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Short Communication

EORTC Phase II Study of Daily Oral Linomide in Metastatic Renal Cell Carcinoma Patients with Good Prognostic Factors

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Following a previous EORTC GU-Group study, in which linomide showed some activity in poor prognosis patients, this study was initiated to determine the effect of linomide in more favourable patients. 35 patients with metastatic renal cell carcinoma with good prognostic factors, i.e. good performance status, prior nephrectomy, no prior systemic therapy, and no liver, bone or brain metastases, were treated with linomide, a quinoline derivative with immunomodulating properties, at a dose of 10 mg daily, after an initial dose escalation during the first 4 weeks of treatment. In 29 evaluable patients, no responses were observed (95% confidence interval 0–10%). Best overall response was no change in 9 patients, for a median duration of 4 months. Linomide in this schedule was poorly tolerated, with 17% (6 patients) of patients being withdrawn and 23% (8 patients) having dose reductions due to adverse events, mostly influenza-like symptoms of myalgia, arthralgia and fatigue. Several cases of pericarditis and neuropathy were observed. In spite of selection of favourable prognosis patients and an optimal daily dosing schedule, linomide was not an effective treatment in renal cell carcinoma. In view of toxicity and lack of efficacy, there is no rationale in further testing the drug in this disease.

Key words: linomide, immunotherapy, renal cell carcinoma

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INTRODUCTION

LINOMIDE (*N*-phenylmethyl-1,2-dihydro-4-hydroxyl-1-methyl-2-oxoquinolone-3-carboxamide) is a quinoline 3-carboxamide which has previously been demonstrated to produce immunomodulator and antitumour effects when given *in vivo* [1–5]. The EORTC GU-Group recently carried out a phase II study (EORTC 30905) in patients with renal cell cancer with linomide in a twice weekly dosing schedule [6]. In a total of 63 evaluable patients, all of whom had disease progression at entry, 28 patients had no change and 3 had a response, with a median time to progression of 5 months (range 1–32). This disease stabilisation and concurrently observed significant white blood cell (WBC) increase during treatment was suggestive of activity of linomide. Since almost half the patients had failed previous immunotherapy and/or had very extensive disease (liver, bone metastases), which is associated with poor response to treatment [7, 8], it was decided to re-investigate the drug in patients with optimal prognostic factors and no prior systemic therapy. To avoid plasma level fluctuations of linomide when administering the drug twice weekly, a daily dosing schedule was used, which would also enable a higher total dose per week.

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PATIENTS AND METHODS

Patients

Eligibility criteria were: the presence of renal cell adenocarcinoma with demonstrated disease progression in the 2

months preceding entry; measurable distant metastases or local recurrence not amenable to local regional treatment; performance status (WHO scale) 0 or 1; serum creatinine <150 μmol/l; and bilirubin < 20 μmol/l. In addition, all patients were required to have had their primary tumour removed. Exclusion criteria were: previous chemo-, hormono- or immunotherapy; the presence of liver, bone or brain metastasis; radiotherapy within 12 weeks prior to study entry; or poor medical risk. All patients gave their informed consent.

Study design

Linomide was administered once daily. During the first two weeks, the dose was 5 mg daily. During the following two weeks, the dose was 7.5 mg daily. From the fifth week onwards, the dose was to be 10 mg once daily. If moderate or WHO grade 2 adverse events occurred, the dose was not to be increased as described above, but was kept unchanged. No further dose escalation was performed in these patients. If severe or WHO grade 3 or 4 but no serious adverse events occurred, the administration was postponed temporarily for up to 2 weeks. When the severe toxicity subsided to mild or none, the treatment was to be restarted at the dose level below the level at which the toxicity occurred. If serious or unacceptable toxicity occurred, linomide was to be withheld and not restarted. Patients were to be treated until progression of disease. Patients who were treated for a period of 8 weeks, or had progressive disease within this period, were considered evaluable for objective tumour response. All patients who had received at least one dose of trial medication were considered evaluable for toxicity. Response was assessed according to WHO criteria. Response duration was calculated from the start of therapy to the day of first observation of progressive disease.

RESULTS

35 patients were entered into the study. Patient characteristics are shown in Table 1. 4 patients were ineligible because they had no measurable lesions [2] or liver metastasis [2]. 2 patients were not evaluable for response because they stopped treatment before 8 weeks due to toxicity. Therefore, 29 patients were evaluable for response. All 35 patients were considered evaluable for toxicity. None of the evaluable 29 patients achieved a response (95% confidence interval 0–10%). Best overall tumour response was NC in 9 patients (29%) for a median duration of 4 months, whereas 20 patients had progressive disease, of whom 6 were withdrawn before 8 weeks due to early progression. The median time to progression for all patients was 2 months (range 1–7 months). In one non-evaluable patient, for whom linomide was permanently stopped after 10 days of administration due to pericarditis, the pulmonary metastases appeared smaller on the chest X-ray upon admission, notwithstanding the difference in the technique used (AP instead of PA). The patient was treated with prednisone 30 mg daily. Six weeks later a customary PA chest X-ray revealed that there was a further reduction in the size of the pulmonary metastases of more than 50%. Unfortunately, the patient from then onwards was treated with interferon-α and for one reason or another did not progress until one year later. Because of the flaws in documentation and concurrent medication, it was decided not to evaluate this patient as a responder.

Table 1. Patient characteristics

	n	(%)
Total number of eligible patients	31	(100)
Sex		
Male	18	(58)
Female	13	(42)
Performance status		
0	19	(61)
1	12	(39)
Sites of disease		
Total number of measurable lesions	70	(100)
Lung	41	(59)
Lymph nodes	24	(34)
Local recurrence	2	(3)
Other	3	(4)

Toxicity

The median treatment duration for all 35 patients was 11.8 weeks (1.3–43.7). 22 patients (63%) were treated for at least 8 weeks, 14 of whom received the last administration of treatment after documented progression, for logistical reasons or incorrect tumour evaluation. In 6 of these patients, linomide was given for more than one month after progression. The maximal linomide dose reached was 10 mg in 26 patients, 7.5 mg in 6 patients and 5 mg in 3 patients. Reasons for not reaching the final dose were withdrawal due to early progression in 2 patients, withdrawal due to adverse events in 4 patients and no further escalation due to adverse events in 3 patients. Myalgia was the most common adverse event which was experienced by 20 patients (57%), 6 of whom had mild, 11 moderate and 3 severe complaints, notwithstanding concurrent or subsequent use of analgestics (mostly paracetamol) in all patients. Also, arthralgia (11 cases, 31%) and skeletal pain (5 cases, 14%) were frequently reported. Mild nausea and vomiting was seen occasionally in 14 patients, 7 of whom used anti-emetic drugs at regular intervals. The treatment was withdrawn in 6 patients due to adverse events; in 2 patients, pericarditis occurred with the first 2 weeks of treatment, 2 patients had severe myalgia, 1 patient had a gastric ulcer and 1 patient had deep vein thrombosis. Although in one of the 2 patients with pericarditis, aspiration of the pericardial fluid revealed adenocarcinoma, the development of symptoms shortly after the beginning of treatment in both patients and the complete disappearance of symptoms upon withdrawal after 2–5 weeks was suggestive of a relationship with linomide. Fatigue, constipation and coughing were also frequently reported, each of these symptoms occurring in 8 patients (23%). 7 patients (20%) reported mild or moderate paraesthesia during linomide treatment, and 3 patients had mild or moderately painful neuropathy, which in several cases only resolved slowly upon discontinuation of the drug, and was considered possibly or probably related to the treatment. In 10 patients, the dose of linomide was reduced, escalation delayed, or treatment temporarily postponed, due to adverse events, mainly for reasons of myalgia and fatigue. No myelotoxicity was encountered, and, in fact, after 2 and 8 weeks of treatment (median), WBC and neutrophils were slightly higher as compared to baseline (data not shown).

Table 2. Comparison of results of both EORTC linomide trials 30905 and 30923

	30905 [6]	30923 (current study)
Inclusion criteria		
Nephrectomy patients only	No	Yes
Non-pretreated patients only	No	Yes
Liver, brain, bone metastases excluded	No	Yes
Performance status = 2 excluded	No	Yes
Treatment dose (mg/week)		
Week 1	10	35
Week 2	18	35
Weeks 3 and 4	27	52
Thereafter	27	70
Total number of eligible patients	70	31
Tumour response (%)		
CR or PR	(4)	(0)
NC	(40)	(29)
Median duration of NC (in months)	5	4

DISCUSSION

In the present study (EORTC 30923), in patients with metastatic renal cell carcinoma with favourable prognostic factors, i.e. good performance status, prior nephrectomy, no prior systemic therapy, and no liver, bone or brain metastases, linomide was found not to be an effective drug. No objective responses were observed in a total of 29 evaluable patients. The median time to progression in a total of 9 patients with NC was no more than 4 months.

The daily dosing regimen that was used in this study, and which had also been used in previous animal experiments which yielded antitumour effects, enabled a higher cumulative dose as compared with a twice weekly schedule as was applied in the previous study (EORTC 30905) [6]. However, linomide in this daily regimen did not appear to be very well tolerated, with 6 patients (17%) being withdrawn due to adverse events. Additionally, 8 patients (23%) had dose reductions or treatment postponements due to adverse events, mostly influenza-like symptoms of myalgia, arthralgia and fatigue. Several cases of neurotoxicity were observed, which were not rapidly reversible. Pericarditis was observed in 2 patients, which was possibly related to linomide and resolved within 2 and 5 weeks after withdrawal. To date, in a total of 700 patients treated with linomide in investigational programmes in cancer and multiple sclerosis, several other cases of pericarditis, or pericarditis accompanied with pleuritis, have now been observed. In some cases, a causal relationship was considered unlikely, but in others an association with the drug could not be ruled out (Pharmacia, data on file).

It is concluded that linomide is not an effective treatment in patients with renal cell carcinoma, in spite of selection of the patients in the present study on the basis of favourable prognostic factors. When combining the results of the present study, EORTC 30923, with the previous study EORTC 30905 (Table 2), linomide demonstrated only minimal activity in renal cell carcinoma. In addition, linomide at a dosing schedule of 10 mg daily is poorly tolerated in these patients. Therefore, there appears no rationale in further testing the drug in patients with renal cell carcinoma.

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