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CLINICAL TRIAL REPORT

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Gemcitabine: a phase II study in patients with advanced renal cancer

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Abstract Gemcitabine is a fluorine-substituted cytarabine analog with broad experimental antitumor activity. It's activity was explored in chemotherapy-naive patients with advanced progressive renal-cell carcinoma. A total of 39 patients were included in the study, of whom 37 were fully evaluable. In five patients the primary tumor remained in situ. Gemcitabine at 800 mg/m^2 was given as a weekly 30-min infusion for 3 consecutive weeks followed by 1 week of rest. One complete response and two partial responses were observed giving a response rate of 8.1% [95% confidence interval (CI), 2–22%). The duration of the responses is currently 32, 15, and 19 months, respectively. The median survival for all patients was 12.3 months. Gemcitabine was generally well tolerated, with nausea and vomiting (20.5% grade III) and neutropenia (5.3% grade III) being the most significant side effects. Gemcitabine given at this dose level and on this schedule has only limited activity in advanced renal-cell carcinoma.

Key words Gemcitabine · Renal-cell cancer · Metastatic disease

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Introduction

Patients with renal-cell carcinoma (RCC) currently have few therapeutic options once metastatic disease has developed. Approximately 25% of the patients have metastatic disease at the time of first presentation [1]. The median survival for these patients is 6–12 months, independent of treatment [2]. Spontaneous regression of metastases after tumor nephrectomy occurs in less than 1% of cases [3]. Treatment with hormones has no proven impact on survival [4, 5]. The results of chemotherapy have been consistently disappointing, with most studies revealing response rates below 10%. Agents with some activity are vinblastine and floxuridine. One of the explanations for this relative chemotherapy insensitivity is the high level of expression of the multi drug resistance gene in the proximal tubular cell, known to be the origin of renal-cell carcinoma. Several forms of immunotherapy with interferons and interleukin-2 have been applied, resulting in a limited number of sometimes durable responses [6, 7]. Further studies with new agents are therefore indicated.

Gemcitabine (2′2-difluorodeoxcytidine), a pyrimidine antimetabolite, has been developed as a new deoxycytidine analogue. In several murine solid-tumor and human xenograft models, gemcitabine has been identified as an active compound with a very broad therapeutic index. The dose-limiting side effects in phase I studies were myelosuppression and, for a more frequent, daily-times-5 regimen, a flu-like syndrome consisting of fever, malaise, headache, and rigors; in rare cases, hypotension was observed. The regimen chosen for further exploration in the phase II setting was weekly administration times 3 every 4 weeks. In this paper we report on the results we obtained in a multicenter phase II study in advanced progressive RCC.

Patients and methods

This was an open, nonrandomized study to determine the objective response rate to gemcitabine of patients with advanced RCC who had not had previous chemotherapy. The study was conducted from three centers in Germany and one in The Netherlands. The principles of good clinical practice and the Declaration of Helsinki were adhered to and the protocol was approved by the local ethics committees. Informed consent was obtained from all patients before their inclusion in the study.

Criteria for entry

To be included in the study, patients (aged 18–75 years) had to have histologically or cytologically confirmed metastatic or inoperable advanced renal cell adenocarcinoma. They had to have a life expectancy of at least 3 months and a performance status of 0–2 on the WHO scale. Nephrectomy was permitted, but this had to have been at least 3 weeks before the start of the study together with documentation of disease progression. If an area had been irradiated, there had to be measurable disease outside this area. Palliative radiotherapy was allowed in areas outside the axial skeleton. There had to be adequate bone marrow reserve (leukocytes, $\geq 4 \times 10^9$/l; hemoglobin, 10 g/dl [6.7 mmol/l], platelets, $\geq 100 \times 10^9$/l). The following laboratory criteria had to be fulfilled: plasma creatinine levels of ≤ 160 mmol/l, plasma bilirubin concentrations lower than twice the normal value, and aspartate transaminase/alanine transferase (AST/ALT) levels lower than 3 times the normal value. AST and ALT could be elevated to 5 times the normal value in patients with known metastatic disease in the liver. The prothrombin time (PT) and partial thromboplastin time (PTT) had to be ≤ 1.5 times the normal value.

Patients were excluded from the study if they had any of the following: bilateral renal cancer, bony lesions as the only measurable disease, life-threatening metastases, or a second malignancy (except for in situ carcinoma of the cervix or adequately treated basal-cell carcinoma of the skin). Further exclusion criteria were central nervous system involvement, hypercalcemia (> 10.5 mg/dl), active uncontrolled infection, or any serious concomitant systemic disorder deemed by the investigator to be incompatible with the study. Patients could not have received previous chemotherapy, although prior treatment with a biological response modifier was allowed. Concomitant hormonal and corticosteroid treatments were not allowed. Men and women had to take medically approved contraceptive precautions (if necessary) during the trial and for 3 months after receiving the final dose of study drug. Finally, patients who could not be adequately followed for the duration of the study were excluded.

Treatment

Gemcitabine at 800 mg/m^2 was given intravenously (infusion period, 30 min) once a week for a consecutive 3-week period, which was followed by 1 week of rest, this constituting a cycle of 28 days. Patients who completed one cycle of therapy at 800 mg/m^2 could have the subsequent dose increased by up to 20%, provided that they had shown no significant change from baseline in hematological parameters and that nonhematological toxicity had not been more severe than WHO grade 1. If the patient tolerated this escalation for the whole cycle, subsequent cycles could be given in dose escalations of up to 20% to a maximum of 1200 mg/m^2. Dose adjustments were made on the basis of assessments of hematological and non-hematological toxicities. Only 50% of a dose was given if the WBC was ≥ 2.0 but $< 3.0 \times 10^9$/l or the platelet count was $50–99 \times 10^9$/l. If the cell counts dropped below the lower level of either range, the injection was omitted. Patients with a grade 3 nonhematological toxicity could either have their dose reduced by 50% or have therapy withheld, depending on the judgement of the investigator. Patients with a life-threatening grade 4 non-hematological toxicity were removed from the study unless they were responding, in which case a 50% dose reduction could be instituted when the toxicity resolved.

Evaluation of response and toxicity

All patients who completed one cycle of therapy (including those withdrawn within this period for toxicity) qualified to be analyzed for efficacy, and all patients who were enrolled in the study were analyzed for safety. Efficacy was examined in each patient before each therapy cycle, i.e., every 4 weeks (medical history and physical examination, performance status evaluation, analgesics use), and before every other therapy cycle, i.e., every 8 weeks [chest X-ray, computerized tomography (CT) scan if appropriate, radiological tests]. Patients were then reviewed at 1 month after the last dose of study drug for assessment of efficacy and every 3 months for evaluation of survival and disease-free survival.

All responders were evaluated by a panel of independent experts, the Oncology Review Board (ORB). The evaluations were conducted using standard WHO criteria for measurable disease, duration of response, and survival. Efficacy data-analysis methods included determination of the tumor response rate and calculation of the 95% confidence intervals (CIs). Data for supportive response parameters such as performance status, weight, and analgesics consumption and for other disease-related symptoms reflecting either patients benefit or their clinical condition were also collected prospectively for all patients. Improvement had to be maintained for at least 4 weeks to be considered clinically relevant.

Results

Between February 1990 and July 1991, 39 patients (29 men and 10 women) were enrolled in the study. All received at least 1 dose of gemcitabine, and 37 were eligible for evaluation of efficacy. The disease characteristics at baseline are shown in Table 1. The median interval from diagnosis of the tumor to entry into the study was 12.6 months (range, 0–92.5 months). Of the 37 qualified patients, 43.2% had undergone previous surgery in an attempt at curative resection and 13.5% were receiving analgesics.

Efficacy

Of the 39 patients enrolled, 18 withdrew from the study due to lack of efficacy. Three patients were confirmed by the ORB as being responders to treatment with gemcitabine, giving a response rate of 8.1% (95% CI, 1.7–21.9%). One patient experienced a complete response (CR). This was a 51-year-old man with a local recurrence after previous nephrectomy, who experienced a partial response (PR) after two cycles and a CR after four cycles. Disease progression has not been reported to date (32 months after the start of treatment).

Two patients achieved a PR. One was a 47-year-old man who entered the study at 36.5 months following

Table 1 Summary of patients and disease characteristics at baseline

Eligible Patients	37
M/F	29/8
Age (years):	
Mean ± SD	56.62 ± 9.31
Range	38–74
Site of disease:	
Lung	30 (81.1%)
Lymph node	15 (40.5%)
Bone	7 (18.9%)
Liver	4 (10.8%)
Kidney	5 (13.5%)
Other	15 (40.5%)
Prior therapy:	
Any surgery	34 (91.9%)
Radiotherapy	5 (13.5%)
Immunotherapy	20 (54.1%)
Performance status:	
0	15 (40.5%)
1	19 (51.4%)
2	2 (5.4%)
3	1 (2.7%)
Level of analgesia:	
0	32 (86.5%)
1	3 (8.1%)
2	1 (2.7%)
3	1 (2.7%)
Number of sites ($n = 39$):	
1	20 (51.2%)
2	10 (25.6%)
3	7 (17.9%)
> 3	2 (5.1%)

a nephrectomy for the primary tumor, when a CT scan revealed recurrent disease in a retrocrural lymph node. A PR was seen after two cycles, and the patient was withdrawn from the study after three cycles at his own request. At disease progression (after 12 months), he was treated further with gemcitabine (five cycles) and again achieved a PR after two cycles, but his disease progressed in the retrocrural nodes thereafter and treatment was discontinued. The second patient who showed a PR was a 57-year-old man. He was pretreated with alpha- and gamma-interferon. On entering the study, he showed 13 measurable lung metastases. After ten cycles a PR was noted with concomitant improvement of his performance status. He received a total of 16 cycles. At 9 months after discontinuation, clear progression was documented. Gemcitabine treatment was restarted and continued for a total of 16 months, resulting in disease stabilization. In all, this patient has received up to 100 gemcitabine infusions. His survival from the start of treatment is currently 48 months.

A third case reported by the investigator as a PR was not confirmed by the ORB. The radiology was difficult to interpret, but it was thought that the patient had a mixed response, with some lesions responding while others progressed. The patient clearly progressed both locally and in his lung after five cycles, and this resulted in study termination.

The median time to disease progression after the study was 3.7 months; the minimum was 0.7 months and the maximum was 33.9 months at the data cutoff date. Six patients had not declared disease progression. The median overall survival was 12.3 months; the minimum was 0.7 months and the maximum was 33.9 months at the data cutoff date. In all, 13 patients were not reported to have died.

Disease progression data were available for 31 qualified patients and, as at baseline, were typical for patients with renal carcinoma. The major site of metastatic failure was the lung in 23 patients, the lymph nodes in 4 patients, and the brain in 3 patients, with a wide distribution of disease progression occurring at other anatomical sites. There was no meaningful improvement in any of the secondary efficacy parameters assessed.

Safety

Dose administration

During this study, a total of 39 patients received at least 1 dose of gemcitabine. A mean of 3.7 (range 0–16) cycles were completed. Gemcitabine was generally well tolerated, with only 1.6% of all injections being omitted and only 12.8% being reduced in dose. Hematological toxicity accounted for four dose omissions; diarrhea, for three omissions; and edema, for one omission. One further omission occurred when the patient failed to attend the clinic. Most dose reductions (70%) occurred during the first three cycles, usually as a result of leukopenia (83% of all dose reductions). In addition, 4.6% of injections were escalated above the protocol-defined starting dose.

WHO laboratory toxicity

WHO laboratory toxicities are reported in Table 2 as the maximal toxicity experienced by the patient. The overall tolerance of gemcitabine was good. There was no WHO grade 4 toxicity, and grade 3 toxicity for anemia, leukopenia, and thrombocytopenia were reported in only 13.2%, 5.3%, and 7.9% of patients, respectively. Although disturbances in hepatic enzymes were commonly found, these were mostly mild (only one patient had grade 3 toxicity) and of little clinical significance. When the data were analyzed according to therapy cycle, there appeared to be no trend toward increased toxicity as multiple cycles were given.

Table 2 WHO grades for laboratory and clinical toxicity (% of patients, all 39 patients)[a]

Toxicity parameter (laboratory)	Number of patients with data	0	1	2	3	4
Alkaline phosphatase	38	71.1	18.4	7.9	2.6	0
Alkaline transaminase	38	36.8	50.0	5.3	7.9	0
Aspartate Transaminase	38	63.2	28.9	2.6	5.3	0
Bilirubin	36	97.1	8.3	0	0	0
Blood urea nitrogen	38	73.7	21.1	5.3	0	0
Creatinine	38	57.9	42.1	0	0	0
Hemoglobin	38	28.9	31.6	26.3	13.2	0
Hematuria	37	54.1	27.0	16.2	2.7	0
White blood cells	38	26.3	34.2	34.2	5.3	0
Segmented neutrophils[b]	38	31.6	21.1	28.9	15.8	2.6
Platelets	38	76.3	7.9	7.9	7.9	0
Proteinuria	38	44.7	47.4	7.9	0	0

Toxicity parameter clinical)	0	1	2	3	4
Allergic	92.3	7.7			
Cutaneous	71.8	20.5	7.7		
Fever	64.1	17.9	17.9		
Cardiac function	92.3	2.6		2.6	2.6
Hair	89.7	5.1	5.1		
Infection	89.7	7.7		2.6	
Nausea/vomiting	38.5	28.2	12.8	20.5	
Pain	87.2	7.7	5.1		
Peripheral neurotoxicity	92.3	7.7			
Pulmonary	92.3	5.1		2.6	

[a]Maximal recorded WHO grade
[b]Segmented neutrophil counts have been coverted to WHO scores using granulocyte count criteria

WHO clinical toxicity

The clinical toxicity is summarized in Table 2. There was one grade 4 toxicity: cardiac function. This patient had a history of cardiac disease, including a myocardial infarction, and died of heart failure and arrhythmia, which was not thought to be drug-related. A second patient developed pneumonia after two injections of gemcitabine and rapidly deteriorated and died. The pneumonia was thought to be both disease- and drug-related by the investigator, but there was no concomitant leukopenia.

As expected, nausea and vomiting were the most common adverse events encountered, with only 38.5% of patients remaining unaffected. Grade 1 toxicity (nausea) was reported by 28.2% of patients: grade 2 toxicity (transient vomiting), by 12.8%; and grade 3 toxicity (vomiting requiring therapy), by 20.5%. However, no grade 4 toxicity (intractable vomiting) was reported. Other frequently reported adverse events included fever (35.9%), asthenia (35.9%), flu-like syndrome (17.9%), and skin rash (17.9%). Grade 3 toxicity was reported by two patients, one with dyspnea and one with a myocardial infarction.

The occurrence of alopecia was minimal. There was no grade 3 or 4 toxicity, and 89.7% of patients reported no hair loss at all. The majority of patients reported no pain during the study (87.2%).

Seven patients were withdrawn due to the following adverse events experienced during the study irrespective of drug causality: persistent pretibial edema (one patient); worsening exanthema (one patient); severe nausea and vomiting (one patient); asthenia, pain, nausea, and vomiting (one patient); myocardial infarction (one patient); and thrombocytopenia (one patient).

Discussion

In view of the overall response rate of 8.1%, gemcitabine monotherapy delivered at a dose of 800 mg/m^2 weekly for 3 weeks followed by 1 week of rest should

not be considered active in advanced renal-cell carcinoma when used at the tested dose and regimen. The population studied had a WHO performance status of 0 or 1 in 91.9% of cases, and the majority had pulmonary and nodal disease. Therefore, the present cohort is a reflection of the type of patient entered in study protocols with biological response modifiers, the exception being that five patients had their primary tumor in situ.

The responses observed were of good quality, and the appearance of a response in our third patient after ten cycles was remarkable. This patient never progressed during treatment, and after the restart of gemcitabine, disease stabilization occurred but no regression was observed, suggesting more of a cytostatic than a cytotoxic effect in this particular patient. The median survival of 12.3 months compares favorably with that obtained in many other studies but is probably more a reflection of the patient population than a result of therapy.

The toxicity of gemcitabine was fairly acceptable, with nausea and vomiting being the most prominent feature. It is unclear whether the newly available 5-hydroxytryptamine$_3$ antagonist might prevent this side effect, as it was not routinely applied in the present study. Bone marrow toxicity was generally mild, and there was no incidence of neutropenic fever. In one patient, grade IV granulocytopenia was seen. A more recently completed phase I study revealed a maximal tolerated dose (MTD) of 1250 mg/m^2 per week given for 3 weeks followed by 1 week of rest in nonpretreated patients [8]. A review of 201 chemotherapy-naive patients treated at the same dose showed the occurrence of grade III neutropenia in 23% of the patients and of grade IV neutropenia in 6% [9]. In our study, only in 4.6% of the injections was the dose escalated, on the other hand, only 12.8% involved dose reductions due to bone marrow toxicity. It is unclear whether a dose-response relationship exists for gemcitabine in renal-cell cancer. In view of the phase I data presented thus far, a further dose escalation might be possible. The results of our study are in agreement with those obtained in an earlier reported, smaller phase II study applying the same dose and regimen, where only one PR was noted [10].

References

1. Ritchie AWS, Chisholm GD (1983) The natural history of renal cell carcinoma. Semin Oncol 10:390–400
2. De Forges A, Rey A, Klink M, et al (1988) Prognostic factors in adult metastatic renal carcinoma: a multivariate analysis. Semin Surg Oncol 4:149–154
3. Montie JE, Stewart BH, Straffon RA, et al (1977) The role of adjunctive nephrectomy in patients with metastatic renal cell carcinoma. J Urol 117:272–275
4. Harris DT (1983) Hormonal therapy and chemotherapy of renal cell carcinoma. Semin Oncol 10:422–430
5. Yagoda A, Bander NH (1989) Failure of cytotoxic chemotherapy, 1983–1988, and the emerging role of monoclonal antibodies for renal cancer. Urol Int 44:338–345
6. McCune CS (1983) Immunologic therapies in kidney carcinoma. Semin Oncol 10:431–436
7. Rosenberg SA, Yang JC, Topalian SL, et al (1994) Treatment of 238 consecutive patients with metatastatic melanoma or renal cell cancer using high-dose bolus interleukin-2. JAMA 271:907–913
8. Pollera CF, Ceribelli A, Grecco M, et al (1992) Weekly gemcitabine: a phase I study with short and prolonged infusion schedules (abstract). Proc Am Soc Clin Oncol 11:329
9. Tonato M (1993). Gemcitabine safety overview. In: Gemcitabine novel combination of efficacy and tolerability. Proceedings European Conference Clinical Oncology 7 Satellite Symposium, Jerusalem, Israel. pp 14–16
10. Mertens WC, Eisenhauer EA, Moore M, et al (1993) Gemcitabine in advanced renal cell carcinoma. A phase II study of the National Cancer Institute of Canada Clinical Trials Group. Ann Oncol 4:331–332