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Phase II study of LU 103793 (dolastatin analogue) in patients with metastatic breast cancer

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Abstract

LU 103793 is a synthetic analogue of Dolastatin 15 that inhibits tubulin polymerisation. The aim of this study was to evaluate the efficacy and tolerability of LU 103793 in patients with metastatic breast cancer who had been previously treated with two lines of chemotherapy for advanced disease. Patients received LU 103793 at a dose of 2.5 mg/m^2/day over 5 min for 5 consecutive days every 3 weeks. Thirty-four patients were enrolled and 23 patients were eligible for the evaluation of efficacy. Eleven patients experienced grade 4 neutropenia. Other related grade 3/4 adverse events included asthenia (three patients), stomatitis (1), myalgia (1) and increase of serum bilirubin (2). The main toxicity was hypertension occurring in seven out of 34 patients. There were no objective responses, 7 patients had stable disease. These results do not support the further evaluation of LU 103793 in metastatic breast cancer patients using this dose and schedule.

Keywords: Phase II; Breast cancer; LU 103793; Dolastatin

1. Introduction

The Dolastatins are a group of structurally unique peptides isolated from the Indian Ocean sea hare, *Dolabella auricularia* [1]. All contain unusual amino acid residues and display a strong anti-proliferative potential. In particular, Dolastatins 10 and 15 have demonstrated excellent anti-neoplastic activity in various experimental systems *in vitro* most likely through the inhibition of tubulin polymerisation, and, thereby, interfering with cell division [2]. In the National Cancer Institute (NCI) human tumour cell line screen, they produced an inhibitory pattern typical of tubulin binding agents with the greatest activity being observed in cell lines derived from colon, ovarian, and breast cancers [3].

A series of analogues of Dolastatin 10 and 15 were synthesised to enhance the safety, efficacy and pharmacological characteristics of the natural compounds. LU 103793, the hydrochloride salt of a pentapeptide containing some of the unusual amino acids found in Dolastatin 15, was selected for clinical development. In the United States and Europe, several phase I trials were performed exploring both safety and potential activity. Since the preclinical data showed a possible advantage of more frequent dosing and since the day×5 schedule tested in phase I was better tolerated than other phase I schedules, this schedule was chosen to perform the current phase II studies [4]. Biochemically relevant plasma concentrations of LU103793 in the 0.1–1.0 micromolar range have been achieved at the 2.5 mg/m^2/day dose level.

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2. Patients and methods

This was an open label, non-randomised Phase II study in two stages, based on the Simon's Two Stage Design. The trial had to be stopped at the end of stage one if there was one or no responders out of twenty eight patients, or if there were medical or ethical objections with regard to the safety data or adverse experiences. The Ethics Committee of each hospital approved the study and all patients gave their written informed consent.

Patients were eligible if they were at least 18 years old with locally advanced unresectable or metastatic breast cancer, which was measurable. They were required to have received two prior chemotherapy regimens for advanced disease, to have an Eastern Cooperative Oncology Group (ECOG) Performance Status of 0, 1 or 2, a life expectancy of at least 3 months and an adequate haematological reserve (neutrophils $> 3.0 \times 10^9$/l and platelets $> 100 \times 10^9$/l), liver biochemistry (bilirubin < 35 μmol/l, transaminases and alkaline phosphatase $\leqslant 2.5$ upper limits of normal) and renal function (serum creatinine $\leqslant 140$ μmol/l). In addition, patients should have a normal cardiovascular function with a normal blood pressure and electrocardiogram (ECG) and no concomitant treatment of hypertension. Patients were ineligible if they presented with a symptomatic brain or leptomeningeal involvement or with a history of haemorrhagic or thrombotic cerebro-vascular event or had received a prior high dose chemotherapy regimen.

LU 103793, provided by Knoll A.G. laboratories, was administered at a dose of 2.5 mg/m^2 on the first 5 days of an every 3-week cycle. It was delivered as a 5-min intravenous (I.V.) infusion. The initial dose was reduced to 1.9 mg/m^2 daily in cases of grade 3 or 4 neutropenia associated with fever, grade 4 neutropenia lasting more than 5 days, grade 4 thrombocytopenia or grade 3 associated with bleeding. Patients were to be treated until disease progression, unacceptable toxicity or until they or their physician considered further LU 103793 as not being appropriate. No prophylactic anti-emetic agents were used.

Blood pressure, pulse and physical signs of acute toxicity were registered immediately before and every thirty minutes, for the first 120 min after the end of the infusion.

Tumour measurements were repeated every two cycles. Response was assessed according to the World Health Organization (WHO) criteria. Treatment toxicity was graded according to the Common Toxicity Critiera (CTC), version 2.0.

3. Result

Thirty-four patients were entered at 18 institutions. Eleven patients were ineligible: 4 for pre-existing cardiovascular disease, 1 for absence of measurable disease, 3 because they had another concomitant or recent (less than 4 weeks) anti-cancer treatment, 1 presenting biological hepatic abnormalities at baseline and 2 for a combination of the above-mentioned factors.

The prior treatments and clinical characteristics of the enrolled patients are shown in Table 1.

All patients, except one whose treatment was stopped after 4 days of LU 103793, received at least one cycle. One hundred and three cycles were delivered. Five patients received six cycles and one patient received 18 cycles because of a long stabilisation. The initial dose was reduced only for four patients (five cycles), three for haematological toxicity and one for unknown reasons. Twenty-two cycles were delayed, mainly for haematological toxicity.

Treatment was generally well tolerated. Non-haematological toxicity per cycle is reported in Table 2 for the 34 enrolled patients. Grade 4 toxicity was only reported in two patients with an increase of bilirubinaemia, one episode was concomitant with *Candida* septicaemia. The major toxicity was cardiac, with seven of 34 patients experiencing hypertension. Only one patient requested treatment for this cardiac side-effect. Haematological toxicity is shown in Table 3. There was no major difference between the entire population and the eligible patients. One grade 4 episode of anaemia was reported for a patient with a grade 2 pre-existing anaemia at baseline. Grade 3 or 4 neutropenia occurred, in 7 and 11 patients, in 20 and 18 cycles, respectively, but only three grade 2 infectious episodes were observed.

Table 1
Patients, clinical and disease characteristics

Total	
Number of patients enrolled	34
Number of eligible patients	23
Age (years)	
Median (range)	53 (40–67)
Performance status	
0	11
1	18
2	5
Prior treatment	
Hormonal therapy	27
Chemotherapy (2 lines)	34
Anthracyclines	31
Taxanes	16
Target lesions	
Lymph nodes	11
Liver	18
Lungs	10
Skin and soft tissue	13

Table 2
Non-haematological toxicity per cycle, all patients (103 cycles, 34 patients)

Grade	CTC[a] grade			
	1	2	3	4
Nausea	23	2	–	–
Vomiting	5	1	–	–
Diarrhoea	5	–	–	–
Constipation	10	3	–	–
Asthenia/malaise	21	9	3	–
Stomatitis	7	–	1	–
Alopecia	10	2	–	–
Myalgia	6	3	1	–
Liver	17	7	3	–
Anorexia	2	–	–	–
Headache	7	1	–	–
Cardiac	4	12	1	–
Fever without infection	8	3	–	–
Infection	–	3	–	–
Hyperbilirubinaemia	–	–	–	2

[a] CTC, common toxicity criteria.

Table 3
Haematological toxicity (all patients $n = 34$)

	Maximum CTC grade				n
	1	2	3	4	
Per patients					
Anemia	8	11	–	1	20
Leucopenia	3	7	14	4	28
Neutropenia	2	7	7	11	27
Thrombocytopenia	10	4	1	–	15
Per cycle					
Anemia	28	14	–	1	43
Leucopenia	16	36	29	5	86
Neutropenia	18	26	20	18	82
Thrombopenia	35	5	2	–	42

Table 4
Best response to treatment

Total	34
Ineligible	11
Evaluable	23
Response	
Progressive disease	–
Partial response	–
Stable disease	7
Progressive disease	12
Early progression	3
Not evaluable	1

The best response for all patients is shown in Table 4. There were no responses. Seven stabilisations (SD) were observed in the eligible group and eight for the entire population.

4. Discussion

The European Organisation for Research and Treatment of Cancer—Early Clinical Studies Group (EORTC—ECSG) included 34 patients in this trial over a six month period. Eleven were ineligible: four had cardiac disease with hypertension or ECG changes, which was an exclusion criteria, because this side-effect has been observed during animal studies and phase I trials. In our study, we observed hypertension in 17 cycles, but only one patient needed medication.

LU 103793 was generally well tolerated and only a few dose reductions were required. Haematological toxicity was moderate: grade 3 or 4 neutropenia was frequently noted during the weekly follow-up, but infections were rare. Only one grade 3 thrombocytopenia was reported. Non-haematological toxicities were mild.

In the group of 23 eligible patients, we did not observe any objective responses. This was also the case, if we considered the eight ineligible patients with measurable lesions, where only stabilisations were observed. These data led us to stop the study, with the conclusion that the LU 103793 response rate will be inferior to 15%.

This low activity may be related to the inclusion of patients who had received two lines of chemotherapy in the metastatic setting, of whom 16 had received prior anthracyclines, 1 prior taxanes, 15 prior anthracyclines plus taxanes, and two had received other chemotherapies. In addition, the majority of patients presented with visceral disease, especially liver metastasis. Nevertheless, another study confirmed the low activity of dolastatin analogues as second-line chemotherapy for metastatic disease with only one partial response in 21 patients [5].

A lack of response has also been observed in other tumours, such as non-small cell lung cancer [6]. In melanoma patients, the EORTC—ECSG recently described a weak activity of LU 103793, with four responses in 80 chemotherapy-naive patients [7].

In conclusion, LU 103793 given by this route and schedule does not have clinically useful activity in patients with advanced breast cancer given as third-line chemotherapy.

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