A Phase II Study of Gemcitabine at Fixed Infusion Rate of 10 mg/m²/min with or without Immunotherapy in Advanced Renal Cancer

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Abstract. *Background: Advanced renal cancer remains a challenge for oncologists since no treatment other than surgery has demonstrated a clear survival advantage. Patients and Methods: Gemcitabine was given to suitable patients at a fixed infusion rate of 10 mg/m²/min. Eighteen patients received concomitant immunotherapy, mostly low doses of interleukin 2 (IL2). Results: Thirty patients were enrolled. The overall response rate was 14% (22% in the subset of patients treated with both chemotherapy and immunotherapy) with a median progression-free survival time of 4.1+ months. Toxicity was not mild, mostly fatigue, nausea and anaemia, even though not life threatening. Conclusion: Gemcitabine at the fixed infusion rate of 10 mg/m²/min with concomitant low doses of IL2 could be useful in the palliative treatment of symptomatic patients with renal carcinoma progressing after tyrosine kinases inhibitor.*

Renal cell carcinoma represents about 3% of all malignant tumors. In the U.S.A. there were 31,900 new cases in 2003 with 11,900 related deaths (27% rate) (1).

The treatment strategy is based on surgery, and overall survival depends on the pathological stage and some prognostic factors, such as Fuhrman's grade and performance status (PS) (2). No adjuvant treatment has demonstrated a survival advantage.

The median survival of metastatic disease is 10 months with a report of few long-term survivors (8.5% at 5 years) (3). Nephrectomy in addition to immunotherapy (alfa-interferon, α-INF) has given a survival benefit (4, 5). Recently, tyrosine kinase inhibitors, sutinib and sorafenib, have shown a progression-free survival (PFS) advantage in randomized studies. Sunitinib compared to α-INF in previously untreated advanced renal cancer patients gave a PFS advantage of 11 *vs.* 5 months and sorafenib compared to placebo in patients refractory to immunotherapy gave a PFS advantage of 5.5 *vs.* 2.8 months (6, 7). A survival benefit was also possible with a high-dose interleukin 2 (IL2) based regimen but only for a subset of patients with a good-prognosis (8).

Chemotherapy has failed to demonstrate a survival gain. Fluorodesoxyuridine, fluorouracil and vinblastine are considered the most effective agents in the palliative treatment of advanced renal cell carcinoma, with response rates (RR) within 13% (9).

Among the new chemotherapic agents, gemcitabine seems to give the highest RR, even up to 31% (10). Gemcitabine is a pyrimidine analogue and replaces cytidine along the DNA helix during DNA replication. Gemcitabine did not affect lymphocyte immune-reactive activity in patients with solid tumors and seemed to be synergistic with immunotherapy in animal models (11, 12). Prolonged infusion (time over 30 min) was able to increase the intracellular rate of gemcitabine's active metabolites enhancing therapeutic and toxic effects (13). Our previous experience in lung cancer patients has shown that gemcitabine doses up to 1200 mg/m² infused in 120 min on day 1, 8 and 15 every 4 weeks are safe, while lower doses are recommended in patients with a poor PS (14).

Considering the promising RR achievable with the standard 30 min schedule of gemcitabine a Phase II study of gemcitabine administered at the fixed infusion rate of 10 mg/m²/min with or without immunotherapy was initiated.

Patients and Methods

Patients were prospectively enrolled into the study from June 2002 to March 2007. No particularly restrictive selection criteria were adopted and patients with advanced progressive renal cancer suitable for chemotherapeutic treatment were recruited. Gemcitabine was administered at a fixed infusion rate of 10

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Table I. *Characteristics of the 30 patients enrolled.*

Characteristic	Pts N.
Gender	
Male	22
Female	8
Age (years)	
Median	59.7
Range	29.3-76.5
Histology	
Clear cell	29
Sarcomatoid	1
Stage	
Locally advanced	0
Metastatic	30
Metastases number	
Median	2
Range	1-4
Bone metastases	14
Fuhrman's grade	
Median	3
Range	1-4
ECOG PS	
Median	2
Range	0-3
Prior therapy	
Nephrectomy	30
Immunotherapy	18
Chemotherapy	9
One	5
More than one	4
Pall. radiotherapy	6
Other*	16

*Including surgery for metastasis.

Table II. *Toxicity of the 27 evaluable patients.*

Type	Gemcitabine (n=11)		Gemcitabine and immunotherapy (n=16)	
	Grade 1-2	Grade 3-4	Grade 1-2	Grade 3-4
Granulocytopenia	2	-	4	-
Anemia	2	2	1	1
Thrombocytopenia	2	-	-	-
Nausea	4	-	2	4
Vomiting	2	-	2	-
Constipation	-	-	3	-
Mucositis	1	1	3	-
Fever	-	1	2	-
Infection	1	-	-	-
Fatigue	1	-	2	4
Cutaneous	2	1	2	-
Vascular venous	1	-	-	2
Edema	1	1	5	1

mg/m^2/min on day 1, 8 and 15 of a 28 day cycle and response evaluation was performed every 2 cycles. The time of infusion was established according to age and Eastern Cooperative Group (ECOG)-PS. Immunotherapy was added if no immunotherapy had previously been given. Combination chemotherapy with doxorubicin was used in a case of sarcomatoid variant of renal cancer (15). Topotecan in combination with gemcitabine was administrated to a single patient undergoing a valuation of peripheral lymphocyte topoisomerase induction as a response to gemcitabine administration (16).

Results

Thirty patients, whose characteristics are shown in Table I, were enrolled. All the patients had undergone nephrectomy. All patients had metastatic disease at the time of entering the study. Eleven patients had metastases at disease presentation. The median ECOG PS was 2. Bone metastases were present in 14 patients (46%) and 6 of them (20%) needed surgery for vertebral stabilization. One patient had the sarcomatoid variant of renal cancer, while all the others were clear cell carcinomas. Eighteen patients received prior immunotherapy and 9 received 1 or 2 prior regimens of chemotherapy. Palliative radiotherapy was administered to 6 patients.

Eighteen patients out of 30 received gemcitabine with concomitant immunotherapy, IL2 at the dose of 3 MU for 6 days a week in 16 cases and α-INF at the dose of 3 MU for 3 days a week in the other 2 cases. Six patients treated with α-INF before entering the study were received the combination of gemcitabine and IL2. Gemcitabine doses ranged from 500 to 1250 mg/m^2 infused respectively in 50 to 125 min (median dose, 1000 mg/m^2 in 100 min). A total of 150 cycles were administered with a median of 4 (range 1-15).

Thirty gemcitabine administrations (7.5%) had to be delayed due to toxicity, mostly neutropenia and fatigue. Overall toxicity of the 27 evaluable patients is shown in Table II.

Among the 29 patients evaluable for response no complete response was achieved, 4 patients had a partial response with a RR of 14%. Eleven patients (38%) had stable disease and 14 (48%) had progression. PFS and overall survival (OS) were respectively 4.1+ months (range 1.1-34.0) and 12.3+ (range 2.9-56.0+) months.

Discussion

Among the new drugs tested in renal cell carcinomas, gemcitabine has shown appreciable response rates (see Table III) and a safe toxicity profile. Prolonged infusion administration of gemcitabine (more than 30 min, *i.e.* 10 mg/m^2/min) was an attempt to obtain a major anti-cancer activity. Two Phase II randomized clinical trials have

Table III. *Gemcitabine in renal cell carcinoma.*

Authors	Year	Pts N.	Schedule	Concomitant immunotherapy	RR%	Time to progression (months)	Overall survival (months)
Mertens *et al.* (17)	1993	18	Standard	//	6.0%	//	//
Casali *et al.* (10)	2001	18	Standard	//	31.0%	//	//
De Mulder et al (18)	1996	39 (54% pretreated)	Standard	//	8.1%	3.7	12.3
Rohde *et al.* (19)	1998	9 (pretreated	Standard	Alfa and γ-INF	15.0%	//	13.5
Rini *et al.* (20)	2000	41 (83% pretreated)	Standard +5FU	//	17.0%	7.1	11.6
Ryan *et al.* (21)	2002	41	Standard +5FU	IL2 and α-INF	14.6%	6.6	20.6
Porta *et al.* (22)	2004	41 (pretreated)	Standard +Oxaliplatin	//	14.0%	2.5	9.5
Waters *et al.* (23)	2004	19 (pretreated)	Standard + Capecitabine	//	15.8%	7.6	14.2
Stadler *et al.* (24)	2006	56 (75% pretreated)	Standard +Capecitabine	//	11.0%	5.6	14.5
George *et al.* (25)	2002	21 (50% pretreated)	Standard +Cisplatin +5FU	//	5.0%	//	10.0
Massacesi *et al.* (26)	2005	11 (pretreated)	Infusional	Alfa-INF	18.0%	7.1	13.0
Present study	2007	29 (60% pretreated)	Infusional 90%IL2	18 Pts out of 29	14.0%	4.1+	12.3+

evaluated the efficacy of fixed infusion rate of gemcitabine *vs.* the standard 30 min schedule respectively in non-small cell lung cancer and pancreatic cancer patients. Both the studies showed a favourable trend for a fixed infusion rate (27, 28).

In our renal cancer patient series, the overall RR was 14% but all the 4 partial responses were obtained among the 18 (RR=22%) patients treated with the combination of gemcitabine and immunotherapy. This is in agreement with the previously reported data showing a RR ranging between 5 and 31% (see Table III). In particular, only Massacesi *et al.* administered a prolonged infusion of gemcitabine combined with immunotherapy (interferon) and reported a response rate of 18% in 11 pre-treated patients (26).

The median PFS of our series (4.1+ months) was encouraging if the poor PS of our patient population is considered. Data extrapolated from a Phase III study evaluating the efficacy of sunitinib *vs.* immunotherapy showed a PFS of 5 months for patients belonging to the arm treated with interferon (6).

Toxicity was manageable but not mild (see Table II). In particular an high incidence of fatigue, grade 3-4 in 4 patients (15%) was noted but only in patients treated with the combination of gemcitabine and immunotherapy. Anemia was frequent (all grades in 6 patients – 25%) as well as cutaneous toxicity (all grades in 5 patients – 20%), mostly with an allergic pattern. Also peripheral edema was common (all grades in 8 patients, 33%) and one patient had a singular erysipeloid-like skin toxicity.

To date, the number of patients treated is not sufficient to evaluate possible correlations between the types of treatment schedule (immunotherapy or not, gemcitabine dosage and time of infusion) and toxicity or efficacy. Moreover efficacy data would be conditioned by the fact that gemcitabine alone was administered only to those patients progressing after immunotherapy while the combination was offered to patients as front-line treatment. Nevertheless, some useful information about toxicity has merged from the data. The patients receiving the combination of gemcitabine and IL2 exhibited more fatigue, nausea and peripheral edema compared with those treated with gemcitabine alone as shown in Table II (median gemcitabine dose of 1000 mg/m^2 in 100 min for both groups).

In conclusion, gemcitabine at the fixed dose rate of 10 $mg/m^2/min$ is a valid option in treating advanced renal cell carcinoma. The combination with immunotherapy is feasible and safe enough to be considered when the treatment is focused on symptom relief for those patients experiencing disease progression after tyrosine kinases inhibitors.

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