Retrospective review in patients with pulmonary metastases of renal cell carcinoma receiving inhaled recombinant interleukin-2

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Pulmonary metastases of renal cell carcinoma are associated with poor prognosis. Systemic interleukin-2 is used to treat pulmonary metastases of renal cell carcinoma; however, its toxicity limits its use. The objective of this study was to evaluate the efficacy and safety of inhaled interleukin-2 in pulmonary metastases of renal cell carcinoma patients. The study was designed as a retrospective chart review in pulmonary metastases of renal cell carcinoma patients treated with inhaled interleukin-2. Between 2000 and 2004, 19 centres in Spain and two in Portugal recruited 51 patients. The treatment schedule was as follows: three cycles of 36 MIU interleukin-2 per day for 5 days/week for 12 weeks (with 1 treatment-free week between cycles) in Spain and for 3 weeks (out of each 4 weeks) for 12 weeks in Portugal. Efficacy was assessed by best response following each treatment cycle and at final evaluation. Kaplan–Meier method was used to estimate progression-free survival and overall survival. Safety data were analysed using descriptive statistics, with toxicities expressed in number of weeks, which were reported. Overall objective response rate was 13.7% (95% confidence interval: 5.7–26.3). Median progression-free survival and overall survival were 8.6 (95% confidence interval: 3.45–16.5) and 23 (95% confidence interval: 11.5–34.5) months. The most common toxicities were cough (40% of cycles) and fatigue (7%). The majority of weeks of toxicities were reported to be only grade 1 or 2 in severity. Inhaled interleukin-2 shows efficacy and mild toxicity of pulmonary metastases of renal cell carcinoma patients, and might be considered as an alternative treatment to the systemic administration of this drug in these patients. *Anti-Cancer Drugs* 18:291–296

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Introduction

Patients with metastatic renal cell carcinoma have a poor prognosis, with 74% mortality at 1 year and 96% mortality after 3 years [1]. Interleukin-2 (IL-2) has demonstrated its activities as a T cell growth factor, and activator of T cells and natural killer cells. Additionally, several clinical trials have shown that close to 7% of patients with metastatic renal cell carcinoma treated with systemic administration of IL-2 achieve perdurable complete response [2,3]. These results led to the approval of IL-2 by the US Food and Drug Administration as the only currently approved therapy for this disease. Pulmonary metastases of renal cell carcinoma (PMRCC) are associated with particularly poor prognosis and local delivery of IL-2 in these patients is an attractive method to treat such lesions [4]. Several studies have examined the use of inhaled IL-2 in patients with renal cell carcinoma and lung metastases, with reports of improved progression-free survival and overall survival, and less toxicity compared with systemic IL-2 [5]. Although not previously labelled for administration via the pulmonary route, many centres have been administering the injectable formulation of IL-2 via a nebulizer in patients with PMRCC. Several centres have gained considerable experience, with one German centre publishing 10 years of experience of inhaled IL-2 in 188 patients and reporting median survival of 12.4 months (rather than the expected 5.3 months) with only mild toxicity [6]. The objective of this review was to obtain efficacy and safety data on inhaled IL-2 used in clinical practice in patients with metastatic renal cell carcinoma in different hospitals in Spain and Portugal.

Material and methods

The study was designed as a retrospective chart review in patients being treated with IL-2 in clinical practice. The study was initiated and planned independently by the Spanish Kidney Cancer and Melanoma Research Group.

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Centres in Spain and Portugal known to be treating patients with metastatic renal cell carcinoma were contacted (20 in Spain and three in Portugal) by the Spanish Kidney Cancer and Melanoma Research Group by mail in January 2003, and requested to review the records of any patients ever treated with inhaled IL-2 in their centres and complete the provided patient review form. Of the 23 centres contacted, all subsequently returned patient review forms with the exception of two (one in Spain and one in Portugal).

The objective was to obtain data on the efficacy and safety in patients already receiving inhaled IL-2 in clinical practice. Centres were asked to review the charts of all patients with metastatic renal cell carcinoma who had been treated with inhaled IL-2 at any time.

In Spain, the treatment schedule recommended by physician groups for the use of inhaled IL-2 at the time of the study was as follows. Three cycles of 36 MIU IL-2 per day (via five divided inhalations) for 5 days per week for 12 weeks (with 1 treatment-free week between cycles). In addition, there were recommendations for a maintenance regimen of 36 MUI IL-2 per day for 5 days per week for 2 weeks of each month. In Portugal, the treatment schedule recommended by physician groups was three cycles of 36 MUI IL-2 per day (via five divided inhalations) for 5 days per week for 3 weeks (out of each 4 weeks) for 12 weeks. Maintenance treatment schedule was the same as the one decided in Spain.

Centres using inhaled IL-2 generally administer the commercially available product via a nebulizing unit including a Salvia Lifetec 'Jetair δ20' compressor (Salvia Lifetec Geräte für Medizintechnik GmbH & Co. KG; Kronberg, Germany). Commercially available vials for systemic administration (Proleukin, Chiron; Emeryville, California, USA) contain 18 MIU IL-2 as a powder for reconstitution. Centres administering inhaled IL-2 generally reconstitute two vials [total 36 MIU with 10 ml of sterile solution (5% glucose)]. Patients are then treated with 2 ml of solution via a nebulizer five times daily.

The patient review form collected general demographic and baseline data on the patients. In addition, information was collected on sites of metastases and duration of disease. For each treatment cycle, data were collected on response [according to World Health Organization criteria (complete response, partial response, stable disease, progressive disease, nonevaluable)] [7], on toxicities and on routine blood parameters. The patient review form also had space for similar information on up to six maintenance cycles, with final follow-up information collected on reasons for finishing IL-2 treatment and the vital status of the patient. It also included a table requesting information on whether patients had experienced (by week of treatment cycle) any of the following events (in this order): cough, nausea, vomiting, mucositis, diarrhoea, dermatological toxicity, alopecia, peripheral or central nervous system toxicity, fever, cardiovascular, pulmonary, hepatic or renal toxicity, fatigue. The table also requested information on severity of any toxicity, according to the World Health Organization grades [7].

Statistical analysis

Efficacy was assessed by best response following each treatment cycle and overall. Descriptive statistics were used, showing number (%) of patients with complete response, partial response, stable disease, disease progression and nonevaluable. Regarding efficacy, on intent-to-treat population basis, a patient was considered valuable for response if at least a cycle of treatment was administered. Nevertheless, all patients (the 51 patients) were included in the denominator in the response evaluation.

For survival, overall survival (OS) and progression-free survival (PFS) estimates were calculated on the basis of Kaplan–Meier curves for censored data and stratified uses Cox regression models (log-rank test for equality hypotheses) [8].

OS was defined from the start date of treatment (cycle 1, month 1) until last follow-up date (or last available date as treatment finalization if alive and study finalization if dead, but no available date of death). PFS was calculated from the same treatment start date (cycle 1, month 1) to date of first registered disease progression.

Safety data were analysed using descriptive statistics only, with toxicities expressed as number of weeks, which reported each toxicity by cycle and by grade.

The sample size of this retrospective study was determined by the number of patient review forms returned from centres using inhaled IL-2 in patients with metastatic renal cell carcinoma in Spain and Portugal.

Results

Retrospective chart data were received on 51 patients with metastatic renal cell carcinoma who had been treated with inhaled IL-2. The data were provided by 19 centres in Spain (45 patients) and two centres in Portugal (six patients), covering use of inhaled IL-2 from September 2000 to February 2004. Of the 51 patients, 43 had received inhaled IL-2 alone, with the remaining eight receiving IL-2 in addition to systemic immunotherapy.

Patient demographics were concordant with a population with metastatic renal cell carcinoma, with a preponderance of males and median age of 62 years (Table 1). As expected, time since primary diagnosis of renal cell

carcinoma varied considerably, with approximately one-third being less than 12 months and one-third being more than 24 months from primary diagnosis (Table 1). All except one patient had metastases involving at least one site, with the remaining patient having a primary renal tumour only. Median time from primary diagnosis to metastases was 13 months (range from 0 to 132 months). The majority of patients had Eastern Clinical Oncology Group performance status 0 or 1 and most had not received previous therapy with chemotherapy or radiotherapy. In contrast, most patients had undergone previous surgery (nephrectomy) and the majority (94.1%) had received prior systemic immunotherapy with IL-2, interferon-α or both (Table 1).

Table 1 **Demographic data and baseline characteristics**

Male/female gender, *n* (%)	41/10 (80/20)
Median age (range) (years)	62 (31–80 years)
Time since primary diagnosis of renal cell carcinoma, *n* (%) (months)	
<12	15 (29.4%)
12–24	10 (19.6%)
>24	16 (31.4%)
missing	10 (19.6%)
Number of metastatic sites, *n* (%)	
0	1 (2%)
1	22 (43.1%)
>1	19 (37.3%)
missing	9 (17.6%)
ECOG, *n* (%)	
0	20 (39.2%)
1	23 (45.1%)
2	3 (5.9%)
missing	5 (9.8%)
Prior therapy, *n* (%)	
chemotherapy	
yes	9 (17.6%)
no	42 (82.4%)
radiotherapy	
yes	8 (15.7%)
no	43 (84.3%)
surgery	
yes	48 (94.1%)
no	3 (5.9%)
immunotherapy	
yes	36 (70.6%)
no	15 (29.4%)

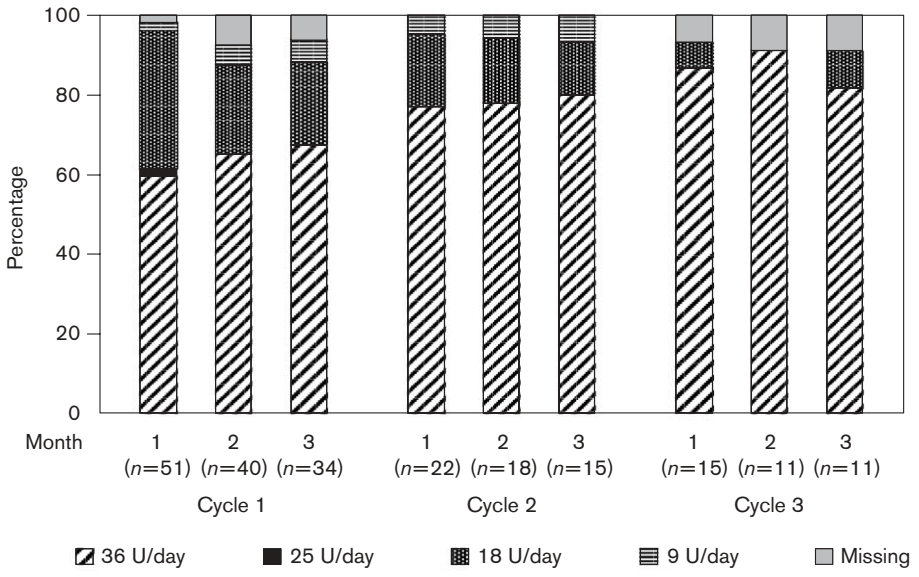
ECOG, Eastern Clinical Oncology Group.

Safety and toxicity

The majority of cycles (78.4%) were not associated with any need for interruption or dose reduction of inhaled IL-2. Of the total 236 cycles started, 51 (21.6%) were associated with interruptions or dose reductions. Of these, only 17 (7%) were definitive interruptions of therapy. The most common cause of interruption or dose reduction was toxicity, although this related to only 20 (8%) cycles out of a total of 236 cycles started. Medical decision was the second most frequent cause of interruption or reduction (18 cycles). Patients were treated with various IL-2 doses, ranging from 9 to 36 MIU/day, with a median dose of 30.4 MIU (range 9–36 MIU) in cycle 1, 31.3 MIU (range 9–36 MIU) in cycle 2 and 34.1 MIU (range 18–36 MIU) in cycle 3. Over 60% of patients received 36 MIU/day in the first cycle, increasing to approximately 80% in subsequent cycles. The median dose administered in this analysis was of 32 MIU a day (Fig. 1).

The safety data collected covers 1000 weeks of treatment cycles of inhaled IL-2, of which 488 were from cycle 1, 220 from cycle 2, 140 from cycle 3 and 152 from

Fig. 1



Proportion of patients receiving dose (MIU) by cycle.

Table 2 Most common toxicities by cycle (number of weeks in which toxicity was reported)

	Total weeks				
	All cycles 1000	Cycle 1 488	Cycle 2 220	Cycle 3 140	Maintenance 152
Cough	399 (39.9%)	223 (45.7%)	59 (26.8%)	12 (8.6%)	24 (15.8%)
Fatigue	70 (7.0%)	39 (8.0%)	31 (14.1%)		
Pulmonary[a]	50 (5.0%)	30 (6.1%)	20 (9.1%)		
Liver	21 (2.1%)	5 (1.0%)	8 (3.6%)		8 (5.3%)
Depression[b]	20 (2.0%)		8 (3.6%)		12 (7.9%)
Fever	18 (1.8%)	18 (3.7%)			
Weight loss[b]	18 (1.8%)	18 (3.7%)			
Peripheral nervous system	8 (0.8%)	4 (0.8%)	4 (1.8%)		
Nausea	8 (0.8%)	8 (1.6%)			
Renal	5 (0.5%)	4 (0.8%)	1 (0.5%)		
Diarrhoea	3 (0.3%)	1 (0.2%)	2 (0.9%)		
Vomiting	2 (0.2%)	2 (0.4%)			

[a]Pulmonary signs and symptoms were reported by 11 patients, and included four cases of dyspnoea/difficulty breathing, two cases of dyspnoea and sibilancies, two cases of bronchospasm, and one case each of asthma, bronchospasm and sibilancies.
[b]Although depression and weight loss did not appear as toxicities in the table on the patient review form these were reported as free text. In addition, two other toxicities were reported as free text, one spontaneous brain haemorrhage and one 'cardiovascular problems for peritoneal metastases'.

Table 3 Best response by treatment cycle

	Cycle 1 evaluation ($n=46$)	Cycle 2 evaluation ($n=15$)	Cycle 3 evaluation ($n=9$)	Maintenance evaluation ($n=2$)
Complete response	2 (4.3%)	1 (6.7%)	1 (11.1%)	0 (0%)
Partial response	6 (13.0%)	2 (13.3%)	0 (0%)	0 (0%)
Stable disease	10 (21.7%)	5 (33.3%)	3 (33.3%)	0 (0%)
Progressive disease	16 (34.8%)	7 (46.7%)	4 (44.4%)	2 (100%)
Not evaluable	12 (26.1%)	0 (0%)	1 (11.1%)	0 (0%)

maintenance cycles. Of the toxicities included in the patient review form table, the most commonly reported was cough, which occurred in 399 (40%) of 1000 weeks of treatment (Table 2) and appeared to become less frequent with each subsequent cycle. The second most common toxicity was fatigue, which occurred in 70 (7%) weeks and increased with each cycle. The majority of weeks of toxicities were reported to be only grade 1 or 2 in severity. Only 45 (4.5%) of the weeks of toxicity were reported to be of grade 3 or 4 [cough (27 weeks at grade 3), pulmonary (10 weeks at grade 3), liver (1 week at grade 4) and weight loss (7 weeks at grade 3)]. Of the prespecified toxicities, no weeks of toxicity were recorded for mucositis, dermatological toxicity, alopecia, central nervous system or cardiovascular toxicity. No important effects on laboratory parameters were observed and all side-effects reported were reversible by removing the treatment.

Efficacy

Evaluation of response of pulmonary lesions was available in 47 patients (identified as valuable in $n = 20$, measurable in $n = 21$ and not stated in $n = 6$). In the remaining four patients, response data were reported with respect to other sites (lymph nodes for one patient, primary tumour for two and peritoneum for one). In most patients, response was assessed by computerized tomography (42 patients, 82.4%), with the remainder being assessed by radiography (seven patients, 13.7%), nuclear magnetic resonance (one patient, 2.0%) or missing (one patient, 2.0%). All the partial and complete responses were confirmed by a computed tomography. Overall best objective response rate (complete or partial response) per cycle was 17.3% in cycle 1, 20.0% in cycle 2 and 11.1% in cycle 3 (Table 3). In addition, stable disease was reported in 21.7% patients in cycle 1, and in 33.3% in both cycles 2 and 3. At final evaluation, overall response rate (complete and partial response) was 13.7%, with stable disease in 15.7% (Table 4). All cases of complete response at final evaluation ($n = 3$) occurred in patients who had received previous immunotherapy. We have not seen any statistical difference in response rate between the schedule used in Portugal and the one used in Spain.

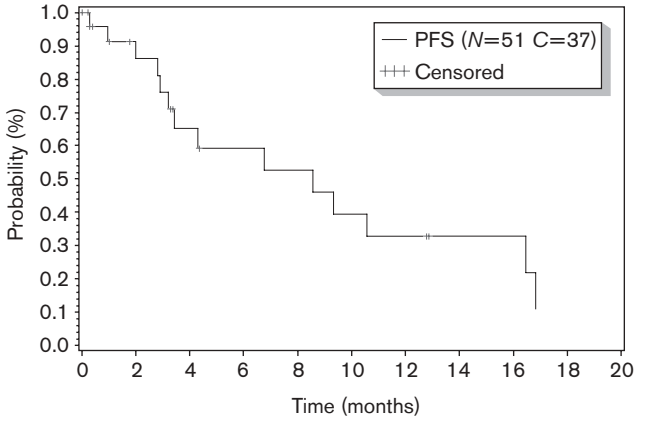
Table 4 Best response at final evaluation

	Total ($n=51$[a])	Previous immunotherapy ($n=36$)	No previous immunotherapy ($n=15$)
Complete response	3 (5.9%)	3	0
Partial response	4 (7.8%)	2	2
Stable disease	8 (15.7%)	6	2
Progressive disease	22 (43.1%)	16	6
Not evaluable	10 (19.6%)	8	2

[a]Final evaluation data were not provided for four patients.

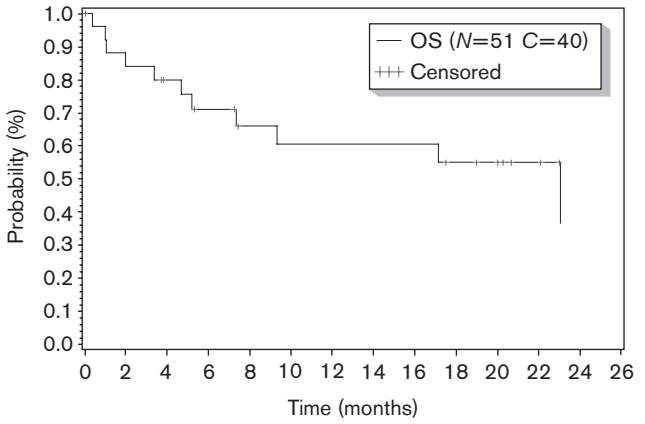
Data on PFS and OS were reported for only 40 patients. Thirty-six of them had a PFS greater than 6 months with a median of 8.57 months (Kaplan–Meier estimate, 95% confidence interval: 3.45, 16.46, Fig. 2). Forty-four

Fig. 2



Kaplan–Meier curve for progression-free survival (PFS).

Fig. 3



Kaplan–Meier curve for overall survival (OS).

patients had an OS greater than 12 months with a median of 23.03 months (Kaplan–Meier estimate, 95% confidence interval: 11.5–34.5; Fig. 3).

Comment

This retrospective chart review was designed to obtain efficacy and safety data in nonselected patients receiving inhaled IL-2 for PMRCC in clinical practice. The population characteristics of the study are as expected for patients with this pathology, suggesting that the results of our analysis are likely representative of the real value of IL-2 using this route of administration.

The efficacy data of inhaled IL-2 schedules suggests an overall best response rate of 13.7%. This is similar to the response rate of 15% reported by a large centre in Germany [9] and to response rates of around 20% reported in another study [10]. In addition, there was disease stabilization in a further 15.7%, giving an overall disease control rate and clinical benefit of 29.4%. The 1-year survival of 44% is also in keeping with the 47% reported in a large retrospective analysis [11] and considerably higher than would be anticipated without therapy [1]. The response rate, however, is much higher than the one reported by Merimsky *et al.* [5], 13.7 versus 2.5% (no complete response reported), although that mentioned study showed a higher disease stabilization rate (55%), with a similar median PFS (8.7 months). The difference in the response rate in favour of our study may be explained by our patients having a more favourable risk factor profile compared with Merimsky's set. As a clear example, the percentage of our patients having an Eastern Clinical Oncology Group score of 0–1 is 84.3%, higher than any of the previous subsets described. Our results confirm the findings reported by Lorenz *et al.* [12] in a phase I study of inhaled IL-2, showing similar complete and partial response rates. The different dosage and schedule of the Merimsky study, however, may be involved in the inferior response rate as well, as they used half of the dose of IL-2 (18 MUI) administered only three times a day. No OS data from this study were present. The optimal dosage and schedule of inhaled IL-2 is not a closed issue yet and additional studies must be carried out to clarify these important points.

Globally, efficacy data of inhaled IL-2 seem to be similar to those reported with the systemic administration, either intravenous or subcutaneous. In a systematic review reported by Baaten *et al.* [13], the overall response range was 14–21%, depending on the administration route.

Overall safety and tolerability appeared to be acceptable with a low number of patients requiring interruption or dose reduction owing to toxicity. The safety profile is in keeping with that already reported, with cough being the most common side-effect. In other studies, cough has been reported to occur mainly during the last inhaled dose of the day and during the first 4–8 weeks of treatment [11]. In our study, no data were recorded on timing of cough during the day, but in keeping with previous reports, cough occurred more frequently in the first cycle of treatment and become less frequent with each subsequent cycle, which may be due to improved tolerance to inhaled IL-2 or could be explained by cough being related to the underlying disease, which improved with treatment. On the other hand, the second most common toxicity was fatigue, which increased with each cycle and might suggest that this symptom was related to therapy, as this symptom is a well-recognized side-effect of systemic IL-2 therapy, but also with progression of disease. Anyway, most of the side-effects described were

reported to be only grade 1 or 2 in severity and reversible by removing the treatment.

Conclusions

Although interpretation of results from retrospective studies is always limited, the data of our study are concordant with the previous inhaled IL-2 reported experiences. We can conclude that inhaled IL-2 shows efficacy and only mild toxicity in patients with PMRCC. Inhaled IL-2 might be considered as alternative treatment to the systemic administration of this drug in these patients, as the risk/benefit ratio can be improved with the locoregional route, although further studies are needed to clearly define the advantage of this route of administration.

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