Ilmofoesine (BM 41.440) in Renal Cell Cancer – A Multicenter Phase II Study

R.		Herrmann ^a
C.		Manegold ^b
K.		Bremer ^c
R.		Becher ^d
H.		Kriegbaum ^e
L.		Edler ^f
W.		Queißer ^g

^aAbteilung Onkologie, Department Innere Medizin, Kantonsspital (Universitätsklinik), Basel, Schweiz ^bKrankenhaus Rohrbach, Heidelberg ^cAugusta Krankenhaus, Bochum ^dWestdeutsches Tumorzentrum, Essen ^eBoehringer Mannheim Deutsches Krebsforschungszentrum, Heidelberg ^fOnkologisches Zentrum, Klinikum Mannheim der Universität Heidelberg

Key Words

Ilmofoesine
Renal cell cancer
Phase II study
Gastrointestinal toxicity

Summary

Background: Ilmofoesine is an ether lipid with antineoplastic activity in experimental systems. Since there is no established systemic treatment for metastatic renal cell cancer, a trial with this new agent seemed to be warranted. **Patients and Methods:** Patients with measurable metastatic renal cell cancer without prior systemic treatment received Ilmofoesine between 150 and 300 mg per day orally until disease progression. **Results:** There have been no objective responses among the 19 evaluable patients. **Dose-limiting** toxicity was gastrointestinal intolerance. **Conclusions:** Oral Ilmofoesine is ineffective in metastatic renal cell cancer.

Prof. Dr. R. Herrmann, Abteilung Onkologie, Department Innere Medizin, Kantonsspital, CH-4031 Basel (Switzerland)

Schlüsselwörter

Ilmofoesin

Nierenzellkarzinom Phase-II-Studie Gastrointestinale Toxizität

Zusammenfassung

Hintergrund: Ilmofoesin ist ein Ätherlipid mit antineoplastischer Aktivität in verschiedenen experimentellen Systemen. Da es für das metastasierte Nierenzellkarzinom keine etablierte Therapie gibt, schien es sinnvoll, diese neue Substanz bei dieser Erkrankung zu testen.

Patienten und Methoden: Patienten mit meßbarem, metastasiertem Nierenzellkarzinom, die zuvor noch nicht systemisch behandelt worden waren, erhielten täglich zwischen 150 und 300 mg Ilmofoesin per os bis zum Nachweis einer Krankheitsprogression.

Ergebnisse: Bei den 19 evaluierbaren Patienten gab es in keinem Fall eine objektive Remission. Dosislimitierend war die gastrointestinale Intoleranz.

Schlußfolgerungen: Orales Ilmofoesin ist beim metastasierenden Nierenzellkarzinom unwirksam.

Introduction

Metastatic renal cell cancer is one of the human malignancies least responsive to chemotherapy. Recently α -interferon and interleukin-2 have shown some activity. However, even with biological agents objective responses are still obtained in less than 20% of unselected patients. Therefore it is justified to study new agents in metastatic renal cell cancer in previously untreated patients.

Ilmofofosine (BM 41.440) is an ether lipid which has shown activity in preclinical systems including xenotransplanted human tumors growing in nude mice [1, 2]. In a multicenter phase I study it has been tested in an oral formulation [3]. Dose-limiting toxicity was upper abdominal discomfort at doses ranging between 225 and 375 mg daily. Because of this broad spectrum of individual tolerance it was decided for this study to find out the individual tolerance of the dose of ilmofofosine by individually escalating the dose up to the tolerated level.

© 1994 S. Karger GmbH, Freiburg

Patients and Methods

Table 1. Patient characteristics

For inclusion into the study, patients were required to have histologically confirmed renal cell cancer, primary tumor removed, bidimensionally measurable metastases, WHO performance status 0 or 1, no previous systemic antineoplastic treatment, normal function of the liver, the remaining kidney and the bone marrow, and informed consent. After registration the patients were started on ilmofofosine 75-mg tablets 3 times every day. The daily dose was increased by one 75-mg tablet after the 1st week if there was no adverse effect and reduced to 2 tablets daily if there were grade 2 or higher drug-related symptoms. Response was first evaluated after 8 weeks of treatment and then in 8 weekly intervals or as clinically indicated. Objective responses were supposed to be confirmed after 4 weeks. Treatment was to be continued until disease progression. From September 1989 to June 1990 26 patients have been registered. Of these, four had to be excluded because of ineligibility (2 prior cytotoxic treatment, 2 WHO performance grade 3). Three additional patients with WHO performance grade 2 have been included since this was felt to be a minor protocol violation only. 22 patients were evaluable for toxicity, 19 for response (3 missing bidimensionally measurable disease). Patient characteristics are shown in table 1.

Age, years Median Range

Males/females

WHO performance status 0 1

2

Metastatic sites Lung Liver

Lymph nodes Locoregional Bones Other

63.8 41-78

15/7

4 15

3

15

6 6

4 4 5

Results

Discussion

The median duration of treatment was 17 weeks (1-187+ weeks). All but one patient had their dose increased to 4 times 75 mg per day. 12 patients had to have their dose reduced later on because of toxicity. The median cumulative dose of ilmofosine was 26,212.5 mg (1,500-392,700). Reasons for discontinuation of treatment were tumor progression 15, patient refusal 2, toxicity 1, other or unknown 3, still on treatment 1. Among the 19 patients evaluable for response there were 14 patients with no change, 4 progressions and 1 early death. There have been no objective responses, with a 95% confidence interval of 0.0-17.7%. The median duration of 'no change' was 18 weeks (4-187+). One patient is still on treatment with no change after more than 31/2 years. His mediastinal lymph node metastases had been histologically confirmed to contain clear cell type renal cell cancer. Toxicity was restricted to the gastrointestinal tract. 82% of the patients reported nausea/vomiting, 68% WHO grade 1 or 2, 14% grade 3 or 4. 55% developed anorexia, 32% WHO grade 1 or 2, 23% WHO grade 3. 32% developed diarrhea WHO grade 1 or 2. There was neither hematological nor any organ toxicity.

In this phase II study in good-risk patients with metastatic renal cell cancer, ilmofosine did not achieve objective responses in 19 evaluable patients. In some patients long progression-free intervals have been seen suggesting a possible beneficial influence of ilmofosine in tumor progression. However, in the setting of a phase II study, progression-free interval cannot be accepted as a study endpoint.

Due to the observed gastrointestinal toxicity the dose of 300 mg daily cannot be increased. Therefore, higher systemic drug levels can only be achieved by intravenous application. Since no other toxicity has been observed, it is likely that higher drug levels would be tolerated. This may then allow to achieve drug levels that are required for the antineoplastic action of ilmofosine. Phase I studies with intravenous ilmofosine have been completed in the meantime [4]. Phase II studies are presently ongoing.

Acknowledgement

This study was supported in part by Boehringer Mannheim.

References

- 1 Runge MH, Andreesen R, Pfeleiderer A: Destruction of human solid tumors by alkyllysophospholipids. *J Natl Cancer Inst* 1980;64:1301-1306.
- 2 Berdel WE: Ether lipids and derivatives as investigational anticancer drugs. *Onkologie* 1990;13:245-250.
- 3 Herrmann BDJ, Neumann HA, Heim ME: Short- and longterm tolerability study of the thioether phospholipid derivative ilmofosine in cancer patients *Contrib Oncol* 1989;37:236-247.
- 4 Koeller J, Rodriguez G, Smith L, Eckardt J, Schaffer D, Weiss G, Higashi L, McPhillips J, Von Hoff D: Phase I study of ilmofosine given as a 120-hour continuous infusion in patients with solid tumors. *Proc Am Soc Clin Oncol* 1993;12:155.