Cancer Chemother Pharmacol (2008) 62:347–354
DOI 10.1007/s00280-007-0594-5

CLINICAL TRIAL REPORT

Phase I trial of PEG-interferon and recombinant IL-2 in patients with metastatic renal cell carcinoma

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Received: 24 May 2007 / Accepted: 1 September 2007 / Published online: 2 October 2007

Abstract
Purpose Pegylated interferon α-2b (PEG-Intron®) is a conjugate of polyethylene glycol (PEG) and interferon alpha-2b, has a prolonged half-life, and an increased area under the curve (AUC) for interferon α-2b. The combination of PEG-Intron® with recombinant interleukin-2 (rIL-2) was investigated in a phase 1 trial. To determine the maximal tolerable dose (MTD) and preliminary efficacy of concurrent subcutaneous (SC) administration of PEG-Intron® and rIL-2 in patients with metastatic renal cell carcinoma (RCC).
Methods Cohorts of 3–6 patients received escalating doses of PEG-Intron® (I-1.5, II- 1.5, III-3.0, IV-3.0, V-4.5 μg/kg SC) given weekly in combination with rIL-2 administered three times weekly (TIW) for 6 weeks. rIL-2 dose levels were escalated in weeks 1 and 4 (I-10.0, II-15.0, III-15.0, IV-20.0, V-20.0 MIU/m^2 SC), and 5.0 MIU/m^2 SC TIW was administered during weeks 2, 3, 5 and 6.
Results Thirty-four patients (24 men; 10 women) were accrued at dose levels I ($n = 4$), II ($n = 4$), III ($n = 6$), IV ($n = 14$), and V ($n = 6$) between October 2000 and October 2002. All but one patient had prior nephrectomy ($n = 33$) and all but one patient (97%) had received no prior systemic therapy. Patients received a median of four cycles of treatment (range 1–9). Dose limiting toxicity occurred at dose level V and included grade 4 neutropenia and hypoxemia. A partial response was found in 5 pts (15%). Median progression-free and overall survival were 9.0 (95% C.I. 5.6–13.1 months) and 31.9 months (95% C.I. 17.2–61.9 months), respectively.
Conclusion The combination of PEG-Interferon and SC rIL-2 can be administered with acceptable toxicity.

Keywords Kidney cancer · Cytokines · Clinical trial · Interferon · Interleukin-2

Supported by a grant from Schering-Plough Inc. and the Zito Chair for Cancer Research and the Rudy Fund for Cancer Research.

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Background

Renal cell carcinoma (RCC) is the most common malignancy of the kidney and accounts for approximately 3% of adult tumors. Annual estimates of the incidence for RCC indicate steady increases, with over one-third of newly diagnosed patients presenting with metastatic disease [1–4]. In this setting, standard chemotherapeutic regimens have been investigated, but overall response rates are low (<7%), with a limited survival improvement [2, 5]. A variety of cytokines have been studied in patients with metastatic RCC. Treatment with either interleukin 2 (rIL-2) or interferon α (IFNα), have antitumor effects that are reproducible with objective response rates of 5–30% which may be durable in some patients [6–18]. Several randomized trials utilizing the combination of rIL-2 and IFNα have been completed [7, 19–21].

Studies evaluating this combination have demonstrated improvements in objective tumor response, without increases in survival and with significant toxicity. Toxicities reported with these agents include fatigue, fever, rigors, nausea/vomiting and capillary leak syndrome. The severity makes high doses difficult to administer. In addition, because of rapid clearance from the circulation, both cytokines require frequent dosing, which is cumbersome and poorly tolerated.

The therapy for advanced RCC has changed during the past 18 months, with the availability of sunitinib and sorafenib, two oral tyrosine kinase inhibitors recently approved for patients with RCC. A median progression free survival (PFS) of 11 versus 5 months (HR 0.42, 95% confidence interval—CI, 0.32–0.54; $P < 0.001$) in RCC patients was reported with sunitinib when compared to IFNα in a phase III trial, in the first-line setting [22]. The response rates were 37 versus 9% ($P < 0.001$) for sunitinib and IFNα with stable disease (SD) rates of 47 and 57%, respectively. Currently sunitinib is considered the standard of care in the first-line for treating metastatic RCC. In a phase III randomized, double-blind, placebo-controlled study of sorafenib, the median PFS was 5.5 months in the sorafenib arm (HR 0.44; 95% CI, 0.35–0.55; $P < 0.01$) in cytokine refractory patients [23]. The same trial showed an overall response rate (ORR) of 10% in the sorafenib arm with SD rate of 74%. The commonly observed toxicities with sunitinib and sorafenib are diarrhea, fatigue, nausea, stomatitis, vomiting, hypertension and hand–foot syndrome. In addition, phase II clinical trials have investigated the potential efficacy of sorafenib in combination with cytokine therapy. One trial of sorafenib and IFNα in combination in RCC was conducted in the front-line setting [24]. This study utilized sorafenib standard dose of 400 mg BID in combination with IFNα 10 MU SC three times weekly (TIW). The overall response rate was 19% (17% PR, 2% CR, 95% CI: 9%, 32%). In a similar Phase II RCC trial conducted in the first- or second-line (in IL-2 - refractory) setting that utilized sorafenib in combination with IFNα-2b, the patients tolerated the combination reasonably well and the ORR was 42% and an impressive 38% PR with 4% CR [25]. In the same trial, SD was seen in 46% of patients, which included 8% who demonstrated tumor shrinkage of ≥20%. Finally the AVOREN trial was recently reported, and compared the combination of bevacizumab and IFNα2a to a placebo and IFNα2a in untreated metastatic RCC patients. The overall response rates were 31 and 13% and median PFS of 10.2 and 5.4 months, respectively. Toxicity was increased in the combination arm and included fatigue, proteinuria, hypertension and hemorrhage. These data suggest that the combination of a cytokine and bevacizumab can produce enhanced clinical results.

Pegylated IFNα-2b (PEG-Intron; Schering-Plough Corporation, Kenilworth, NJ) is a novel conjugate of IFNα-2b and a single polyethylene glycol (PEG; molecular weight 12 kDa) moiety developed to improve the pharmacokinetic profile of IFNα-2b. The safety and efficacy of pegylated IFNα-2b has recently been reported in patients with advanced solid tumors [26]. The maximum-tolerated dose (MTD) of pegylated IFNα-2b when administered subcutaneously was 6.0 μg/kg/week with a toxicity profile equivalent to that seen in registrational trials of pegylated IFNα-2b in patients with chronic hepatitis C and CML [27, 28]. In 57 patients with metastatic RCC from this Phase I/II trial, the objective response rate was 14% with a median survival of 13.2 months, similar to the published experience of non-pegylated IFNα-2b in this patient population [7, 14, 26]. Although there was no direct comparison between pegylated IFNα-2b and IFNα-2b, the 6.0 μg/kg/week dose may achieve exposure comparable with 18 MIU/week of IFNα-2b [26]. Given the pharmacokinetics and pharmacodynamics of pegylated IFNα-2b and preliminary assessment of tolerability, pegylated IFNα-2b may widen the therapeutic index for conventional IFNα-2b and offer an improved risk benefit ratio and possibly enhanced response rates.

Single-agent trials of pegylated IFNα in metastatic RCC resulted in dose-limiting toxicity (DLT) at a much higher equivalent non-pegylated IFNα dose without compromising efficacy [26, 29]. The potential of pegylated IFNα-2b to be administered at higher doses when used concurrently with rIL-2 or, alternatively, the potential for a higher rIL-2 dose to be administered is therefore of interest. On this basis, the present study was initiated to determine the MTD of pegylated IFNα-2b administered concurrently with rIL-2 in an outpatient setting, and to establish the safety profile and preliminary efficacy of the combination in patients with metastatic RCC.

Patients and methods

Patients

Patients were eligible if they had histologically proven RCC with clinical or biopsy proven metastases. All patients were older than 18 years of age, had bi-dimensionally measurable or evaluable disease, had a life expectancy of ≥3 months; had a performance status Eastern Co-operative Oncology Group (ECOG) of ≤1; had complete recovery from toxicity related to prior hormonal, radiation, or biologic therapy; had pretreatment laboratory values above stated minimum values (WBC ≥ 3.0×10^9/l, platelets ≥ 100×10^9/l, hemoglobin ≥ 9.5 g/dl, serum creatinine ≤ 1.5 mg/dl, bilirubin (total) ≤ 1.5 ml/dl, calcium ≤ 12 mg/dl and DL_{CO} ≥ 50% predicted); had absence of significant effusions or

ascites; had no major surgery requiring general anesthesia within the preceding 28 days; and, had received ≤ 1 prior systemic regimens for metastatic RCC. Informed consent was obtained from all patients in accordance with institutional and federal guidelines.

Exclusion criteria included the following conditions: a history of a serious cardiac arrhythmia, congestive heart failure, angina pectoris, or other severe cardiovascular disease producing limitations of physical activity (i.e. New York Heart Association Class III or IV); active peptic ulcer disease, autoimmune disease, or inflammatory bowel disease; local or systemic infections requiring intravenous antibiotics within the past 28 days; pregnant or lactating women, and fertile women or men unless surgically sterile or using effective contraception; known CNS metastases or known seizure disorder; positive for HIV, HB_sAg, or HCAg; history of a malignancy other than a renal cell carcinoma or melanoma (exceptions basal or squamous cell carcinomas of the skin, carcinoma in situ of the uterine cervix, and any malignancy treated with curative intent and in complete remission for ≥3 years); and patients with organ allograft.

All inclusion and exclusion criteria were assessed within 14 days prior to initiation of therapy, with the exception of X-ray (radiographic) studies not required for determination of tumor measurements, or laboratory studies not used for organ evaluation, which were performed within 28 days of therapy initiation.

Study drugs

The PEG-Interferon was supplied by Schering Plough as a 150, 300 or 600 μg/vial lyophilized powder, stored under refrigeration. The powder was reconstituted with 0.7 ml of sterile bacteriostatic water for injection prior to administration. Recombinant IL-2 (Chiron) was utilized, and consisted of 1 mg/vial lyophilized powder with a nominal specific activity of 18×10^6 International Units (IU), stored under refrigeration. The lyophilized product was reconstituted with 1.2 ml of sterile bacteriostatic water and administered within 3 h of initial reconstitution. PEG-Intron® and rIL-2 were administered by subcutaneous injection.

Dose schedule

Eligible patients were enrolled in cohorts of 3–6 patients and treated with escalating doses of PEG-Interferon (I-1.5, II- 1.5, III-3.0, IV-3.0, V-4.5 μg/kg SC) given weekly and rIL-2 (I-10.0, II-15.0, III-15.0, IV-20.0, V-20.0 MIU/m^2) SC in weeks 1 and 4, and 5.0 MIU/m^2 SC during weeks 2, 3, 5, 6 given TIW. Cycles consisted of 6 weeks of therapy followed by 2 weeks rest until unacceptable toxicity or disease progression was noted. No accrual to subsequent dose levels occurred until all patients at previous dose level finished the first 6 weeks of treatment.

Response was assessed every 8 weeks. Patient evaluations for toxicity and vital signs (with the exception of temperature which was measured before each dose throughout the study) were performed prior to every dose during cycle one; in subsequent cycles, toxicities were noted weekly and vitals signs measured at the beginning and end of each cycle. Physical examination and laboratory studies (CBC with differential, platelets, urinalysis, basic metabolic panel, and coagulation times—PT/INR, PTT) were performed on a weekly basis during the first cycle, and at the end of each cycle thereafter. Radiographic studies, as required for assessment of measurable disease, were performed every cycle. Treatment was continued if toxicity was acceptable, and performance status remained ≤ 1. Therapy was continued in patients with clinical responses or stable disease.

Dose limiting toxicity was defined as the occurrence of any of the following toxicity (NCI common toxicity criteria, version 2.0) during cycle one: (1) Grade 3 or higher non-hematologic toxicity; (2) Grade 4 neutropenia for seven or more days associated with fever or infection; (3) other Grade 4 hematologic toxicity. The MTD was defined as the dose level below which ≥ 2 of six patients experienced DLT. After DLT was observed in two or more patients at a given dose level, no additional patients were entered at that or higher dose levels.

Statistical considerations

The primary goal of the study was to identify the MTD of SC PEG-Intron and rIL-2. Five dose levels were assessed using a standard "3 + 3" design. Three patients were initially treated at a given dose level. The dose was escalated to the next higher level if no DLT was observed among these patients. If one DLT was observed three additional patients were treated, and escalation to the next higher dose level occurred only if no additional DLT was observed. The MTD was defined as the dose level below which ≥ 2 of three to six patients experienced DLT. Once the MTD was determined, an additional ten patients were treated at that dose level to better characterize the toxicity.

Individual patient and disease characteristics, response, and toxicity were summarized as frequency counts or medians and ranges, depending on whether the factor was categorical or continuous. Progression-free and overall survivals were measured from the time of study entry to documented progression and death, respectively. Patients not known to have progressed (died) at the time of analysis were censored. The method of Kaplan and Meier was used to summarize these outcomes.

Results

Patient characteristics

Thirty-four patients (24 men; 10 women) with metastatic renal cell carcinoma (97% clear cell histology) were treated with subcutaneous PEG-Intron and rIL-2 at dose levels I ($n = 4$), II ($n = 4$), III ($n = 6$), IV ($n = 14$), and V ($n = 6$) in 8-week cycles between October 2000 and October 2002. The median age was 56 years (range 40–70) and 33 (97%) had prior nephrectomy (Table 1). Thirty-three patients (97%) had received no prior systemic therapy. Twenty-eight patients (82%) had an ECOG performance status of zero. Memorial Sloan-Kettering (MSK) [30] prognostic criteria were utilized, and patients were low risk ($n = 28$, 82%) or intermediate risk ($n = 6$, 18%).

Treatment administered and toxicity

Patients received a median of four cycles (range 1–9) of treatment. Dose limiting toxicity occurred at dose level V (PEG-Intron®4.5 μg/kg and rIL-2 20.0 MIU/m^2 SC in weeks 1 and 4; 5.0 MIU/m^2 SC during weeks 2, 3, 5, 6), and the MTD was dose level IV (PEG-Intron®3.0 μg/kg and rIL-2 20.0 MIU/m^2 SC in weeks 1 and 4; 5.0 MIU/m^2 SC during weeks 2, 3, 5, 6). All patients experienced the constitutional symptoms (fatigue, chills, fever, etc.) associated with IFNα-2b and rIL-2 during the first treatment cycle. In three patients (dose levels I, II, and V) the symptoms were severe, but did not require dose reduction or interruption. Most patients also experienced mild to moderate nausea and vomiting during cycle one (3 patients, dose level I; 4 patients, dose level II; 4 patients, dose level III; 13 patients, dose level IV; and 5 patients, dose level V).

Table 1 Patient characteristics

Characteristic	No (%)
Patients	34
Male/female	24 (71)/10 (29)
Median age (range)	56 (40–70)
ECOG[a] performance status	
0	28 (82)
1	6 (18)
Prior local treatment	
Nephrectomy	33 (97)
Radiotherapy	3 (9)
Prior systemic treatment	
None	33(97)
IL-2	1 (3)
MSK[b] risk stratification (30)	
Low	28 (82)
Intermediate	6 (18)
Histology	
Clear cell renal cell carcinoma	33 (97)
Chromophobe renal cell carcinoma	1 (3)

[a] Eastern Co-operative Oncology Group

[b] Memorial Sloan Kettering risk stratification

During cycle one of treatment, two of four patients at dose level I experienced a grade 3 toxicity (Table 2). One patient experienced grade 3 fever without evidence of infection which was transient and resolved with antipyretics; and, one patient experienced grade 3 neutropenia which resolved within 1 week after therapy was held. The most common reported toxicities in this group were mild nausea/vomiting ($n = 3$), transient elevation in liver transaminases ($n = 3$) leucopenia ($n = 3$), and anemia ($n = 3$). Two of four patients treated at dose level II experienced grade 3 toxicity during cycle one which included fever ($n = 1$), leukopenia ($n = 1$), and neutropenia ($n = 2$). No grade 4 toxicities occurred at either dose level. At dose level III, three of six patients experienced grade 3 or worse toxicity. All six patients developed neutropenia ($n = 1$, grade 3; $n = 2$, grade 4), which was transient and resolved within 1 week after therapy was held. Five of 14 patients treated at dose level IV experienced grade 3 toxicity during cycle one which included neutropenia ($n = 1$), anemia ($n = 2$), and transient elevations in liver transaminases ($n = 3$). There were no grade 4 toxicities at this dose level. Dose limiting toxicity occurred at dose level V. Four of six patients at this dose level experienced grade 3 ($n = 2$) or grade 4 ($n = 2$) toxicity. At this dose level, one patient developed grade 4 neutropenia and one patient developed grade 4 respiratory distress manifesting as dyspnea with transient hypoxia. Chest radiographs revealed mild pulmonary edema. Both patients had resolution of their toxicity within 2 weeks after therapy was discontinued. Other grade 3 toxicities at this dose level included neutropenia ($n = 1$) and fatigue ($n = 1$).

During subsequent cycles, toxicity was similar, however, the severity of toxicity increased at all dose levels. Two of four patients at dose level I, all patients at dose level II, and five of six patients at dose level III experienced grade 3 toxicity during subsequent cycles. At dose level IV, 10 of 14 patients experienced grade 3 or 4 toxicity with additional treatment cycles which included anemia ($n = 3$), neutropenia ($n = 5$), and elevation in liver transaminases ($n = 3$). All patients treated at dose level V experienced a grade 3 or 4 adverse event and one patient had a cardiopulmonary arrest possibly related to treatment. Treatment related toxicities resulted in treatment delays in 10 patients and dose reductions in 11 patients. All six patients treated at dose level V had a treatment delay or dose reduction. Overall, the toxicity of PEG IFNα and rIL-2 was severe, but therapy was tolerated with

Table 2 Cycle one toxicity

Dose level	I		II		III		IV		V	
Number of patients	4		4		6		14		6	
Grade	½	¾	½	¾	½	¾	½	¾	½	¾
Toxicity										
Nausea	3	0	4	0	4	0	13	0	5	0
Vomiting	0	0	2	0	1	0	4	0	1	0
Diarrhea	2	0	1	0	3	0	6	0	3	0
Fatigue	2	0	3	0	3	0	13	0	5	1
Arthralgia/Myalgia	2	0	0	0	2	0	3	0	0	0
AST/ALT	3	0	1	0	3	0	11	2	5	0
Alkaline phosphatase	2	0	1	0	3	0	6	1	4	0
Fever	2	1	3	1	6	0	13	0	6	0
Neutropenia	2	1	2	2	3	3	10	1	1	2
Thrombocytopenia	1	0	1	0	3	0	7	0	4	0
Anemia	3	0	3	0	6	0	7	2	4	0
Leucopenia	3	0	2	1	3	0	7	0	1	0
Hypoxia	0	0	0	0	2	0	1	0	0	1

appropriate dose reductions and delays. The toxicity profile of this combination may be more severe than that associated with the tyrosine kinase inhibitors, but direct comparison is not possible.

Efficacy

Of the 34 patients entered onto this study, 5 patients (15%, 95% C.I. 5–31%) achieved a partial response (PR), 6 patients (18%) progressed, and 23 patients (68%) had stable disease as their best response. There was one PR in each dose level. One of the responders was of chromophobe histology, whose response lasted for 8 months and had a survival of 61 months, belonged to the dose level IV. Of the 23 patients with stable disease, 21 had stable disease lasting longer than 3 months. The median duration of response was 10.2 months (range 3.8–33.1 months; one patient is censored at 12.1 months). Median duration of stable disease for all 23 patients with a best response of SD was 11.4 months (range 0.7 + to 61.0 + months). The responses were mostly seen in lung, lymph nodes, abdomen, liver and bone.

Survival data

Survival and progression data were available for all 34 patients. Overall 31 (91%) patients have progressed, and 22 (65%) have died. Median follow-up for the 12 patients still alive is 55.5 months (range 9.2–70.4 months). Median survival was 31.9 months (95% C.I. 17.2–61.9 months) and median PFS 9.0 months (95% C.I. 5.6–13.1 months; see Fig. 1).

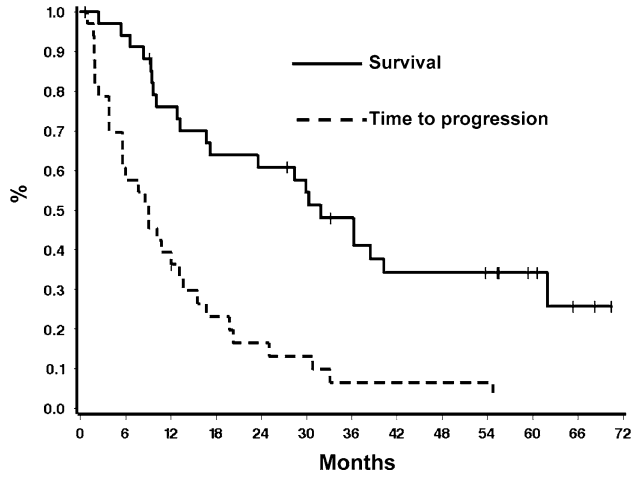

Fig. 1 Overall survival and time to progression by Kaplan–Meyer method

Discussion

Given the requirements for frequent injections and underlying toxicity of chronic treatment with IFNα, alternative formulations with the potential for greater efficacy and less toxicity have been investigated. The most studied formulation has been the conjugation of the IFNα molecule with polyethylene glycol (PEG), a process known as pegylation. A single dose of pegylated IFNα-2b (≥1.0 μg/kg) remains in the circulation for more than 168 h (7 days) due to impaired renal clearance resulting in approximately a 10-fold increase in the elimination half-life (approximately 40 vs. 4 h for IFNα-2b) and an increased AUC when compared

to IFNα-2b [31–33]. Single agent pegylated IFNα-2b has been evaluated in patients with metastatic RCC demonstrating similar efficacy in untreated patients (14% response rate [26] to non-pegylated IFNα-2b,) 7.5–14% response rate [14, 16, 21], as well as comparable safety with the advantage of weekly administration.

Several preclinical tumor models suggest synergistic antitumor activity when IFNα is combined with rIL-2 and this combination has been extensively studied [34]. Studies evaluating this combination have demonstrated marginal improvements in objective tumor response with significant toxicity limiting dose escalation [6, 7, 10, 19–21, 35]. The treatment regimens and reported response rates differ considerably in these trials, which may be partly explained by patient selection. In the present study, we selected a dose and schedule based upon data from a previously reported phase I/II trial of pegylated IFNα-2b in which the starting dose level and MTD were 0.75 and 6.0 μg/kg/week, respectively [26]. Based upon data evaluating the pharmacokinetics from single-dose and multiple-dose studies of pegylated IFNα-2b and IFNα-2b, the dose range of pegylated IFNα-2b utilized in our study may achieve a weekly exposure comparable to between 30 and 180 MIU of subcutaneous IFNα-2b [26, 28, 32, 33]. The dose and schedule of rIL-2 was similar to that used in previous non-pegylated IFNα-2b and rIL-2 combination trials [7, 19, 20]. All but one patient in our trial was treatment naïve and all were good or intermediate risk. Five (15%) of 34 patients had a partial response, which is consistent with previous observations [7, 10, 19, 20, 35]. Responses were observed at all dose levels and occurred both in visceral and non-visceral sites of disease.

The MTD of pegylated IFNα-2b (3.0 μg/kg/wk) and rIL-2 (20.0 MIU/m^2 SC in weeks 1 and 4; 5.0 MIU/m^2 SC during weeks 2, 3, 5, 6) in this phase I trial is higher than reported in a similar phase I trial using a different schedule of rIL-2 (5.0 MIU/m^2 subcutaneous every 8 h × 3 days then daily × 5 days a week for a total of 4 weeks) [36]. This dose level is recommended for future studies involving the combination of pegylated IFNα-2b and rIL-2. In addition, the MTD of pegylated IFNα-2b (2.0 μg/kg/week) was lower suggesting that the toxicity of rIL-2 and pegylated IFNα-2b may be schedule dependent. Common adverse events observed in this study were constitutional symptoms (fatigue, fevers and chills), nausea and vomiting, and transient hematologic toxicities (anemia, leukopenia, and thrombocytopenia). With prolonged dosing, fatigue was the most prominent symptom. The adverse events and laboratory profiles observed are also similar to those previously reported for the combination of rIL-2 and non-pegylated IFNα-2b [7, 10, 19, 20, 35]. Grade 3 toxicities included nausea/vomiting/dehydration, transient liver transaminase (AST and/or ALT) elevation and neutropenia which are similar to those observed in the phase I trial of pegylated IFNα-2b and rIL-2 reported by Clark et al. [36]. Although, previous trials of non-pegylated IFNα-2b and rIL-2 [7, 10, 19, 20, 35] have reported an increase in the total number of grade 3 and grade 4 adverse events with a resultant decrease in patient's performance status, in our trial, with appropriate treatment delay or dose reduction, all patients were able to continue receiving therapy. Of particular interest, one patient in our trial treated at dose level V developed grade 4 respiratory distress manifesting as dyspnea with minimal hypoxia. Respiratory distress due to a capillary leak syndrome has been described in patients treated with rIL-2, however, this patient had minimal pulmonary edema on chest radiographs [6, 37].

This study confirms that pegylated IFNα-2b appears tolerable when combined with rIL-2 in patients with metastatic RCC. Although the response rate is similar to previously reported trials of IFNα-2b and rIL-2 used as single agents and in combination, the ability to administer pegylated IFNα-2b weekly without compromising efficacy provides greater convenience and will likely improve patient compliance. The PFS for IFNα treated patient groups were 5.6 months in the phase II sorafenib versus IFNα trial and 5.0 months in the phase III sunitinib versus IFNα trial [22, 38]. In contrast, the PFS in the current trial was 9.0 months. Comparison across studies is problematic, and may represent patient selection; however, the PFS duration in the current trial is of interest.

The recent clinical trials have changed standard of care in RCC from cytokine-based therapy to sunitinib. It is unlikely that cytokine combinations such as IL-2 and IFNα will be utilized in advanced RCC in view of the recent studies demonstrating the effectiveness of kinase inhibitors and bevacizumab [39]. Nevertheless, the use of pegylated IFNα in combination with agents such as bevacizumab and sorafenib may be of interest. The combination of sorafenib and IFNα in both front-line and treatment-refractory setting may improve response rates [24, 25]. Since PEG IFNα maybe easier for patients to tolerate, and is administered once weekly, combinations with multitargeted kinase inhibitors such as sorafenib may be of interest. Additionally, the use of PEG IFNα in combination with bevacizumab can be considered in view of the recent report by Escudier et al. demonstrating a significant increase in over all response rate and progression free survival compared to monotherapy with IFNα [39].

Acknowledgement We thank the Nursing Staff of the Experimental Therapeutics Program of the Cleveland Clinic Taussig Cancer Center.

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