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Short Communication

An EORTC Phase II Study of the Efficacy and Safety of Linomide in the Treatment of Advanced Renal Cell Carcinoma

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The aim of this study was to determine the objective tumour response rate and duration of response and toxicity of linomide (Roquinimex) treatment in patients with disseminated renal cell carcinoma, pretreated or not pretreated with immunotherapy. From March 1991 to July 1992, 72 patients with metastatic and progressive renal cell cancer were entered of whom 9 (12%) were not evaluable for response. Linomide was given orally, twice weekly, 5 mg during the first week with dose escalation to 10 mg during the second week and 15 mg thereafter. Treatment was continued until disease progression or unacceptable toxicity. No haematological toxicity but slight anaemia was observed. A significant WBC (white blood cell count) increase ($P < 0.0001$, paired T-test) was found during treatment. The most often reported non-haematological side-effects were: flu-like syndrome (54%, grade III–IV 7%), nausea/vomiting (41% and 3%, respectively) and neurotoxicity (34% and 2%). Most side-effects were of mild or moderate intensity (WHO grade 1 or 2). The objective overall response rate was 4%: 1 CR and 2 PRs. Stable disease was reported for 28 patients (40%). The duration of response was 17, 22 and 30 (CR) months. Median time to progression was 5 months. Linomide at the given dose and schedule is well tolerated, but has limited antitumour activity in metastatic renal cell carcinoma.

Key words: linomide, advanced renal cell carcinoma, phase II study

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INTRODUCTION

THE TREATMENT of advanced renal cell carcinoma (RCC) with Interferon alpha (INFα) has yielded a 7–26% response rate [1]. A similar response rate, 9–33%, was reported for Interleukin 2 (IL-2) with or without INFα in phase I/II studies [2]. However, the combination of limited response rates and therapy limiting side-effects has prevented both INFα and IL-2 from becoming generally accepted standard therapy for patients with advanced RCC. This emphasises the need to continue the evaluation of other immunotherapeutic agents.

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Linomide (Roquinimex) is a quinoline with a pleiotropic immune modulating capacity, which strongly reduces intratumoral microvessel density with a subsequent decrease in tumour blood flow and increase of cancer cell death [3, 4]. A phase II study with linomide in renal cancer patients has indicated that the drug has some activity in this disease since four responses (2 CR, 2 PR) were observed among the 20 patients [5]. Therefore, an extended phase II study in a multicentre setting was warranted to confirm these data.

The primary objective of this trial was to study the objective tumour response rate of linomide in patients with renal cell carcinoma either not pretreated or previously pretreated with IL-2 and/or INF based immunotherapy. The second objectives were to study time to disease progression and toxicity.

PATIENTS AND METHODS

Eligibility criteria

Patients with measurable or evaluable metastases (>2 cm in size) of histologically proven RCC with documented progression in the 2 months preceding entry, aged under 75 years old, performance status of 0 to 2 (WHO scale) as well as adequate renal (serum creatinine <150 μmol/l) and liver function (bilirubin <20 μmol/l) were considered eligible for the study. Exclusion criteria were pregnancy, previous chemotherapy, WBC $<4.0 \times 10^9/1$, platelet count $<<125 \times 10^9/1$, presence of brain metastases, second malignancy and congestive heart failure, or significant arrhythmia. Pretreatment investigations included complete medical history, physical examination, laboratory data (haemoglobin, WBC and platelet count, clinical chemistry), chest X-ray, initial measurement investigations (CT-scan or ultrasound of intra-abdominal or mediastinal masses) and electrocardiogram. Bone scan and IVP were optional.

Treatment

Linomide was administered orally. During the first week, the dose was 5 mg, twice weekly, thereafter the treatment dose was escalated to 10 mg during the second week and 15 mg, twice weekly from the third week onwards. The dose escalation was postponed if WHO grade 2 toxicity occurred. The dose was to be temporarily reduced to the previous dose or was to be postponed whenever a severe (WHO grade 3 or 4) adverse event occurred.

Response was defined according to the WHO criteria [6]. Patients treated for at least 2 months were considered evaluable for tumour response. Progressive disease (PD) within the first 2 months was defined as early progression. All eligible patients who had received at least one dose of medication were evaluable for toxicity. Early death was defined as a death occurring during the first 4 weeks. Patients who died from non-malignant disease before evaluation were considered inevaluable. Response duration was defined from the first day of treatment to the date of reported progression.

RESULTS

From March 1991 to July 1992, 72 patients entered the study. 2 patients were ineligible. Patient characteristics and prior treatment are presented in Table 1. The median age was 60 years (range 20–75 years). Of 30 patients pretreated with immunotherapy, 14 received adjuvant immunotherapy (IL-2, INF) after nephrectomy, the other 16 were treated for advanced disease. The median duration of linomide treatment was 11 weeks (range 1 week–34 months). 17 patients were treated for ≥6 months and 9 for more than one year. The linomide dose was reduced in 19 patients. 11 patients had a treatment delay of 1–2 weeks: 3 because of side-effects and 8 for other reasons, not related to study medication.

Response

Response was seen in 3 patients. One CR (lungs) and 2 PR (lungs and lymph nodes) were observed. The complete response was reported in the ninth month of the treatment in a patient who progressed after nephrectomy and IL-2. The patient received in total 3330 mg of linomide in 124 weeks with no severe side-effects. Partial remissions were notified in another 2 patients in the third and seventh

Table 1. Patients characteristics at start of treatment

	No prior immunotherapy	Prior immunotherapy	Total	
WHO response	*n*	*n*	*n*	(%)
Total number of eligible patients	40	30	70	(100)
Sex				
Male	30	21	51	(73)
Female	10	9	19	(27)
Performance status (WHO)				
0	21	17	38	(54)
1	13	10	23	(33)
2	6	3	9	(13)
Localisation of metastases				
Lung	30	24	54	(77)
Local relapse	21	11	32	(46)
Lymph nodes	11	8	19	(27)
Liver	8	8	16	(23)
Bone	4	3	7	(10)
Other	8	12	20	(29)
Prior nephrectomy				
Yes	33	28	61	(87)
No	7	2	9	(13)

month of treatment, both patients had prior nephrectomy. The duration of response in all three responders was 30, 22 and 17 months, respectively. Among 28 patients (40%) tumour stabilisation was reported. The overall median time to progression (TTP) was 5 months.

Toxicity

No haematological toxicity, but slight anaemia was observed. A steady, statistically significant rise of WBC was observed ($P < 0.0001$, paired t-test) over the first 10 weeks of treatment. The most often observed adverse event, flu-like syndrome, was reported among 37/69 patients (54%). 5 of them (7%) had severe symptoms (grade 3–4). 22 of 69 patients (34%) suffered from neurological side-effects. Nausea and vomiting occurred in 28 patients (41%); 2 had grade III–IV (3%). Most were reported mild or moderate, with transient paresthesias, somnolence or headaches. In 4 patients, cardiac side-effects were reported: 2 patients had chest pain, which in one patient disappeared gradually over the next days after drug withdrawal, and one patient had a myocardial infarction complicated with hypotension. In one patient, pericarditis was reported. No late side-effects after linomide were reported.

DISCUSSION

A prominent feature of Roquinimex are its anti-angiogenic properties. Linomide inhibits angiogenesis induced by several angiogenic factors like aFGF and bFGF, TNF-α and VEGF. The mechanism of anti-angiogenic action of linomide is based on inhibition of endothelial cell proliferation with blockage of migration and subsequent formation of new capillaries [4, 7]. The drug decreases intratumoral microvessel density resulting in an increase in necrosis and apoptotic index in non-necrotic areas. A favourable anti-tumour effect of linomide was confirmed against several implantable mouse and rat tumours *in vivo*, including the mouse B 16 melanoma, Lewis Lung carcinoma, colon, prostate and breast cancer [8–10].

Data are now available from two phase I studies and another phase II study in patients with autoimmune or malignant disease. The most often observed adverse events reported in these trials were musculosceletal discomfort (69% of all cases) and gastrointestinal adverse events (58%), often accompanied by headache (41%), fever (32%) and tiredness (29%), rapidly reversible upon treatment cessation. Peripheral neuropathy and pericarditis are rare, but can be severe. The dose limiting toxicity was muscle and joint pain as well as headache. The characteristics of mostly mild or moderate side-effects reported in our study is generally in agreement with earlier observations [3, 5, 11].

It was shown recently, that suppression of tumour angiogenesis induces a specific clinical behaviour on treatment, different from this seen after cytotoxic treatment [12–17]. The reason is that tumour vasculature and not proliferating malignant cells are the target. According to a recent review by Folkman, anti-angiogenic therapy is generally well tolerated. Objective responses are reported in some patients, but stable disease is more often seen and the optimum effect of the treatment, if given regularly, appears over a longer time period. No significant drug resistance in long-term animals studies has been seen [13].

It has been suggested that anti-angiogenic therapy may be administered as a sole, safe, long lasting palliative or better adjuvant treatment. The aim of this "dormancy therapy" strategy is, after initial cancer regression to microscopic dormant foci, to balance tumour cell proliferation by apoptosis in the presence of blocked angiogenesis [12, 13]. However, angiosuppression may also be an attractive partner in combined treatment [17].

The results reported in this study are consistent with characteristics described in Folkman's "dormancy therapy" strategy, showing a "dormant type of response" in 44% of progressive patients with advanced metastatic disease. In conclusion, linomide is a safe, oral drug with a low response rate, according to classical response criteria, but it seems to confirm anti-angiogenic activity observed *in vivo*.

Further investigations are warranted evaluating other endpoints, such as the determination of angiogenic growth factors serum levels during linomide treatment or its role in combination with other drugs, such as cytokines or cytotoxic agents.

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