Original article

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Targeting pulmonary metastases of renal cell carcinoma by inhalation of interleukin-2

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Introduction: Pulmonary metastases of renal cell carcinoma (RCC) are associated with poor prognosis. Inhalation therapy with interleukin-2 (IL-2) is thus an appealing method for palliation. This multicenter study summarizes the national experience of IL-2 inhalation in patients with lung metastases of RCC.

Patients and methods: Forty patients (median, 66.5 years of age) with radiologically documented progressing pulmonary metastases were enrolled. All patients had to be able to comply with inhalation technique, and were not candidates for other treatment options. Twenty-eight patients were systemic treatment-naïve. The protocol included three daily inhalations of IL-2 to a total dose of 18 MU. Treatment had to be continued until one of the following occurred: progression; a complete response; a life threatening toxicity; or patient refusal. Response was assessed using the Response Evaluation Criteria in Solid Tumors (RECIST) system.

Results: The disease–control rate reached 57.5%, with a partial response rate of 2.5% and a disease stabilization rate of 55%. Median time to progression was 8.7 months. The main side-effects were cough and weakness.

Conclusions: Inhalation of IL-2 for the treatment of pulmonary metastases in RCC is feasible, tolerable and beneficial in controlling progressive disease for considerable periods of time. The definition of response of biological therapy may need to be re-assessed and modified: stable disease should be regarded as a favorable response.

Key words: inhalation therapy, interleukin-2, pulmonary metastases, renal cell carcinoma, response criteria

Introduction

One-third of renal cell carcinoma (RCC) patients have metastatic disease at the time of diagnosis [1]. The 5-year overall survival rate of all RCC patients is 40–45%, which has not appreciably improved in the last 25 years [2]. The median survival of patients with metastatic RCC is 10 months, with long-term survival <2% [3]. Effective treatment of metastatic RCC remains disappointing, even in the era of smart immunotherapy and targeted therapy. In the last 15 years, a variety of biological therapies [4] have been demonstrated to provide objective responses in 15–35% of patients with disseminated metastases. High-dose bolus interleukin-2 (IL-2), although very toxic and suitable for a highly selected patient population, remains a treatment that leads to durable complete remissions [5]. Interferon α (IFNα) [6, 7] is moderately active and may be used alone or in combination with IL-2 and chemotherapy. The site most responsive to immunotherapy is the lung. On the other hand, respiratory insufficiency is a common cause of death in patients with RCC due to lung metastases. Regional therapy by inhalation is thus an appealing option in both high or low performance status patients, especially when systemic absorption of the inhaled agent and toxicity are limited. Any treatment that yields regression of lung metastases or even long-term disease stabilization may be justified in patients with

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otherwise gloomy prognosis, pending respiratory failure and short life expectancy. Inhalation of IL-2 has been suggested as an optional treatment for patients with metastatic RCC [8–11]. This multicenter study summarizes the national experience of IL-2 inhalation in patients with lung metastases of RCC.

Patients

Forty patients (30 males, 10 females) with ages ranging from 45 to 88 years (median, 66.5 years) with a histological or cytological diagnosis of RCC were enrolled. All patients had to have radiologically documented progressing lung metastases, to comply with inhalation technique and were not candidates for other treatment options. Nephrectomy was performed in a total of 32 patients, of whom 17 underwent nephrectomy as surgical treatment of the primary disease. The other 15 patients underwent nephrectomy in the presence of metastatic disease, proceeding on the notion of improved results of consequent immunotherapy. Stage IV as presentation of disease was observed in 23 patients. In the other 17 patients a loco-regional disease was first treated by cure-intended resection of the primary tumor and kidney, and lung metastases developed post-operatively. Time to pulmonary metastases ranged from 0 (for stage IV patients) to 240 months (in case of late relapse), with a median of 10.5 months. Twenty-two patients reported pulmonary symptoms, such as dyspnea, cough and hemoptysis, while 18 patients were asymptomatic. In 15 patients the lungs were the only site of metastases, while in 25 patients the lung plus at least another extra-pulmonary site were involved. The extra-pulmonary sites of metastases were bones in 11 patients, retroperitoneal nodes in six, renal bed mass in five patients, mediastinal nodes in four, viscera (liver, gastrointestinal tract) in two, and skin and soft tissues in three. Previous treatments for metastatic disease included various combinations of systemic chemo-immunotherapy in 12 patients. Twenty-eight patients were systemic treatment-naïve.

Protocol

All the patients signed an informed consent form. Pretreatment evaluation included physical examination, CT studies of the chest, abdomen and pelvis, complete blood count and biochemistry panel. Other ancillary tests were performed on a clinical basis according to signs and symptoms. Treatment monitoring was based on repeated studies that documented the disease extent at baseline, and at intervals of 3 months.

Treatment protocol included three daily inhalations of IL-2 (Proleukin; Chiron Corporation, Emeryville, CA, USA) to a total dose of 18 MU, by using a Salvia Lifetec Jetair δ 20c inhalator (Kronberg, Germany). The IL-2 was dissolved in 12 ml 5% glucose solution, out of which 4 ml were taken for each of the three-daily administrations. A once-daily subcutaneous injection of 5–10% of the inhaled dose (0.9–1.8 MU) was to be given in order to get a systemic effect. This injection was omitted from protocol after the first 10 patients refused to get it because of intolerable systemic side-effects. Treatment had to be continued until progression or complete response or life threatening toxicity or patient's refusal. Analysis of toxicity was based on World Health Organization (WHO) criteria, and that of response was based on the Response Evaluation Criteria in Solid Tumors (RECIST) system. All X-ray films and chest CT studies were evaluated by the treating oncologist and by an independent radiologist.

Results

All the patients started with inhalation of IL-2 18 MU. Dose reduction was performed in one patient because of pulmonary intolerance manifested by cough and dyspnea. Dose escalation up to 36 MU was performed in seven patients with disease progression at 18 MU. Intention-to-treat analysis was based on the best response that was achieved by any dose of inhaled IL-2. The observed true response rate was 2.5% (one partial response out of 40 patients) and the disease stabilization rate was 55%. The disease–control rate (partial response plus disease stabilization rate) reached 57.5%. In 15 of 40 patients (37.5%) the disease progressed and in two of 40 patients the response was not assessable. Time to progression ranged from 0.3 (in case of rapidly progressing disease) to >43 months, with a median of 8.7 months. The side-effects included cough in eight patients, weakness in nine, dyspnea in three, fever in two, sleepiness in one, asthenia in one, decreased appetite in one, and abdominal pain in one.

Discussion

Our results highlight several important issues in IL-2 therapy of pulmonary metastases of RCC. The first is the feasibility and tolerability of IL-2 inhalation. While IL-2 is highly toxic when administered intravenously, and moderately toxic when injected subcutaneously, it is only seldom toxic when inhaled at a high dose of 18 MU. Very few pulmonary symptoms and systemic signs could be attributed to inhalation therapy in our patients. The systemic absorption of inhaled IL-2 was practically negligible, as manifested by the low rate of systemic side-effects such as fever and asthenia. None of the patient needed hospitalization in an intensive care unit following daily inhalation of 18 MU. The technique of inhalation is easily carried out at home, with no need for therapy to be carried out at a medical center. The only intolerable part of the protocol was the daily subcutaneous injection of IL-2 at a dose equivalent to 5–10% of the daily inhaled dose. This injection was aimed at augmenting the cellular immune response towards the tumor. According to Huland et al. [12], locoregional administration of IL-2, which acts physiologically as a local hormone, is an effective therapeutic modality against RCC. Regional administration of IL-2 that did not raise intravascular IL-2 levels induced local and systemic immunomodulation and produced objective local tumor responses. As stated in their work, inhaled IL-2 alone was well tolerated and a dose-dependent cough was the major adverse event.

The second point of interest is a tumor control rate of almost 58% achieved in our patients. It is true that the objective response rate according to RECIST was only 2.5%, and was studied only in the targeted pulmonary lesions, while no systemic efficacy could be expected with inhalation therapy. In comparison with the reported results of Huland et al., our true objective response rate

was less impressive than their response rate of 21–29% [12]. However, the disease control rates were very close: 58% in our series for a median of almost 9 months, versus 68% freedom-from-progression rate for a median of 7 months as reported.

Intravenous IL-2 is regarded by many oncologists as the treatment of choice for selected patients with metastatic RCC, including pulmonary and extra-pulmonary involvement. This mode of administration is much more effective, but more toxic and not suitable for all patients [13]. The mode of inhalation is more tolerable and suitable for most of the patients, even for those with low performance status and co-existing medical problems. Besides, it does not require an intensive supportive care service and can be carried out at the patient's home. Inhalation therapy of IL-2 does not substitute for intravenous administration in highly selected patients, but may be applied to almost all elderly patients with co-morbidities, and those with pulmonary-only metastases. Moreover, patients not eligible for systemic IL-2 therapy may be treated with inhalation therapy. Another very important aspect of inhalation therapy is that this mode of treatment preserves the patients' quality of life more than every other way of IL-2 administration.

The third point for discussion is the adequacy of the modern system to assess the efficacy of biological treatments. It is accepted that response is determined according to tumor regression in diameter or volume or two-dimensional surface area for a period of more than 4–6 weeks. According to these criteria, disease stabilization is not regarded as a true response. Several anti-RCC agents (such as thalidomide [14] or troxacitabine [15]) yielded disease arrest without marked overt tumor shrinkage. Some biological reactions or signal transduction steps are targeted and blocked, and the tumor growth arrested. It certainly results from a favorable effect of a drug on the tumor, and should be covered by the definition of a response to biological treatment. The rate of stabilization achieved with IL-2 inhalation was much higher than the spontaneous regression or stabilization of metastatic RCC [3]. This means that in most of the cases with stabilization, the favorable effect resulted from the administration of IL-2 rather than from the unpredictable natural course of the disease. The duration of stabilization was significant and probably led to improvement in survival [12].

Therefore, disease arrest may be regarded as a true response. Consequently, long-term stable disease or a longer time to progression might be a more appropriate treatment end point for biologicals and some of the cytotoxics, than the traditional definitions of response [16]. It should be remembered that from the patient's point of view, stabilization, although traditionally defined as no response, is of course better than progression, especially when it is achieved by a treatment with acceptable side-effects.

Conclusion

Inhalation of IL-2 for treating pulmonary metastases of RCC is feasible, tolerable and useful in arresting progressive pulmonary involvement. The definition of response criteria in biological therapy may need to be re-assessed and modified.

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