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Placebo-associated remissions in a multicentre, randomized, double-blind trial of interferon γ-1b for the treatment of metastatic renal cell carcinoma

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Objective To determine the validity of using an historical maximum spontaneous regression rate (reportedly 0–1.1% in those with lung metastases after nephrectomy) in clinical trials of treatments for patients with metastatic renal cell carcinoma (RCC), as the eligibility criteria for most studies will select patients with better performance status (and thus excluding those who are unlikely to respond) and more modern staging methods would potentially reduce the number of false-positives.

Patients and methods A multicentre randomized, placebo-controlled, double-blind trial was recently completed in which 197 patients with metastatic RCC from 17 study centres across Canada were randomized to receive placebo or recombinant interferon γ-1b (60 μg/m^2) subcutaneously once every 7 days until disease progression. All tumour responses were validated by an independent response committee unaware of the treatment.

Results The median (95% confidence interval) overall response rate (complete, CR, and partial, PR) for those on interferon-γ was 4 (1.4–11.5)% and for those on placebo was 6 (2.5–13.2)% ($P = 0.75$). In the six patients who were receiving placebo the CR and PR (three each) was considered to represent spontaneous remission. Of these six patients (aged 44–64 years) five had undergone nephrectomy, one a tumour embolization, four had clear cell carcinoma and one an adenocarcinoma, and all had regression of lung and/or lymph node metastases.

Conclusion The lack of efficacy of interferon-γ in this trial underlines the importance of continued research to identify alternative therapeutic agents or combinations of agents in phase II studies. However, the threshold response rate for initiating phase III trials should be increased to 18% in the phase II trials, i.e. three times the response rate on placebo.

Keywords Metastatic renal cell cancer, immunotherapy, interferon, spontaneous regression

Introduction

RCC is the 10th most common malignancy in western countries, with 30 600 new cases and 12 000 deaths in 1996 in the USA [1]. The increased incidence in recent years is attributed to the incidental findings of RCC on ultrasonography or CT of the abdomen carried out for other reasons. Despite earlier detection in many patients, the mortality has also increased over the last 5 years [1]. A third of patients are diagnosed with metastatic disease already evident [2] and survival in these patients is very poor, with a mean survival of 6–12 months [3]. Furthermore, of patients diagnosed with clinically localized disease, about half will subsequently develop metastases [2].

The natural history of RCC is unpredictable, both from the initial clinical presentation ('the internist's tumour to radiologist's tumour') and the occasional report of spontaneous regression of metastasis. Everson and Cole [4] defined spontaneous regression as 'partial or complete disappearance of malignant tumour in the absence of all treatment or in the presence of therapy that is considered inadequate'. They reviewed published reports from the first case described in 1908 to 1966, and included 176 cases of all cancers; 31 were RCC. In their series RCC was the tumour most frequently associated with regression. Most of the cases (84%) in that report were regression of a metastatic tumour with histological confirmation of the primary site, but not the metastatic sites. The authors did

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not imply that regression was synonymous with cure, but suggested that temporary regression represents active control of the tumour by the host defence mechanisms. Since this report additional reviews up to 1982 brought the total cases of spontaneous regression of metastatic RCC to 70 [5–7].

The lung remains the most common site of regression (63 of the 70 cases). The most stringent criteria for the histological confirmation of metastatic disappearance is only available for a third of the 70 reported cases. Among large published series the incidence of spontaneous regression was 0–1.1% [2,7–12]. Some of these regressions followed surgery to remove the primary tumour, and occasionally regression of metastasis has been reported after radiotherapy to the primary tumour [13], or to one of the metastases [5]. These reports of spontaneous regression, particularly after surgery, resulted in a surge of nephrectomy in the hope of achieving this elusive spontaneous regression. However, the few successful cases were counterbalanced by the complications of surgery in these high-risk patients. However, the phenomenon heightened interest in biological-response modifiers in the hope of achieving more regression of metastases.

The spontaneous regression associated most frequently with metastatic RCC, with the observations of humoral and cellular immune responses in such patients, suggested the involvement of a host immune mechanism [2]. This also led to studies evaluating several biological response modifiers. The results of these trials were compared with historical controls, as they were not randomized or placebo-controlled. Recombinant human interferon γ-1b has been investigated in phase I and II studies, with a mean response rate of 11.5% [14–18]. These studies used different dosage regimens. Using surrogate markers of immune responses (increase in serum neopterin and B_2 microglobulin) showed that a dose less than the maximum tolerated dose (with less toxicity) was optimal. Using this optimum dose, phase II studies were conducted, with a documented 15–30% objective response rate. This was the basis for initiating the present phase III multicentre Canadian study; this study is particularly important because it is the first placebo-controlled randomized, double-blind study in patients with metastatic RCC. As such, the study therefore provides objective information on the natural history of the disease. The present report describes only the results from the placebo arm of the study, to assess spontaneous regression.

Patients and methods

Between May 1993 and April 1995, 197 patients with metastatic RCC at 17 centres across Canada were included in the study. The criteria for inclusion were: (i) histologically confirmed metastatic RCC considered incurable by surgery or radiation therapy; (ii) bidimensionally measurable disease, to serve as a marker of response to therapy; (iii) the primary tumour was treated by nephrectomy or angio-infarction at least 3 weeks before entry; (iv) a life expectancy of at least 12 weeks and a performance status of $>70\%$ (Karnofsky score). Patients were excluded if they had: only bone metastasis; known brain metastases or seizure disorders; hypercalcaemia of malignancy (>12 g/L); serious chronic cardiac disease or other serious coexisting illnesses; previous cancer (excluding nonmelanoma skin cancer); previous radiotherapy or chemotherapy; systemic corticosteroids or other immunosuppressant medications.

Patients were assigned to receive either recombinant interferon-γ 1b (60 μg/m^2, Actimmune®, Intermune Pharmaceuticals, Burlingame, CA) every 7 days subcutaneously, or a placebo consisting of vehicle (sterile water, mannitol, sodium succinate and polysorbate 20). To help minimize side-effects related to interferon and maintain the double-blind condition, all patients received 650 mg acetaminophen orally before their weekly subcutaneous injection and then every 4–6 h for 48 h after dosing.

Patients were monitored using a complete medical history, physical examination and Karnofsky score, a complete blood count and biochemistry, including immunological markers. All patients underwent a radionuclide bone scan, chest X-rays, and other radiographic imaging as appropriate, to evaluate target metastatic lesions. These were repeated every 8 weeks for the first year. Patients who had complete, partial or stable disease after the first year were followed every 8 weeks and the imaging repeated every 16 weeks.

The metastatic lesions at all sites were assessed by appropriate imaging, whether X-ray, ultrasonography, CT or MRI. All lesions were measured bidimensionally by the physician or radiologist at each study site. These same X-rays were assessed independently by a Response Evaluation Committee unaware of the treatment; the committee consisted of certified oncologists and radiologists who were not otherwise participants in the study.

A complete response (CR) was defined as the disappearance of all tumour. If this was maintained for 12 months it was considered a durable CR. A partial response (PR) was defined as a reduction of $\geqslant 50\%$ in the sum of diameters of all measurable lesions with no new lesions. Progressive disease was defined as an increase of $>25\%$ of any measurable lesion or the appearance of new lesions. The duration of response was measured from the time of the initial response to the time of progression. Patients who had progressive disease were unblinded and those on placebo were offered cross-over to the treatment

arm. Those on interferon were removed from the study and treated at the discretion of the investigator.

The discussion of the therapeutic efficacy and safety, and the statistics used to compare both arms, will be reported separately. The purpose of the present report is to determine the frequency of spontaneous regression in a modern series and its significance when studying biological modifiers.

Estimates of the sample size required to detect efficacy was based on an estimated 1% response in the placebo arm and 15% for the treatment. A two-tailed test was used to determine statistical significance, with $P < 0.05$ considered to indicate significance. With these assumptions, statistical comparisons of 91 patients in each group would have a power of 90% to detect a difference in overall response rates between the treatment groups.

Results

Of the 197 patients, 98 were randomized to receive interferon and 99 to receive placebo; 91 and 90 were evaluable in each arm, respectively. The patients were equally distributed for sex, age and performance status. Two-thirds of the patients had a Karnofsky score of 90–100%, and more than half had more than two metastatic sites. The details of responses and adverse events are reported elsewhere [19].

In this modern series, with complete staging and randomization, there was spontaneous regression in six patients on placebo and four patients on interferon; one patient in each group had a durable response. One case is described in detail and the characteristics of all six are shown in Table 1.

Patient no. 3, a 57-year-old woman, presented with metastatic disease and underwent a left palliative nephrectomy for clear cell carcinoma in August 1994. A chest X-ray showed multiple metastasis (Fig. 1a). They were not biopsied because the patient's general condition was poor (the patient was enrolled in the study in October 1994). The four measurable lesions had a total area of 15.07 cm^2. The patient had a CR (Fig. 1b) from 7.4 months after enrolment and this was maintained until the end of the study (June 1996). Unblinding of the treatment showed that she was on placebo (Table 2).

Discussion

The use of recombinant human interferon-γ1b for the treatment of metastatic RCC has been investigated since the mid-1980s. Phase I and II open-label trials reported an overall mean (range) response rate (CR and PR) of 11.5 (0–33)% [1–10]. There are difficulties in comparing the results from these series because there are differences in the patient populations, treatment regimens and the various interferon γ-1b products used. The early investigations used dosing strategies that approached or met the maximum tolerated dose.

The cumulative Phase II clinical data suggest that 100 μg of interferon administered subcutaneously once every 7 days induces a mean (range) objective response in 22 (15–30)% of patients with metastatic RCC. A CR of >12 months occurred in five of 67 patients (7.5%) treated with this regimen. Surrogate markers for interferon activity have been shown to correlate with the clinical response. This low-dose schedule (100 μg once every 7 days) was a better therapy than others for metastatic RCC.

The results of the double-blind, placebo-controlled trial suggest that the administration of interferon at this dose is no better than placebo in inducing tumour regression, prolonging the time to disease progression, or extending survival [19]. The discrepancies between the Phase II and Phase III results for efficacy may be attributable to the study design (open-label vs randomized, placebo-controlled), patient selection, and single vs multicentre treatment variability. The primary efficacy data were also independently validated in the current Phase III clinical trial, whereas the Phase II data was either unavailable for validation [20], or retrospectively reviewed [21].

The high incidence of patients on placebo who achieved either a CR or PR raises specific questions

Table 1 The characteristics of the six patients with metastatic RCC who had spontaneous regression while taking placebo

Patient no.	*Age (years) /sex*	*Previous therapy*	*Histology*	*Response (months)*	*Regression site (no. of lesions)*	*Site of progression*
1	60/M	Palliative RN	Clear cell	CR (7)	Lung (3), lymph nodes	L frontal lobe
2	44/M	Embolization	Not available	CR (31+)	Lung (6)	
3	57/F	Palliative LN	Clear cell	CR (10+)	Lung (4)	
4	51/M	Palliative LN	Adenocarcinoma	PR (2)	Lung, lymph nodes Bone (after cross-over)	
5	52/M	Palliative RN	Clear cell	PR (8)	Lung (3)	Brain
6	64/M	R radical N	Clear cell	PR (5)	Lung (4), lymph nodes	Lung (after cross-over)

N, nephrectomy; R, right; L, left.

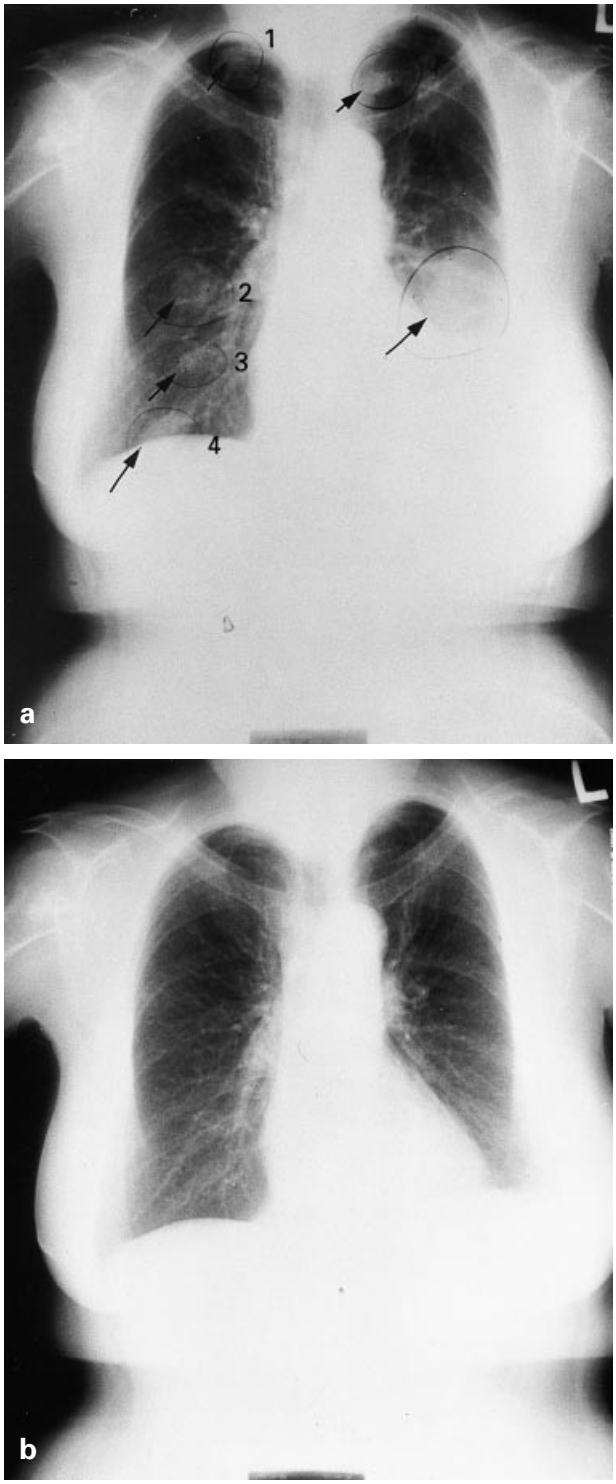

Fig. 1. (**a**) A chest X-ray showing multiple metastases in patient no. 3 on inclusion in the study. (**b**) From 7.4 months after enrolment the patient had a CR and this was maintained until the end of the study (June 1996).

about the evaluation of treatment response in patients with metastatic RCC. Spontaneous remission of RCC, as defined previously [4], has been reported in open-label, non-comparative clinical trials to have an incidence of 0–7% [13,22–35]. Typically, spontaneous remission occurs in men aged 30–76 years and the regression of lung metastases is most commonly reported [22–24]. The incidence of spontaneous regression is greater after nephrectomy, but there has been unexpected complete regression after hormonal therapy or radiation therapy [26,27]. The reported duration of remission is variable, ranging from 3 months to 20 years.

The current study is unique in that it represents the first clinical trial designed to compare the efficacy of a biological response modifier with placebo in patients with metastatic RCC, and that has adequate statistical power. Other molecules, e.g. α-interferon or interleukin-2, have been evaluated for antitumour efficacy in open-label settings, where the incidence of spontaneous regression was not determined. In the present study, 7% (95% CI 2.7–14.5) of evaluable patients randomized to placebo had spontaneous remission and appeared to have demographic characteristics consistent with historical data (Table 1).

Several published reports address the incidence of spontaneous regression after treating the primary tumour. Middleton [36] reported on 503 patients, including 33 with metastases; there was no case of spontaneous regression and all were dead within 2 years. Bloom [12] reported three regressions in a review of several series totalling 1139 cases. Snow and Schellhammer [7] found four patients in 571 who qualified as having spontaneous regression, a rate of 0.7%. This led to the conclusion that spontaneous regression is very rare, such that some authors questioned its existence [36]. The median survival rates with and without nephrectomy in presence of metastases were reported by Johnson *et al.* [37] to be 11.3 and 7.9 months, respectively. Oliver *et al.* [32] reported the incidence of spontaneous regression in 73 patients diagnosed with metastatic RCC who were observed until metastases progressed, when they were treated. In that series there were three histologically documented

Table 2 The disease course in patient no. 3 (on placebo)

Study day	*Tumour size (cm^2)*	*Response*	*Comments*
0	15.07	–	Four lesions
57	8.97	Minimal	40% decrease
113	2.56	Partial	71% decrease
169	0.36	Partial	85% decrease
225 to 6 months	–	Complete	

CRs, two PRs and four patients with stable disease for 12 months. That study, with an incidence of spontaneous regression similar to that in the present series, underlines the importance of a close follow-up and the status of the patients at baseline. Oliver *et al.* [32] raised the issue of performance status, site of metastases and the presence or absence of hypercalcaemia, which they considered to be important indicators of a possibly better outcome, both during observation and treatment. Because these factors are usually used as inclusion criteria in most studies, similar variables should be applied in determining the control group.

In conclusion, the present study showed, in a prospective, randomized, placebo-controlled trial, that the incidence of spontaneous regression in a selected population can be higher than expected. This should be considered in the planning and execution of trials with different agents for the treatment of metastatic RCC.

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