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Interleukin-2 Inhalation Therapy in Renal Cell Cancer: A Case Report and Review of the Literature

GIROLAMO DEL MONTE[1], PATRIZIA FERRONI[2], SABRINA MARIOTTI[1], EMANUELA FOSSILE[1], FIORELLA GUADAGNI[2] and MARIO ROSELLI[1]

[1]*Medical Oncology, Department of Internal Medicine, University of Rome "Tor Vergata", Tor Vergata Clinical Center;* [2]*Department of Laboratory Medicine & Advanced Biotechnologies, IRCCS San Raffaele Pisana, Rome, Italy*

Abstract. *Renal cell carcinoma (RCC) is the most common malignancy of the kidney. One third of RCC presents metastatic disease at the time of diagnosis, usually leading to a fatal outcome. Small response rates were seen with most cytotoxic agents including gemcitabine and vinorelbine, whereas systemic therapy with high doses of interleukin 2 (IL-2) has been shown to provide durable complete remissions. However, in consideration of its severe toxicity, IL-2 immunotherapy is restricted to selected patients. Aerosol IL-2 has been introduced as an alternative therapy in cancer patients. However, only very few data are available on its use in patients with pulmonary metastatic RCC. This paper briefly summarizes current clinical experience with the use of inhaled IL-2 therapy, either as a single therapy or in combination with other treatments. In addition, we report on a male patient with pulmonary metastasized RCC who achieved a durable complete response to combined gemcitabine/vinorelbine and interleukin-2 inhalation therapy.*

Renal cell carcinoma is the most common malignancy of the kidney, accounting for 1.9% of all cancers globally (1, 2). Classic clear-cell RCC originates from the renal cortex and is responsible for 80% to 85% of primary renal tumours (2). One quarter of patients present with advanced disease, and one third who undergo resection of localized disease will have recurrence and a 5-year survival rate of approximately 2% (2, 3).

In contrast to many other malignancies, RCC is generally resistant to therapy (3, 4) and long-term survival is achieved in few patients (4) with a median survival after diagnosis of metastatic RCC of approximately 13 months (2). Indeed, multiple studies performed during the 1980s clearly demonstrated that RCC is resistant to chemotherapy (5) and most cytotoxic agents, including gemcitabine and vinorelbine, have shown poor response rates (6). These are probably attributable either to the presence of the p170 glycoprotein on the tumour cell surface or to the low growth fraction and long doubling time, which reduces the susceptibility of renal carcinoma cells to the effects of chemotherapeutic agents (7).

With the advent of non-specific biological response modifiers in the 1980s and their subsequent approval, single-agent interleukin-2 (IL-2) and interferon-α (IFN-α) achieved response rates (complete response + partial response) of 10% to 20% (8). Though modest, these responses were clearly superior to chemotherapy and represented a significant advance. Most recently, molecularly based targeted approaches against growth factors and their receptors have been introduced as systemic treatment options for metastatic RCC. New targeted therapy such as sorafenib and sunitinib, selective inhibitors of multiple receptor tyrosine kinases, including vascular endothelial growth factor receptor (VEGFR) family, platelet-derived growth factor receptors (PDGFRα, PDGFR-β), c-kit, and Flt-3, are now approved for the first- and second-line treatment of metastatic RCC (9, 10) and are associated with an improvement of progression-free and overall survival when compared to IFN-α monotherapy. Past data for the rationale and use of immunotherapy in light of these new molecularly based target approaches have been the object of recent reviews, to which the reader is referred for further appraisal (2, 3, 11).

Hitherto, no drug other than IL-2 has significantly demonstrated enough antitumor activity for the treatment of metastatic RCC to warrant Food and Drug Administration (FDA) approval. However, in consideration of the severe toxicity, IL-2 immunotherapy is restricted only to selected patients (12). In the early 1990s, aerosol IL-2 was introduced as an alternative therapy in cancer patients. Inhalation therapy deposits a drug into the airways to achieve a high, local,

Correspondence to: Mario Roselli, MD, Medical Oncology, Department of Internal Medicine, Tor Vergata Clinical Center, University of Rome "Tor Vergata", Viale Oxford, 81, 00133 Rome, Italy. Tel/Fax +390620903544, e-mail: mario.roselli@uniroma2.it

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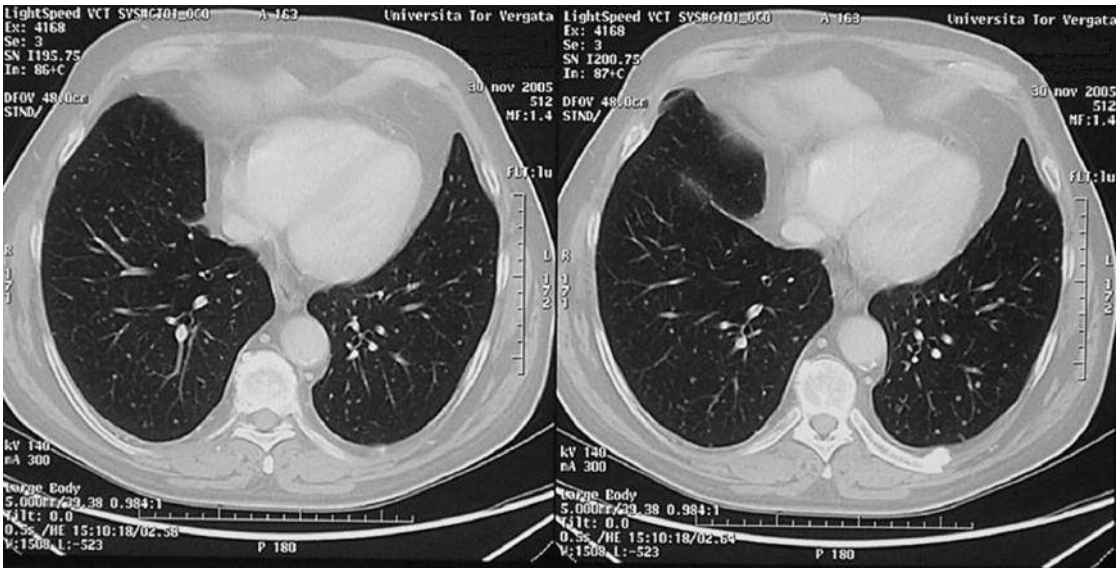

Figure 1. *CT scan after 4 cycles of systemic immunotherapy showing the appearance of pulmonary secondary lesions.*

clinical effect while avoiding serious systemic side-effects. High doses of inhaled IL-2 were, indeed, well tolerated and showed some efficacy for the treatment of lung metastases of RCC (13). However, only few data are available, to date, on its use in patients with lung metastases of RCC.

Here, we report on a male patient with pulmonary metastasized RCC who achieved a durable complete response to combined gemcitabine/vinorelbine and interleukin-2 inhalation therapy. Current clinical experience with the use of inhaled IL-2 therapy, either as a single therapy or in combination with other treatments, is briefly reviewed.

Case Report

A 66-year-old man, with a clinical history of blood hypertension and psoriasis treated with oral methotrexate, underwent left radical nephrectomy in November 1996. The histological examination revealed an RCC without involvement of locoregional nodes (pT2pN0M0). In February 2005, magnetic resonance of the abdomen showed the presence of a mass to the right suprarenal gland; therefore, the patient was submitted to right surrenalectomy. The pathological examination was positive for metastasis from RCC. On March 2005, the patient was referred to the Medical Oncology of the "Tor Vergata" Clinical Center for the presence of bone metastases revealed by a bone scan. A computed tomography (CT) scan did not show visceral metastases, but did confirm the presence of several osteolytic bone lesions (bilateral ribs). Physical examination did not reveal the presence of other secondary lesions. Blood samples drawn for haematological, blood chemistry and coagulation testing produced normal results. The level of serum carcinoembryonic antigen (CEA) was in the normal range and the performance status, according to ECOG criteria, scored 0. Bone metastases were asymptomatic and did not require radiotherapy. From July to October 2005, the patient underwent 4 cycles of the following immunotherapeutic schedule: IL-2 4.5 MUI subcutaneously for 5 days weekly, plus IFN-α 3 MUI/3 times/week, plus medroxyprogesterone acetate 1000 mg/day orally (14). Immunotherapy was repeated for 4 weeks with two weeks' rest. As depicted in Figure 1, the restaging CT scan showed the appearance of pulmonary secondary lesions. On the contrary, a bone scan performed to complete clinical staging, demonstrated stable disease. The performance status remained 0 and haematochemical values (including serum CEA) were within the normal ranges.

Thus, in consideration of the disease progression, systemic treatment was modified, including gemcitabine 1000 mg/m^2 and vinorelbine 25 mg/m^2 every 15 days, plus inhaled IL-2 (6 MUI/3 times/day) for 5 days weekly for 3 weeks with one week's rest. Treatment was well tolerated with no G3/4 toxicity recorded. Only G2 cough was observed during IL-2 administration, while G2 anaemia was related to chemotherapy. No delay or omission of treatment due to toxicity occurred. CT scan, performed after 4 cycles of systemic treatment, showed a complete remission of lung metastases (Figure 2).

The combined chemoimmunotherapy protocol was continued until August 2006, for a total of 8 cycles. Again, no G3/G4 toxicities or delay in recycling were recorded. Restaging evaluation by CT scan confirmed the complete remission of lung metastases. A bone scan showed stable disease. In light of these data, the patient continued treatment

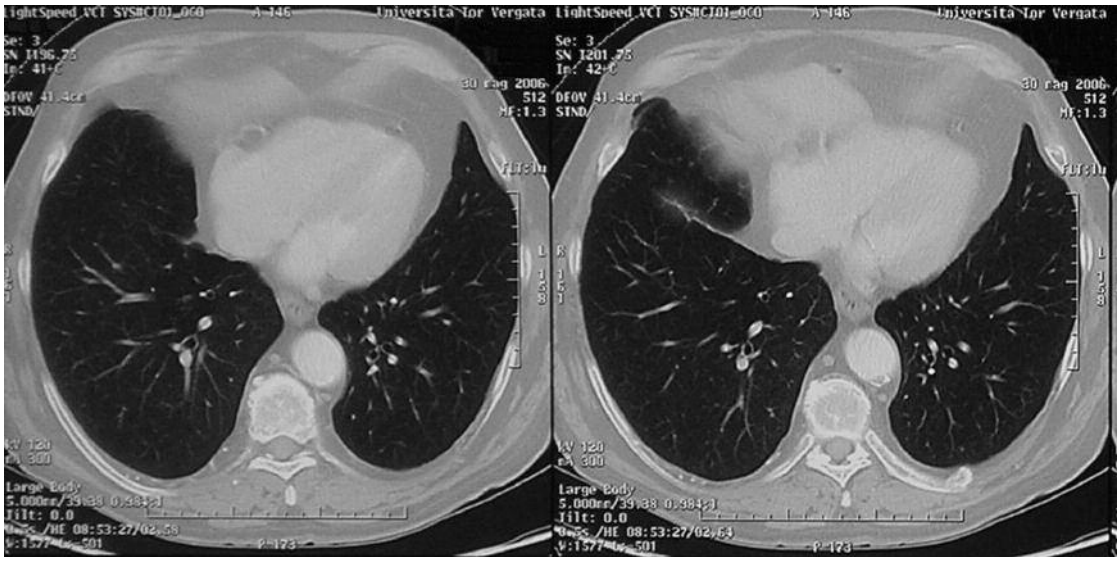

Figure 2. *Restaging CT scan after 4 cycles of combined gemcitabine/vinorelbine plus inhaled IL-2 treatment showing a complete remission of lung metastases.*

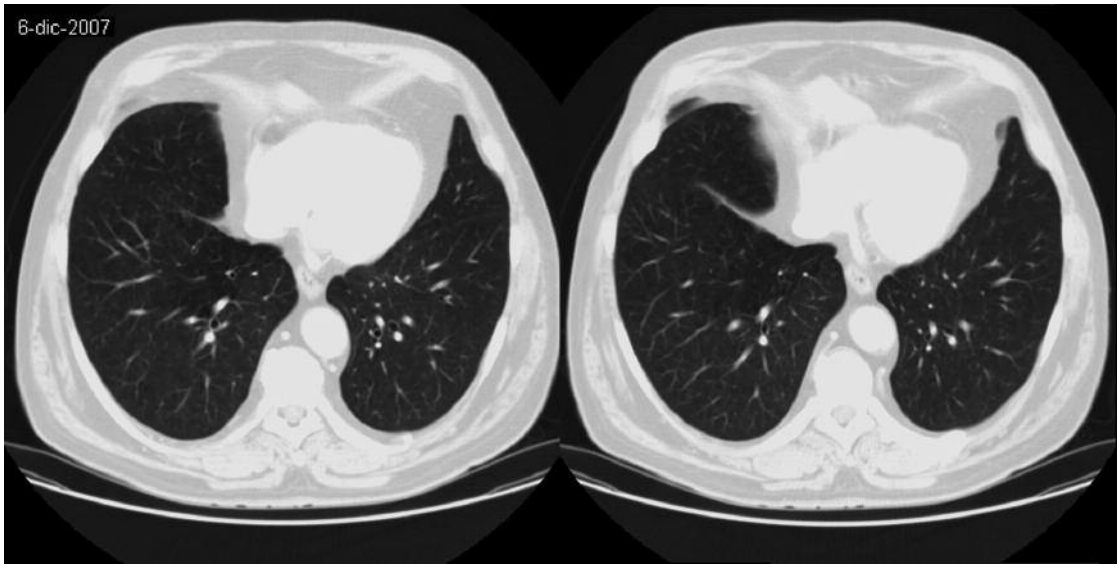

Figure 3. *The most recent restaging CT scan showing the persistence of the complete remission of lung metastases after 19 months (December 2007).*

with immunotherapy alone (inhalatory IL-2 18 MUI for 5 days every 15 days) until December 2006 when he showed an ischemic lesion of the brain, evidenced by CT scan. Therefore, the treatment was discontinued and the patient entered into a surveillance follow-up. As shown in Figure 3, the last CT scan, performed on December 2007, showed no evidence of disease. Moreover, a bone scan showed no progression of disease (Figure 4). The patient is still asymptomatic and of good performance status; the elapsed time from the remission of lung metastases is actually 19 months.

Discussion

Despite RCC being associated with the highest incidence of spontaneous regression of secondary lesions (15), pulmonary metastases of RCC are associated with poor prognosis, with a median survival time of 10-13 months (2, 16). Systemic treatment options for metastatic RCC include palliative measures, such as immunotherapeutic options, chemotherapy and hormonal treatment, but the first-line therapy remains disappointing.

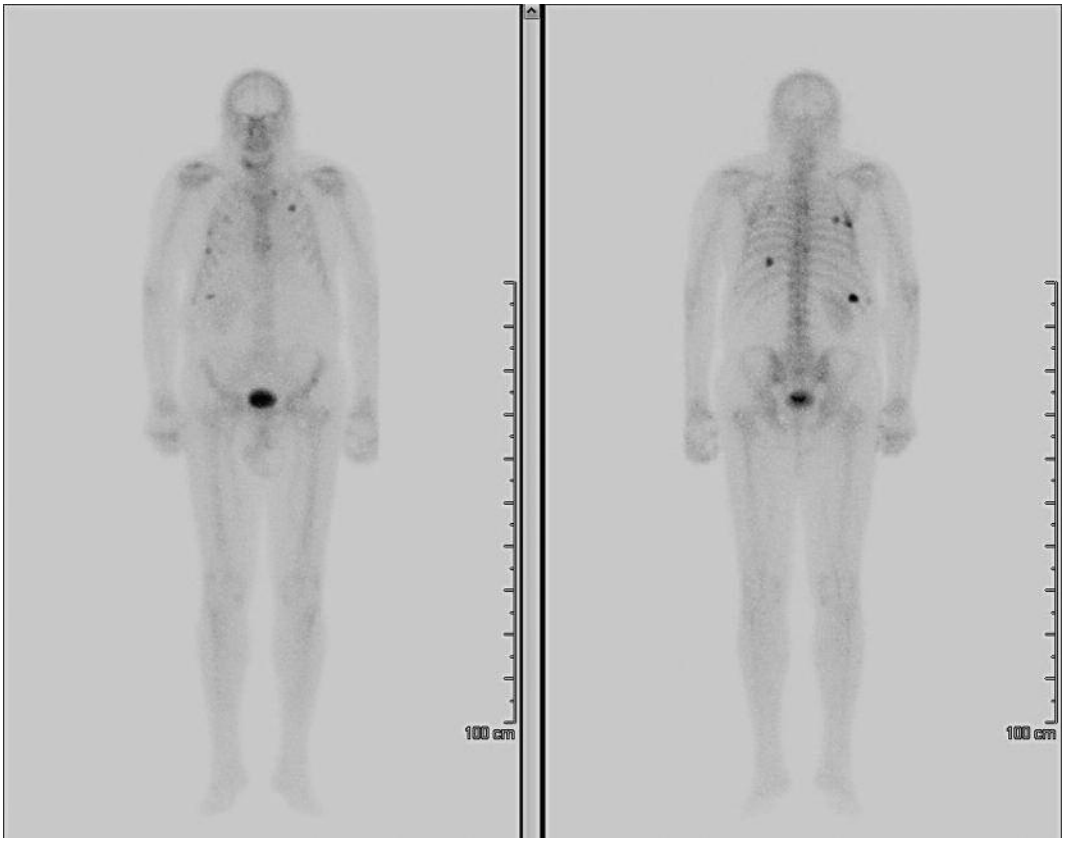

Figure 4. *Bone scan showing stability of disease.*

Many approaches have been investigated, of which IFN-α and IL-2 are the most extensively studied. In Europe, both drugs are registered for treatment of metastatic RCC. To improve the response rates observed with either drug and exploit the impressive synergy observed in *in vitro* models, combination IL-2 plus IFN-α trials were also conducted, but response rates rarely exceeded 20% to 30% (3). Systemic IL-2 administration received Food and Drug Administration approval for the treatment of patients with stage IV RCC in 1992 [reviewed in (2) and (17)] based on studies in which patients receiving high-dose bolus of recombinant human IL-2 (600,000-720,000 IU/kg by 15 minutes' infusion, every 8 hours, during 5-day courses, separated by 5-9 days' rest) showed an objective responses rate of 15% (including 7% complete and 8% partial responses) (15). A median duration of response of 54 months for all of the responders and a median survival of 16 months for all participants were observed. Follow-up data on these patients accumulated until June 2002 (median follow-up of >10 years) showed that 60% of complete responders remained free of disease and that those individuals with partial responses resected to "no evidence of disease" after a response to high-dose IL-2 were unlikely to progress and may actually be cured (17).

However, the treatment was associated with a high frequency of severe adverse effects (17, 18) limiting its use in all the patients. Low-dose IL-2 schedules are associated with a lower response rate and shorter overall survival compared to high-dose, but with better tolerability (19). Various associations of cytokine therapy, including IL-2 and IFN-α have been developed, but the response rates remain unsatisfactory at around 10-20% , as is the impact on overall survival (20, 21). For example, in a series of Phase II trials performed sequentially by the Cytokine Working Group, 3-year progression-free survival was 9% , and median response duration was 53 months for patients who received high-dose IL-2 compared with 2% to 3% and 12 months for lower-dose IL-2 and IFN regimens. Although these trials involved the same treating physicians, relatively constant referral patterns and identical response assessment and patient eligibility criteria, it was impossible to exclude selection bias or chance as an explanation for the apparent superiority of the high-dose IL-2 regimen in terms of response quality (17).

In an effort to determine the value of outpatient subcutaneous IL-2 and IFN-α relative to high-dose IL-2, the Cytokine Working Group performed a prospectively

randomized Phase III trial in which patients with metastatic RCC were randomized to receive a subcutaneous low dose of IL-2 associated with IFN-α, or a high-dose of intravenous IL-2 (22, 23). A better response rate (23% *vs.* 9%, p=0.018) was seen in patients treated with high-dose IL-2. The median response durations were 14 months for high-dose IL-2 and 7 months for low-dose IL 2 and IFN-α, without reaching statistical significance (p=0.12). The median survival time was longer in the high-dose arm. The primary endpoint of the study was 3-year progression-free survival: 9 patients taking high-dose IL-2 were progression free at 3 years *versus* 2 patients taking low-dose IL-2 and IFN-α (p=0.06) (22, 23).

However, there is considerable systemic toxicity during high-dose IL-2 treatment and this remains of major concern. Flu-like symptoms, fever and chills are frequent, and a capillary leak syndrome resulting in severe hypotension, fluid retention, prerenal failure and pulmonary oedema may all cause high morbidity. Neurological sequelae, including somnolence and confusion, are also frequent. Grade 3 to 4 toxicity is common and often retreatment delays or significant dose reductions are required. Despite selection of only the fittest of patients for treatment, most studies are carried out in centres that have readily available intensive care facilities and follow a program of early and protocol-driven intervention (2).

Locoregional therapy of IL-2 is thus an appealing option in both high and low performance status patients, especially when systemic absorption of the locally administered agent and toxicity are limited. The lung is the most responsive site to immunotherapy and respiratory insufficiency is a common cause of death in patients with RCC due to lung metastases. Any treatment that yields regression of lung metastases or even long-term disease stabilization may be justified in patients with an otherwise poor prognosis, pending respiratory failure and short life expectancy.

In 1997, a preclinical study conducted in dogs with naturally occurring pulmonary metastases showed that nontoxic and effective treatment with nebulized IL-2 liposomes was feasible (24). However, the first attempt of IL-2 inhalatory treatment goes back to 1992, when a 40 year-old man with rapidly progressive pulmonary metastases of RCC was treated with a combination of inhaled (60% of total dose) and systemic (40% of total dose) IL-2 plus IFN-α (25). At that time, the contribution of inhaled IL-2 to the clinical response was difficult to evaluate, but the findings obtained suggested that the overall importance of the low toxicity of this novel route of administration made long-term outpatient treatment possible (25). Since then, inhalation of IL-2 has been used as an optional treatment for patients with pulmonary and mediastinal metastatic RCC. These studies have all confirmed the tolerability of inhaled IL-2 (26). Phase I trials performed at different University hospitals in the USA and Germany (26, 27) showed that inhaled IL-2 is well tolerated, mild to moderate cough being the major adverse event. No patient experienced flu-like syndrome, severe side-effects, or capillary leak syndrome. Lung function disturbances were mild to moderate and appeared to be dose- and schedule-dependent. Higher doses led to significant increases in local immunomodulation but also to increases in local toxicity, such as cough. Severe or life-threatening lung function disturbance or pronounced oxygen desaturation was not observed in any patient in these early trials and all respiratory symptoms disappeared rapidly after treatment was completed (26, 27). A comparative analysis of patients with metastatic RCC treated in different protocols with either subcutaneous or inhaled IL-2 showed that, despite using less medication to control systemic side-effects, patients in the inhalation group had no grade 4 toxicity and 24% experienced grade 3 toxicity, compared with 3% grade 4 and 46% grade 3 toxicity in the group receiving subcutaneous IL-2 (28).

A special concern with inhalation of IL-2 is also long-term safety. In patients treated with inhaled IL-2, no chronic inflammation or irreversible fibrotic tissue reactions in the lung have been reported. This issue is particularly important in terms of quality-of-life (QoL) assessment. Indeed, an advantage for all patients in the Hamburg database was the good QoL that they experienced during inhaled IL-2 therapy, which made outpatient treatment possible and permitted patients to carry on with normal daily activities (29). In a prospective analysis performed by Heinzer and colleagues, inhaled IL-2 therapy stabilized QoL for a median of 13.4 months in patients with metastatic RCC compared to a marked decrease in subjective QoL scores in patients receiving intravenous IL-2 administration (29).

Based on these encouraging results, several hundred patients with metastatic RCC have been treated with inhaled IL-2 as a monotherapy or in combination with systemic immunotherapy or immunochemotherapy (13, 26, 30-32), with response rates of up 10-20%, a 5-year survival rate of up to 20% and disease control rates of approximately 60% for a median of 7 to 9 months in the different studies (13, 30). Overall median survival was also significantly prolonged to 17.2 months (range 0.9-67.3 months) compared with Elson's expected survival of 5.3 months (26, 33). There is also evidence that even distant metastases react to this local therapy (26, 34) and, in selected cases, inhalation therapy may have beneficial effects on pulmonary metastases even after the failure of previous systemic immunotherapy (4).

Although inhalation therapy with IL2 appears to be feasible and tolerable, we must keep in mind that metastatic tumour spread is a systemic disease most probably requiring systemic treatment. Local use of IL-2 has therapeutic efficacy against local metastatic lesions while avoiding systemic toxicity. However, progression at distant

metastatic sites is of concern. Therefore, a combination of systemic immunochemotherapy and inhaled IL-2 tailored individually to the patient's performance status and tolerance level might be used to optimize treatment for the individual patient. Several studies clearly demonstrated that most cytotoxic agents have poor response rates (5, 6) and no single chemotherapeutic drug, alone or in combination with IL-2 or IFN-α, has shown activity beyond that expected by immunotherapy alone. New drugs on the market, such as the pyrimidine analog gemcitabine, have shown promising tumour activity in combination with targeted therapy, probably because of their few detrimental effects on cellular immunity. Indeed, combination therapy of metastatic RCC using a biweekly schedule including subcutaneous IL-2, gemcitabine and vinorelbine resulted in an overall response rate of 40% and a median survival of 24 months (35). On the other hand, only few studies evaluated the interaction between chemotherapy and inhalatory IL-2. In a short series of 14 patients with lung metastasis of RCC treated with combination therapy of inhaled IL-2, IFN-α and vinblastine, Varga *et al*. obtained an overall response rate (CR + PR) of approximately 60% (36). Similar results were obtained by Atzpodien *et al*. who obtained a reduction in pulmonary tumour load and long-term pulmonary-disease stabilization in up to 30% of patients undergoing second-line treatment using inhaled IL-2 therapy in addition to immunochemotherapy with IFN-α, IL-2, 13-*cis*-retinoic-acid and vinblastine (37). More recently, the German Cooperative Renal Carcinoma Immunotherapy Group has conducted a multicenter, randomized trial to evaluate the safety and efficacy of adding short-term inhaled IL-2 therapy to systemic immunochemotherapy with subcutaneous IL-2 and IFN-α plus intravenous 13-*cis*-retinoic-acid or 5-fluorouracil (5-FU) in 379 patients with progressive metastatic RCC. The results obtained showed that there was no survival advantage in favour of *po*-capecitabine *vs*. *iv*-5-FU, and in favour of short-term inhaled-IL-2 in patients with advanced RCC receiving systemic cytokines (37).

At our Institution, 8 patients have been administered, to date, the combination of gemcitabine/vinorelbine and inhalatory IL-2 with the previously mentioned schedule. Due to the limited number of patients enrolled, the evaluation of response rate and survival remains anecdotal; however, the addition of chemotherapy to the inhalatory IL-2 does not seem to reduce the feasibility and tolerability of the curative treatment as evidenced in Table I. In particular, G2 cough due to inhaled IL-2 was observed in all treated patients while haematological toxicity (G3 anaemia and leucopoenia) was revealed in three cases only. Nevertheless, in no case was toxicity considered a limiting factor for the completion of treatment. Four individuals (50%) showed progression of disease (PD) during treatment, while in the remaining patients, 1 partial response (PR) and 3 stable disease (SD) were seen. In particular, patients 7 and 8 (Table I) showed long-lasting SD of 12 and 15 months respectively. Furthermore, patient 4 who had a PR as previously described, remains free of progression to date (19 months) (Table I).

Table I. *Treatment-related toxicity and response in metastatic RCC patients.*

Patient	Toxicity	Grading (WHO)	Response	Duration of response (months)	Status
1	Cough	G2	PD	-	Dead
2	Anaemia*	G3			
	Leucopenia*	G3	SD	12	Alive
	Cough	G2			
3	Cough	G2	PD	-	Dead
4	Cough G2	G2	PR	19 +	Alive
5	Anaemia*	G3			
	Leucopenia*	G3	PD	-	Dead
	Cough	G2			
6	Anaemia*	G3			
	Leucopenia*	G3	PD	-	Dead
	Cough	G2			
7	Cough	G2	SD	12 +	Alive
8	Cough	G2	SD	15 +	Alive

*Related to chemotherapy; PD: progressive disease based on RECIST criteria; SD: stable disease based on RECIST criteria; PR: partial response based on Recist criteria.

Conclusion

Metastatic RCC remains a challenging disease, where recently gained new insights in molecular biology might lead to new treatment options. Traditionally, surgery is the mainstay of any curative treatment in this disease. In the case of metastatic disease at presentation, a radical nephrectomy is recommended in patients with a good PS prior to the start of cytokine treatment. IL-2 treatment results in a small but significant overall survival advantage over cytotoxic agents, and complete responders to cytokine therapy might be cured in 60% -80% of cases. This seems to be the case, especially for high-dose bolus IL-2, but inhalation therapy may have beneficial effects on pulmonary metastases while preserving the patients' QoL more than any other means of IL-2 administration. Although inhalation therapy of IL-2 does not substitute for intravenous administration in highly selected patients, it might represent an alternative treatment in elderly patients with co-morbidities and those with pulmonary-only metastases.

To date, therapeutic approaches to metastatic RCC comprise many methods that can only be adapted to the patient's situation by a multidisciplinary effort. Careful selection of patients for immunotherapy on predictive criteria (be they clinical, pathological, or molecular) would allow us

to offer treatment to those who are most likely to benefit. If aggressive surgical interventions and biological therapies are combined, the prognosis of formerly untreatable patients can be dramatically improved. Thus, acceptable survival and at least a significantly longer time to progression are achievable even in metastatic disease.

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