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Phase I clinical and pharmacokinetic study of E7070, a novel sulfonamide given as a 5-day continuous infusion repeated every 3 weeks in patients with solid tumours. A study by the EORTC Early Clinical Study Group (ECSG)

C. Terret[a,*], S. Zanetta[b], H. Roché[a], J.H.M. Schellens[c], M.N. Faber[d], J. Wanders[d], M. Ravic[e], J.P. Droz[b]

[a]*Department of Medical Oncology, Institut Claudius Regaud, Toulouse, France*
[b]*Department of Medical Oncology, Centre Léon Bérard, 28 rue Laënnec, F-69373 Lyon Cedex 08, France*
[c]*Department of Internal Medicine/Oncology, The Netherlands Cancer Institute, Amsterdam, The Netherlands*
[d]*NDDO Oncology, Amsterdam, The Netherlands*
[e]*Eisai Limited, London, UK*

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Abstract

A single-agent dose-escalating phase I study on the novel sulfonamide E7070 was performed to determine the toxicity profile and the recommended dose for phase II studies. The pharmacokinetic profile of E7070 was also determined. E7070 was administered as a continuous infusion over 5 days repeated every 3 weeks. 27 patients were treated at doses ranging from 6 to 200 mg/m^2/day. As with other administration schedules, the dose-limiting toxicities were dose-dependent, reversible neutropenia and thrombocytopenia. Although no objective responses were observed, seven patients had stable disease. E7070 displayed a non-linear pharmacokinetic profile, especially at dose-levels greater than 24 mg/m^2/day, with a reduction in clearance and an increase in the half-life at the higher dose levels. The risk of myelosuppression became significant with an AUC greater than 4000 μg h/ml. The recommended dose of E7070 for further studies is 96 mg/m^2/day when administered on a 5-day continuous infusion schedule every 3 weeks.

Keywords: E7070; Pharmacokinetics; Phase I trial; Sulfonamide

1. Introduction

E7070 or *N*-(3-chloro-7-indolyl)-1,4-benzenedisulfonamide is a novel sulfonamide [1] with a wide range of activity in human tumour cell lines [2]. E7070 acts by inhibiting the activation of cyclin-dependent kinase 2 and cyclin E, which are involved in the transition of the G1 to S phase in the cell cycle [3].

E7070 shows similarities with chloroquinoxaline sulfonamide (CQS) which is known to cause cardiac tachyarrhythmias and hypoglycaemia [4]. E7070 produced a slight prolongation of the QTc interval and some fluctuations of blood glucose at the maximum tolerated dose (MTD) in rat and beagle dogs, respectively. Despite their similarities, E7070 displayed antiproliferative effects that were approximately 10 times more potent than that of CQS in human colon and non-small cell lung cancer models.

The purpose of the current study was to determine the MTD of E7070 when administered as a 5-day continuous infusion repeated every 3 weeks in patients with solid tumours. Other objectives were to determine the toxicity profile of E7070, to propose a recommended dose for phase II evaluation, to study E7070 pharmacokinetics and finally to detect any antitumour activity of the drug.

2. Patients and methods

2.1. Eligibility

Patients with a histologically- or cytologically-confirmed solid tumour not amenable to established forms

* Corresponding author. Tel.: +33-4-7878-2757; fax: +33-4-7878-2716.
E-mail address: terret@lyon.fnclcc.fr (C. Terret).

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of treatment were eligible for this study. Other eligibility criteria included: age $\geqslant 18$ years; a World Health Organization (WHO) performance status (PS) $\leqslant 2$; life expectancy of at least 3 months; no prior anticancer therapy within 4 weeks prior to entry in the study (6 weeks for nitrosoureas, and extensive radiotherapy); absolute neutrophil count [ANC] $\geqslant 1.5\times10^9$ cells/l, platelets $\geqslant 100\times10^9$ cells/l, and haemoglobin $\geqslant 90$ g/l; serum bilirubin $\leqslant 25$ μmol/l, other liver function tests $\leqslant 2.5$ times the upper normal limit ($\leqslant 5$ times the upper normal limit in presence of hepatic metastases); serum creatinine $\leqslant 120$ mmol/l or creatinine clearance $\geqslant 1$ ml/s. Patients were excluded if they had evidence of active infection, other non-malignant disease which was considered to be incompatible with the protocol, clinical signs of brain tumour or leptomeningeal disease, glaucoma, or were receiving treatment with a sulfonylurea agent for diabetes or any anti-arrhythmic agent.

All patients gave written informed consent before the start of treatment.

2.2. Treatment

The drug was supplied by Eisai Co Ltd (Japan) as 100 mg glass vials. E7070 was diluted with saline to a total volume of 500 ml and infused intravenously (i.v.) using a volumetric pump over 24 h each day as a 5-day continuous infusion.

The starting dose was 6 mg/m^2/day which corresponded to 1/10th of the MTD in rats. The dose was escalated in decreasing rates (Fibonacci-like scheme) in accordance with the clinical judgment of the investigators. When no or minimal (grade 1) toxicity was observed, doses were escalated in 100–50% steps. When significant toxicity ($\geqslant$ grade 2, except alopecia, anaemia and untreated nausea, vomiting) was observed, doses were escalated by 33–20% steps. There was no intrapatient escalation.

3 patients were treated at each dose level. When significant and dose-limiting toxicity (DLT) was observed in at least 1 patient at a given dose level, then further patients were treated at the same dose level (minimum 6 patients). DLT was defined as National Cancer Institute-Common Toxicity Criteria (NCI-CTC) grade 3 non-haematological toxicity or grade 4 haematological toxicity.

MTD was defined as the highest dose which could be safely administered to a patient producing tolerable, manageable and reversible toxicity of NCI-CTC grade 3 non-haematological (excluding alopecia and untreated nausea and vomiting) or grade 4 haematological in less than 33% of the patients following the first cycle of E7070.

Patients were scheduled to receive at least two courses of E7070. Treatment was continued thereafter at the same dose, in the absence of progressive disease, provided no serious toxicity was noted.

All patients who received at least one dose of E7070 were evaluable for toxicity. Toxicities were scaled according to the NCI CTC [5].

Tumour measurements were recorded using WHO criteria [6] at baseline and after every other course.

2.3. Pretreatment and follow-up examinations

Medical history, physical examination, WHO performance status were performed at baseline and prior to each course. Routine laboratory studies included a complete blood cell count, electrolytes, chemistries, clotting times and urinalysis. A chest X-ray and a 12-lead electrocardiogram (ECG) were obtained before treatment and before each course.

2.4. Specific toxicity assessment

On the first course, a 12-lead ECG and blood pressure readings (Welch Allyn No. 5200P) were performed prior to the each course and at 24-h intervals throughout the first course. A 24-h continuous holter monitoring was performed using Reynolds Medical tracker I and II holter recorders prior to and for 24 h after starting the infusion of the first course. Traces were reviewed centrally at Hertford Medical Limited, YK.

Blood glucose was monitored, using a glucometer (Glucotrend, Boehringer Mannheim), both before and at 4 h after the start of the first infusion and at approximately 24-h intervals thereafter.

Intra-ocular pressure was measured within 2 weeks before the first infusion and was scheduled to be repeated if clinical signs (visual disturbances, headache) or symptoms of intra-ocular pressure occurred.

2.5. Pharmacokinetics

During the first cycle, blood samples (8 ml) were collected at the following time-points: just prior to administration, and at 30 min, 1, 2, 4, 6, 8, 12, 24, 36, 48, 72, 96, 120 h after the start of infusion, and at 1, 2, 4, 8, 12, 24, 36 and 48 h after the end of infusion. At higher dose levels, the sampling times were amended and an additional number of three blood samples were collected up to 120 h after the end of infusion. Timed urine collections were made throughout the first 24 h after starting E7070 (0–8, 8–16, and 16–24 h). Details of sample processing and analysis have been described previously in Ref. [7].

2.6. Pharmacokinetic and pharmacodynamic analysis

Based on the individual plasma concentration–time data, the following pharmacokinetic parameters were determined after each dose using a non-compartimental analysis: C_{max} (maximal plasma concentration), area

under the curve extrapolated up to infinity ($AUC_{0-\infty}$), k (elimination rate constant), $t_{1/2}$ (terminal half-life), apparent Cl (systemic clearance), Vd_{ss} (steady state volume of distribution), MRT (mean residence time), amount of drug excreted unchanged in urine U_{0-8h}, U_{0-16h}, U_{0-24h}, and Cl_R (renal clearance). $AUC_{0-\infty}$ was determined by applying the linear-logarithmic trapezoidal method and extrapolation of the terminal part by using C_{last}/k, where 'C_{last}' is the plasma concentration at the last measured time-point and 'k' the elimination rate constant. The Pearson correlation coefficient was calculated between the absolute dose administered or dose/m^2 and AUC.

Linear and sigmoidal E_{max} relationships were explored for relationships between pharmacokinetic parameters (C_{max}, $AUC_{0-\infty}$, $t_{1/2}$, Cl, Vd_{ss}) and percent decrease in leucocyte, neutrophil and platelet counts.

Table 1
Patients' characteristics

Characteristics		
Number of patients		27
Age (years)		
	Median (range)	52 (26–61)
	Mean (±S.D.)	48.5 (±9.9)
Gender		
	Female	18
	Male	8
WHO performance status		
	0	8
	1	16
	2	3
Prior therapy		
	Radiotherapy and systemic therapy and surgery	14
	Radiotherapy and systemic therapy	2
	Systemic therapy only	12
Tumour types		
	Ovary	5
	Colorectal	5
	Breast	3
	Renal	2
	Sarcoma	2
	Lung	2
	Endometrial	1
	Gastric	1
	Liver	1
	Osteosarcoma	1
	Cervix	1
	Adrenal	1
	Sarcoma (uterine)	1
	Pelvic adenocarcinoma	1

S.D. standard deviation; WHO, World Health Organization.

3. Results

3.1. Population characteristics

The characteristics of the 29 patients (19 women, 10 men) treated with E7070 are listed in Table 1. All patients were evaluated for toxicity and antitumour activity. The median age was 49 years and PS was 0 or 1 in 26 patients. All patients had received prior treatment for their cancer. The most common tumour types were ovarian, colorectal, renal and breast cancer.

27 patients received 70 courses of E7070 at 10 different dose levels (Table 2). The median number of courses administered per patient was 2 (range 0–8 courses). The administered dose per cycle ranged from 6 to 200 mg/m^2/day.

3.2. Haematological toxicity

As expected, haematological toxicity occurred frequently. These events were mostly of a low grade, but their severity increased with the dose (Table 3) and myelosuppression corresponded to the most common DLT (Table 4).

Grade 4 anaemia was noticed in 1 patient treated at the 96 mg/m^2/day dose level at course 5 and in 1 other patient treated at the 160 mg/m^2/day dose level at course 2. For the first patient, anaemia was associated with disseminated intravascular coagulation, pseudo-membranous colitis and fever. In the other patient, anaemia was considered to be a disease-related event.

Grade 4 leucopenia, neutropenia and thrombocytopenia were observed at the three highest dose levels (130, 160, 200 mg/m^2/day) during course 1 and were considered to be DLT. All these events started at a median time of 12–13 days after the beginning of E7070

Table 2
Dose escalation scheme

Dose level (mg/m^2/day)	Nb Patients N	Courses N
6	3	9
12	3	6
24	3	7
48	3	6
96	5	20
100[a]	1	4
120[b]	1	1
130	6	12
160	3	4
200	1	1

[a] One patient was treated at 130 mg/m^2/day dose level for 1 course, and at 100 mg/m^2 day for the following courses.

[b] One patient was treated at 160 mg/m^2/day dose level for course 1 and at 120 mg/m^2/day dose level for a second course.

Table 3
Haematological toxicity (NCI-CTC grades)

Dose level (mg/m^2/day)	Anaemia				Leucopenia				Neutropenia				Thrombocytopenia			
	1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4
6	0	**1**	**1**	0	0	0	0	0	0	0	0	0	0	**1**	0	0
12	0	0	0	0	**1**	0	0	0	**1**	0	0	0	0	0	0	0
24	0	**1**	0	0	0	0	0	0	0	0	0	0	0	0	0	0
96	0	**1**	0	0	**1**	0	**1**	0	0	**1**	**1**	0	0	0	0	0
130	0	**1**	**1**	0	0	0	**1**	**1**	0	0	0	**2**	0	0	0	**2**
160	0	**1**	**1**	**1**	0	0	**1**	**1**	0	0	0	**2**	0	0	0	**2**
200	0	0	**1**	0	0	0	0	**1**	0	0	0	**1**	0	0	0	**1**

NCI-CTC, National Cancer Institute-Common Toxicity Criteria.

Table 4
Dose-limiting toxicities (NCI-CTC grades)

Dose level	Toxicity	Grade
200 mg/m^2/day (1 patient)	Leucopenia	4
	Neutropenia	4
	Thrombocytopenia	4
	Stomatitis	4
	Increased bilirubin	4
	Hypophosphatemia	3
160 mg/m^2/day (3 patients)	Leucopenia	4
	Neutropenia	4
	Thrombocytopenia	4
130 mg/m^2/day (6 patients)	Leucopenia	4
	Neutropenia	4
	Thrombocytopenia	4
	Nausea	3
	Hypokalemia	3

infusion, and their median duration was 3 days. There was no episode of febrile neutropenia.

All these haematological toxicities were completely reversible within 3 weeks except in 2 patients for whom this event started 2 days before they died due to disease progression.

3.3. Non-haematological toxicity

E7070 5-day continuous infusion was generally well tolerated. Nausea, vomiting, and asthenia represented the most common non-haematological toxicities.

Grade 1 and 2 nausea and vomiting were noticed at all dose levels. Only 1 patient had grade 3 nausea during the first course at the 130 mg/m^2/day dose level, which was considered to be DLT (Table 4).

Grade 1 and 2 asthenia and/or malaise were noticed in 11 patients and were considered to be possibly related to the study drug. One patient who was treated at the 96 mg/m^2/day dose level suffered from grade 3 asthenia at course 4 and grade 4 malaise at course 6.

Grade 2 alopecia was observed in only 2 patients at the highest dose levels ($>$ 130 mg/m^2/day). Mucositis was infrequent. One patient experienced grade 4 stomatitis at the 200 mg/m^2/day dose level, which corresponded to DLT.

Elevated bilirubin was seen in 1 patient at day 11 on the 200 mg/m^2/day dose level and was considered to be DLT. Grade 3 elevations in hepatic transaminases and alkaline phosphatases were observed at different dose levels, but none of these events was considered to be drug-related.

One patient who was treated at the 48 mg/m^2/day dose level experienced a Fanconi-like distal renal collecting tubule abnormality with grade 2 hyponatraemia, grade 1 hypophosphatemia and grade 1 hypokalaemia during course 2. The patient was withdrawn from the study due to excessive toxicity and progressive disease.

Grade 3 hypokalaemia occurred in 2 patients. One of them was treated at the 130 mg/m^2/day dose level, hypokalaemia occurred during course 1 and was considered to be DLT. The other patient was treated at the 96 mg/m^2/day dose level and hypokalaemia was observed during course 6. This event was linked with other side-effects, especially grade 2 diarrhoea and colitis which were considered to be the cause of the hypokalaemia. Only 2 cases of hypoglycaemia were considered to be possibly related to E7070. These events were observed only once in patients at the lowest dose levels (6 and 48 mg/m^2/day) and it was not clear whether this event occurred under fasted conditions or not. No significant changes were observed in holter monitoring, ECG and blood pressure readings. Cardiac monitoring did not reveal any evidence of QTc interval prolongation and no arrhythmia were recorded. No patients complained of symptoms consistent with alterations of intra-ocular pressure and repeated measurements were not performed.

3.4. Maximum tolerated dose

Since we did not observe any significant drug-related toxicity, the dose of E7070 could be increased by 100% steps from 6 to 200 mg/m^2/day. Several DLTs occurred in the first patient treated at 200 mg/m^2/day, including

leucocytopenia, neutropenia, thrombocytopenia, stomatitis and hypophosphatemia. This dose level was also identified as the MTD of E7070 in another phase I study which tested a 5-day daily i.v. infusion repeated every 3 weeks [7]. Therefore, a dose reduction to 160 mg/m^2/day was performed. At this dose level, 2 of 3 patients suffered from dose-limiting myelosuppression. The dose was then decreased to 130 mg/m^2/day. At this level, 6 of 6 patients experienced DLT, including grade 4 myelosuppression, grade 3 nausea and grade 3 hypokalaemia. Therefore, the 130 mg/m^2/day dose level was considered to be the MTD. None of the 5 patients treated at 96 mg/m^2/day encountered DLT and this dose level was recommended for phase II studies.

3.5. Response

21 patients were evaluable for response. There were no objective responses. 14 patients (67%) had progressive disease. 7 patients (33%) had stable disease after a 6-week period of treatment. The median duration of disease stabilisation was 18 weeks (range 6–24 weeks).

3.6. Pharmacokinetics

Pharmacokinetic data were obtained in 24 patients. Representative plasma concentration–time profiles at the different dose levels are depicted in Fig. 1. The mean E7070 C_{max} ranged from 144.7 ng/mL at the dose-level of 6 mg/m^2/day to 37 418 ng/ml at 200 mg/m^2/day (Table 5). The mean plasma $t_{1/2}$ could not be calculated at the lowest dose level, due to the short sampling period. In this study, E7070 displayed a relatively low and variable volume of distribution (range 11.8–95.8 l/m^2) and a relatively long and variable $t_{1/2}$ (range 16.3–67.1 h). Mean urinary excretion of unchanged E7070 accounted for less than 0.25% of the administered dose during the first 24 h after drug infusion. Renal clearance was negligible in all patients (<0.5 ml/min).

$AUC_{0-\infty}$, $t_{1/2}$, Vd_{ss}, MRT and Cl, displayed non-linear patterns. At doses above 24 mg/m^2/day, increasing doses led to a disproportional increase in exposure to the drug with an exponential decrease of mean clearance (from 36.23 ± 5.44 ml/min/m^2 at the dose of 24 mg/m^2/day to 3.70 ± 1.85 ml/min/m^2 at 160 mg/m^2/day) and half-life (from 20.0 ± 6.0 h at the dose of 24 mg/m^2/day to 39.2 ± 24.3 h at 160 mg/m^2/day). The non-linearity of the pharmacokinetics profile is illustrated in Fig. 2 where dose-normalised AUC is plotted against the administered dose/m^2. Despite the non-linearity of the pharmacokinetics, a high correlation coefficient between the dose and AUC (0.76) and dose/m^2 and AUC (0.79) were observed using linear regression.

3.7. Pharmacokinetic–dynamic analysis

We explored possible linear and non-linear relationships between pharmacokinetic parameters and haematological toxicities as measured by the percent decrease in leucocyte, neutrophil and platelet counts during cycle 1. Sigmoid relationships were the best fit between the AUC of E7070 and parameters describing the haematological toxicity, i.e.% decrease leucocytes, neutrophils and platelets (Figs. 3 and 4). The sigmoid curves for all three parameters indicated that clinically relevant decreases of leucocytes, neutrophils and platelets were likely to occur in patients at AUC values higher than 4000 μg.h/ml.

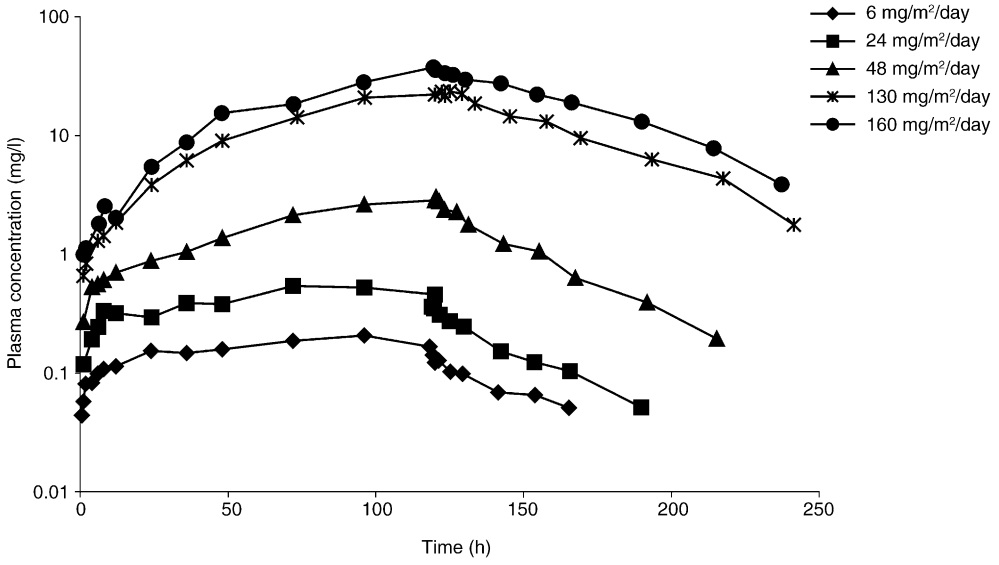

Fig. 1. Representative plasma concentration–time profiles of E7070 at the different dose-levels tested. The bell-shaped terminal phase of the curve especially at dose-levels higher than 24 mg/m^2/day indicate complex non-linear pharmacokinetics.

Table 5
E7070 pharmacokinetic parameters

Dose level (mg/m^2/day)	Patients N	C_{end} (ng/ml)	Half-life (h)	MRT (h)	Vd_{ss} (l/m^2)	Apparent Cl (ml/min/m^2)	$AUC_{0-\infty}$ (μg h/ml)
6	3	114.7±64.06	ND	ND	75.80±59.34	30.87±12.97	–
12	3	264.8±66.43	24.05[a]	81.44[a]	74.51±31.19	34.81±16.88	33.81[a]
24	3	562.3±38.13	20.04±5.955	80.04±3.81	42.83±10.35	36.23±5.44	55.98±77.9
48	3	2133±1126	25.31±3.802	93.36±15.84	39.76±5.94	24.69±16.17	207.0±105.6
96	3	11789±1166	20.00±0.344	108.8±4.5	25.68±2.01	8.72±1.44	934.5±150.9
130	5	15395±4832	21.87±6.736	107.7±10.74	25.28±5.67	9.44±3.54	1364±755.1
160	3	32639±8576	39.2±24.27	131.0±28.0	13.89±1.38	3.70±1.85	4226±1924.5
200	1	37418	21.59	114.4	23.78	3.53	3979

ND, not determined. Cl, denoted as apparent clearance because of the non-linear pharmacokinetics of E7070; Vd_{ss}, steady state volume of distribution; MRT, mean residence time; $AUC_{0-\infty}$, area under curve extrapolated up to infinity.

[a] In all of the patients of the 6 mg/m^2/day group and in 2 out of 3 patients in the 12 mg/m^2/day group, the half-life could not be estimated as the sampling period was too short (initially up to 48 h after the end of infusion).

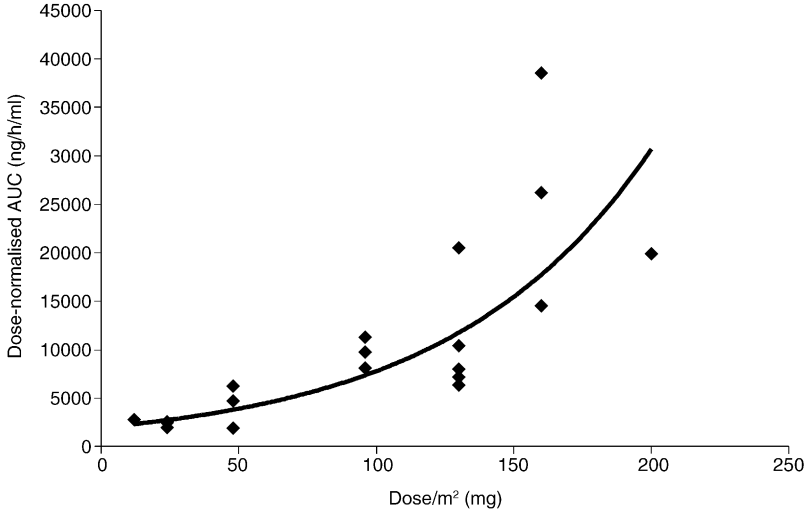

Fig. 2. Dose-normalised AUC (extrapolated to infinity) versus the dose/m^2, indicating non-linear increase of the AUC with dose especially at dose-levels higher than 24 mg/m^2/day.

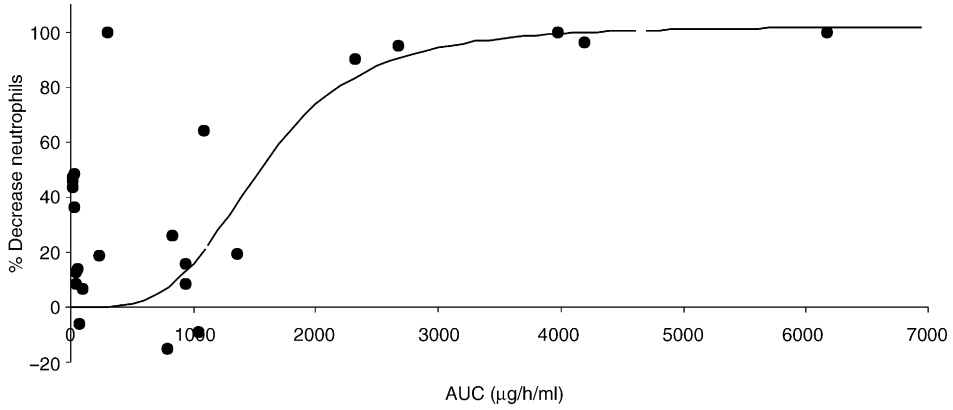

Fig. 3. Neutrophil counts (ANC) versus the AUC (extrapolated up to infinity). The sigmoid E_{max} model revealed the best fit between the AUC and the % decrease ANC.

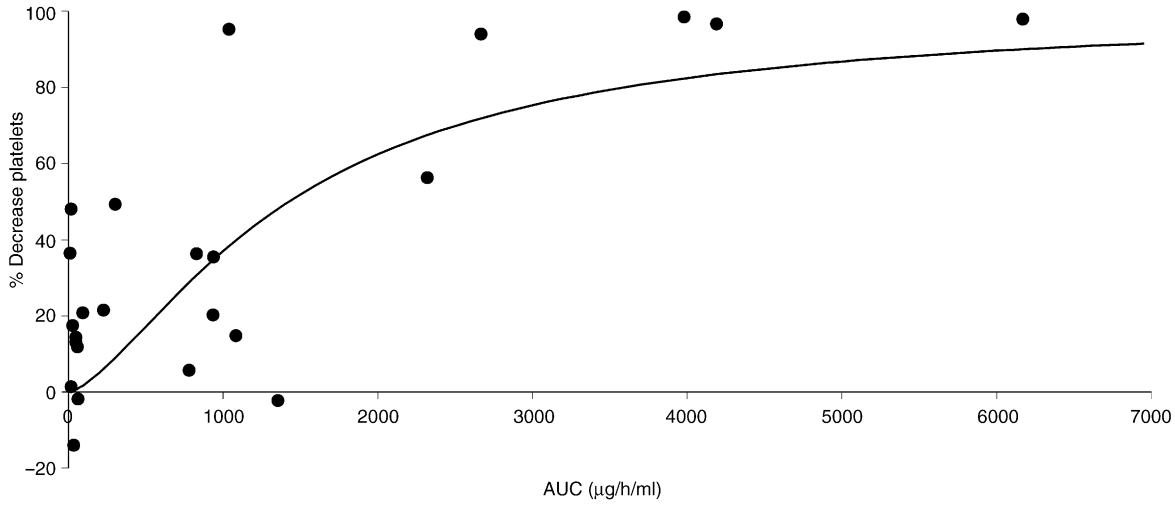

Fig. 4. Platelet count (Thr) versus the AUC (extrapolated up to infinity). The sigmoid E_{max} model revealed the best fit between the AUC and the % decrease Thr.

4. Discussion

In this study, testing a 5-day continuous infusion schedule, the MTD of E7070 was 130 mg/m^2/day. When compared with the other schedules of administration tested, this MTD was the lowest dose obtained (800 mg/m^2 3-weekly to 1000 mg/m^2 3-weekly) [7–9]. This may reflect an increased toxicity of E7070 when administered as a continuous infusion. As with other administration schedules, the DLTs in this phase I study were principally haematological. In all cases, these haematological toxicities were of a short duration, and reversible.

Non-haematological side-effects were grade 1 or 2 nausea and vomiting, and asthenia. We observed some biochemical disturbances, principally hypokalaemia, which were consistent with the ability to inhibit carbonic anhydrase (E7070 Investigator's Brochure Edition 6, 2002), but were more marked in this study than in other administration schedules tested. Cumulative toxicities could not be definitely assessed due to the small number of patients receiving more than four cycles of treatment.

As E7070 has structural similarity with chloroquinoxaline sulfonamide, intensive cardiovascular monitoring and blood glucose monitoring were performed. There were no significant cardiovascular changes during this study. E7070-related hypoglycaemia was observed in 2 patients who were treated at low dose levels (6 and 48 mg/m^2/day). However, blood glucose monitoring was extremely difficult and a wide range of values were recorded. Patients were not requested to fast prior to the blood samples being taken for blood glucose measurements and the time of the last meal was not recorded. The uncertainty of these glucose values did not allow any firm conclusions to be drawn in this study.

As E7070 was suspected to increase intra-ocular pressure in preclinical safety studies, an opthamological follow-up was designed in the protocol. No patient complained of symptoms consistent with intra-ocular pressure and repeat measurements were not performed. Results of repeated measurements in other phase I studies with E7070 did not show any change in intra-ocular pressure after exposure to the drug [7].

Pharmacokinetic parameters of E7070 including $AUC_{0-\infty}$, $t_{1/2}$, MRT, Vd_{ss} and Cl, displayed non-linear patterns with doses above 24 mg/m^2/day. Increasing the dose led to a disproportional exposure to the drug with a decrease in clearance and increase in the terminal half-life. This behaviour was consistent between species and has already been observed in mice, rats and dogs (J.H.M. Schellens, the Netherlands Cancer Institute) and in the other phase I studies [7–9]. Saturation of the metabolism of E7070 at higher doses was proposed to explain the non-linear pharmacokinetic profile of E7070 [10]. Further studies of the distribution and metabolism of E7070 in humans are warranted.

Pharmacodynamic analysis indicated relevant pharmacokinetic–pharmacodynamic relationships between the decrease of leucocytes, neutrophils and platelets and E7070 AUCs higher than 4000 μg h/ml.

No objective responses were observed in this group of heavily pretreated patients. One-third of evaluable patients had stable disease, which is a lower proportion than that reported for other administration schedules. Concentration time plots of E7070 in plasma demonstrated that the peak concentration of E7070 that was achieved *in vivo* using this route of administration was below that required to kill tumour cell lines in culture. As a result of this finding and the limited efficacy seen during this study, this schedule of administration has not been selected for phase II evaluation. Further studies comparing the efficacy of different E7070 schedules are ongoing.

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