatin, doxorubicin, mitoxantrone, and vinblastine.

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We performed a pilot study in which we could confirm the maximum tolerable dose of titanocene dichloride to be 270 mg/m^2 given every 21 days. On the basis of these results the present phase II study was carried out to evaluate the objective responses to titanocene dichloride shown by patients with metastatic RCC.

Patients and methods

From May 1995 to June 1996, 14 patients with advanced RCC were recruited into this phase II trial. Patients were eligible if they had histologically confirmed RCC, bidimensionally measurable metastatic or locally recurrent unresectable disease, no prior medical antineoplastic treatment, a life expectancy of at least 3 months along with a Karnofsky performance status of above 70%, and adequate renal, hepatic, and bone marrow function. Informed consent was obtained from each patient. The patients' characteristics are outlined in Table 1.

Prior to study entry, patients had a complete workup, including a history, physical examination, chest X-ray, abdominal ultrasonography, blood chemistry, and blood count. Additional imaging procedures were performed as indicated by symptoms or history.

All patients were treated with titanocene dichloride (kindly provided by Medac, Hamburg, Germany) given at 270 mg/m^2 on day 1 by i.v. injection. Treatment cycles were repeated every 21 days. Patients who achieved partial or complete responses or stable disease after two cycles were continued on titanocene dichloride until either progression or stabilization of their disease for two cycles.

The response to treatment was assessed after two cycles of therapy and every 3 months thereafter according to WHO response criteria [6].

Results

Response

A total of 11 patients received 2 cycles of titanocene dichloride. One patient who presented with stable disease continued the treatment for a further two cycles and one patient died due to tumor progression within 4 weeks. Due to side effects, one patient dropped out of the treatment schedule after one cycle. There was no

Table 1 Patients' characteristics

Characteristics	Number of patients (%)
Eligible patients	14
Sex:	
Male	11 (79%)
Female	3 (21%)
Age (years):	
Median (range)	60 (33–72)
Karnofsky index (%):	
80	1 (7%)
90	9 (64%)
100	4 (29%)
Nephrectomy	10 (71%)
Sites of metastatic disease:	
Lung	3 (21%)
Lung and others	4 (29%)
Bone	4 (29%)
Lymph nodes	1 (7%)
Local recurrence	2 (14%)

complete or partial response. Three patients (21%) had stable disease (SD) for 1, 3, and 3 months, respectively. Two patients had metastases in the lung; one of them had been nephrectomized. The other patient had bone metastases only. All patients with SD had a good performance status (Karnofsky index 100%). The remaining ten patients (79%) had shown evidence of progression while under treatment with titanocene dichloride. The median survival time of all patients amounted to 50 weeks, and the overall survival was 43% at 1 year.

Toxicity

Mild upper abdominal discomfort with loss of appetite was universally experienced for 1–2 days after the administration of titanocene dichloride by all patients entered into this study. In eight patients (57%) symptoms of nausea, vomiting, and weight loss occurred; three of them suffered from grade 3 WHO toxicity and two patients, from grade 2 toxicity. Subsequently, the dose of titanocene dichloride was reduced to 75% of the original dose in two patients. Although the treatment level had been reduced, one patient chose to withdraw from further participation in the study. There was no other organ toxicity (see Table 2).

Table 2 WHO toxicity of treatment with titanocene dichloride ($n = 14$)

Side effects	WHO grade			Total (%)
	I	II	III	
Loss of appetite	14	0	0	14 (100%)
Nausea/vomiting and weight loss	3	2	3	8 (57%)
Increase in creatinine	3	4	0	7 (50%)

Four patients (29%) developed an increase in serum creatinine concentration corresponding to WHO grade 2 toxicity (maximal 2.6 mg/dl) and three patients (21%) developed grade 1 toxicity. The treatment-related increase in serum creatinine levels resolved after completion of the therapy. With regard to hematologic parameters and chemistry values of liver function, no significant difference it was detectable between baseline levels and control values during the treatment.

Discussion

Metastatic RCC is a poor-prognosis disease for which no effective conventional therapy has been established [8]. The refractory nature of RCC and the nearly uniform expression of P-glycoprotein in this tumor [9] have made reversal of multidrug resistance an important target for therapeutic development in this disease. Kurbacher et al. [4] have reported on the antineoplastic activity of titanocene dichloride in fresh RCC specimens in vitro. Furthermore, these authors demonstrated a lack of cross-resistance between titanocene dichloride and other cytostatic compounds such as anthracyclines, anthracenediones, vinca alkaloids, and platinum analogues [4]. These findings confirmed the observations made in ovarian-carcinoma cell lines [1, 5]. Despite these promising in vitro data, none of the 14 patients admitted to the present phase II trial achieved a complete or partial response.

Yagoda et al. [10] recently reviewed the efficacy of chemotherapy in the treatment of metastatic RCC and reported disastrous results. In all, 63 agents evaluated in 4093 patients achieved a combined complete-plus-partial response rate of only 6%, with responses being mostly of short duration. Vinblastine has been claimed to be the most active antineoplastic drug in RCC, but recent trials failed to demonstrate any antitumor effect for vinblastine, even when given in combination with agents that reverse the multidrug resistance associated with P-glycoprotein [7, 10].

In conclusion, titanocene dichloride is one of many chemotherapeutic agents that have produced responses in proportions too small to justify its use in single-agent therapy. Nevertheless, the study of new agents is indicated in patients who have never had chemotherapy, and systemic therapy should be given whenever possible in the context of a clinical trial.

References

1. Harstrick A, Schmoll HT, Sass G, Poliwoda H, Rustum Y (1993) Titanocene dichloride activity in cisplatin- and doxorubicin-resistant human ovarian carcinoma cell lines. Eur J Cancer 29A: 1000
2. Koepf-Maier P (1987) Tumor inhibition by titanocene complexes influence upon two xenografted human lung carcinomas. J Cancer Res Clin Oncol 113: 342
3. Koepf-Maier P, Moormann A, Koepf H (1985) Activity of titanocene dihalides against human colon carcinoma heterotransplanted to nude mice. Eur J Cancer Clin Oncol 21: 853

4. Kurbacher CM, Nagel W, Mallmann P, Kurbacher JA, Sass G, Hubner H, Andreotti PE, Krebs D (1994) In vitro activity of titanocene dichloride in human renal cell carcinoma compared to conventional antineoplastic agents. Anticancer Res 14: 1529
5. Kurbacher CM, Bruckner HW, Andreotti PE, Kurbacher JA, Sass G, Krebs D (1995) In vitro activity of titanocene dichloride versus cisplatin in four ovarian carcinoma cell lines evaluated by a microtiter plate ATP bioluminescence assay. Anticancer Drugs 6: 697
6. Miller AB, Hoogstraten B, Staquet M, Winkler A (1981) Reporting results in cancer treatment. Cancer 47: 207
7. Motzer RJ, Lyn P, Fischer P, Lianes P, Ngo RL, Cordon-Cardo C, O'Brian JP (1995) Phase I/II trial of dexverapamil plus vinblastine for patients with advanced renal cell carcinoma. J Clin Oncol 13: 1958
8. Motzer RJ, Bander NH, Nanus DM (1996) Renal-cell carcinoma. N Engl J Med 335: 865
9. Thiebaut F, Tsuruo T, Hamada H, Gottesman MM, Pastan I, Willingham MC (1989) Immunohistochemical localization in normal tissues of different epitopes in the multidrug transport protein P170: evidence for localization in brain capillaries and cross-reactivity of one antibody with a muscle protein. J Histochem Cytochem 37: 159
10. Yagoda A, Abi-Rached B, Petrylak D (1995) Chemotherapy for advanced renal-cell carcinoma: 1983–1993. Semin Clin Oncol 22: 42