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Short communication

A phase II study of sulofenur, a novel sulfonylurea, in recurrent epithelial ovarian cancer

Mary ER O'Brien[1], Janet Hardy[1], Sylvia Tan[1], Jackie Walling[1], Brian Peters[2], Sarah Hatty[2], and Eve Wiltshaw[1]

[1] Department of Medicine, The Royal Marsden Hospital, Fulham Rd, London, UK
[2] Lilly Research Centre Ltd, Surrey, UK

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Summary. A total of 16 patients with recurrent epithelial ovarian cancer were treated with sulofenur (LY 186641), a novel oral sulfonylurea. All subjects had received previous chemotherapy. Anaemia occurred in all 16 patients, 14 of whom required a blood transfusion, and 2/16 patients received methylene blue for breathlessness due to methaemaglobinaemia. Treatment was discontinued in 2/16 cases due to rising liver enzyme values, which reverted to normal on cessation of the drug. There was no nausea or alopecia. Only two minor responses were seen. Plasma drug levels were insufficient to result in anti-tumour activity as extrapolated from animal data. Further studies that attempt to increase the bioavailability and improve the therapeutic index are warranted.

Introduction

There is a need for new drugs in the treatment of epithelial ovarian cancer (EOC). At present cisplatin is the main component of treatment regimens, producing response rates of around 60%, with only 10%–15% of patients surviving for more than 5 years [8]. New agents are usually assessed in relapsed patients. However, in ovarian cancer it is difficult to obtain a response in the presence of resistance to or relapse shortly after cisplatin-based treatment. Duration of the response to initial chemotherapy has been shown to be the most important prognostic factor in predicting which patients might respond to second-line therapy [2]. The best rates of response (50%) to a rechallenge with cisplatin-based treatment are seen in patients who have achieved a first remission lasting 18 months or longer [3]. In general, patients entered in phase II studies are not selected for the duration of a prior response to chemotherapy, but activity in the range of 10%–20% would be expected for an active drug in an unselected group of patients.

Offprint requests to: M. E. R. O'Brien, Dept. of Medicine, Royal Marsden Hospital, Fulham Rd, London, SW3 6JJ, UK

Sulofenur [LY 186641; *N*-(5-indanylsulfonyl)-*N'*(4-chlorophenyl)-urea], is a diarylsulfonylurea that was developed after its anti-cancer activity had been discovered during the Lilly screening process. It was found to exert in vitro anti-cancer activity against a broad spectrum of murine tumour models, particularly against the M5 ovarian model [4]. Activity was also noted against human lung, colon and mammary xenografts and against previously treated stage IV human ovarian cancer during phase I studies [4]. The mechanism of action of sulofenur is at present unknown.

In phase I studies investigating oral sulofenur, the dose-limiting toxicity was methaemaglobinaemia and anaemia. Abnormal liver function was also observed, but alopecia was absent [7]. The present report describes a phase II study of sulofenur in 16 patients with relapsed or cisplatin-resistant ovarian cancer.

Patients and methods

Patients exhibiting the following features were eligible: histologically confirmed EOC, an age of 18–75 years, a WHO performance status of 0–2, a life expectancy of >3 months, adequate bone marrow reserve, normal glucose-6-phosphate dehydrogenase levels, methaemaglobin levels amounting to <2% of haemaglobin values, documented progressive disease and treatment with only one previous cytotoxic drug regimen. All patients gave informed written consent to partipate. As the drug was given orally, patients who were vomiting or had intestinal obstruction were ineligible. The schedule and dose used was 700 mg/m^2 given orally for 14 days every 3 weeks [1]. Patients had to receive two courses to be eligible for response assessment.

We began recruiting patients for this study in September 1989. In all, 13 individuals with recurrent disease were ineligible for the following reasons: haemaglobin levels of <10.0 g/dl (n = 2), low glucose-6-phosphate dehydrogenase values (n = 2), methaemaglobin levels amounting to >2% of haemoglobin values, (n = 3), low red blood cell folate values (n = 1), sub-acute obstruction preventing the intake of tablets (n = 3), ischaemic heart disease (n = 1) and a WHO performance status of >2 (n = 1). The remaining 16 subjects were entered into the study.

The patients' characteristics and details of their previous responses to treatment are shown in Table 1. Of the 16 patients, 14 showed an initial documented response to cisplatin compounds, including 5 subjects who achieved complete remissions, 3 of which lasted longer than 18 months.

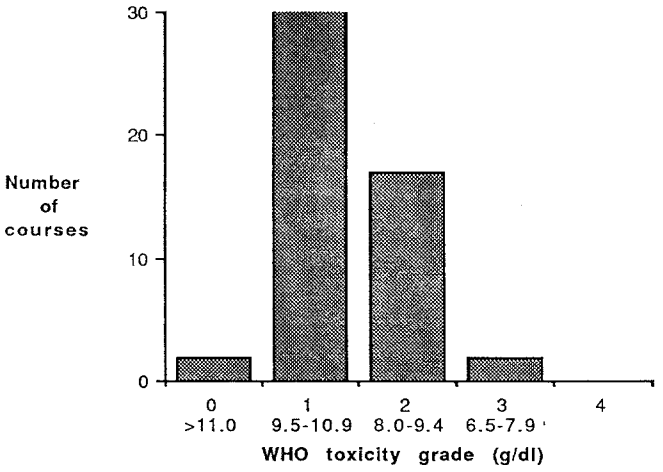

Fig. 1. Incidence of anaemia over all courses according to WHO grade (in all, 3 patients had grade 1 anaemia prior to treatment; the rest had grade 0 anaemia)

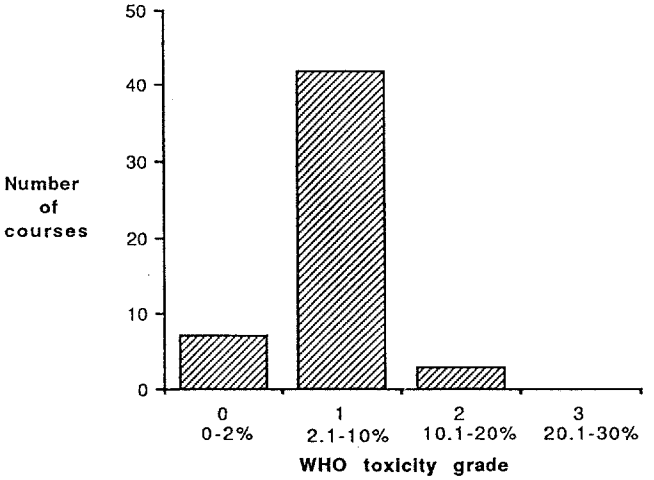

Fig. 2. Incidence of methaemaglobinaemia expressed as a percentage of all courses according to WHO grade

All subjects were treated as outpatients and were monitored weekly for haematology (including methaemaglobin), biochemistry and liver function. Response was assessed using WHO criteria. Tumour size was assessed using computerised tomographic (CT) scans and serum CA 125 determinations after each two courses of treatment.

Trough plasma levels of sulofenur and its hydroxy and keto metabolites were determined in blood samples taken on days 0, 7, 14 and 21 using a modification of the high-performance liquid chromatographic (HPLC) methodology of Taylor et al. [7]. The elution required two buffers: buffer A (75% 0.025 M sodium phosphate, pH 7, and 25% acetonitrile) and buffer B (50% 0.025 M sodium phosphate, pH 7, and 50% acetonitrile). A flow rate of 1.0 ml/min was used for the first 19.5 min, followed by 1.5 ml/min at 19.6 min and 1.0 ml/min at 30 min. The elution profile for buffer A was 100% at time zero, 10% at 18 min and 100% at 19.6 min, and that for buffer B was 0 at time zero, 90% at 18 min and 0 at 19.6 min.

Results

A total of 16 patients were entered, but 1 (patient 2) was ineligible for response assessment as she completed only 2 days of treatment before developing intestinal obstruction. The median age of our subjects was 56.5 years (range, 40–70 years). All patients had previously been treated with cisplatin or carboplatin (Table 1). In addition, two individuals had undergone pelvic radiotherapy and one patient had received but did not respond to cyproterone acetate. The median time from the original diagnosis to the start of treatment with sulofenur was 16 months (range, 8–66 months). The median duration of treatment was 9 weeks (range, from 2 days to 24 weeks). The reasons for discontinuation of therapy included bowel obstruction (n = 1), liver toxicity (n = 2) and progressive disease (n = 13).

The haematological toxicity encountered is shown in Fig. 1. All 16 patients developed anaemia of at least WHO grade 1 (erythrocytes, 9.5–10.9 g/dl) at some stage during treatment, and 14/16 required a blood transfusion. Neutropenia was mild, involving 7 cases of WHO grade 1 (neutrophils, $3.0–3.9 \times 10^9$/l) – 2 patients had presented

Table 1. Patients' characteristics and details of previous treatment

Patient number	Initial stage	Histology	Differentiation	Residual disease after initial surgery	Response to platinum	Response (months)	Response to sulofenur
1	III	Serous	Mod	>5 cm	PR	3	MR
2	III	α-Serous	Poor	Biopsy	PR	17	Bowel obs (2 days)
3	IV	Serous	Mod	>5 cm	PR	7	MR
4	III	Serous	Poor	<2 cm	CR	15	NC
5	IV	Serous	Mod	2–5 cm	PR	8	PD
6	III	Adeno	Poor	<2 cm	PR	12	PD
7	IV	Serous	Mod	>5 cm	PR	5	Liver toxicity
8	IV	Serous	Poor	Biopsy	PR	7	PD
9	IV	Adeno	Mod	>5 cm	PR	8	Liver toxicity
10	IV	Serous	Poor	Biopsy	PR	16	PD
11	III	Serous	Mod	>5 cm	CR	21	PD
12	IV	Serous	Mod	>5 cm	CR	37	PD
13	II	Serous	Poor	Nil	NE		PD
14	III	Serous	Mod	<2 cm	CR	11	PD
15	I	Clear-cell	Mod	Nil	PD		PD
16	III	Mucinous	Mod	2–5 cm	CR	19	PD

Adeno, Adenocarcinoma; Bowel obs, bowel obstruction; Mod, moderate; CR, complete response; PR, partial response; MR, <50% response; PD, progressive disease; NC, no change; NE, no evaluable disease; Nil, no initial surgery

Table 2. Liver function – worst toxicity noted per patient among a total of 16 patients

	Grade			
	1 1.26–2.5× normal	2 2.6–5× normal	3 5.1–10× normal	4 >10× normal
γ-GT[a]	6/16	2/16	1/16	1/16
Alkaline phosphatase[b]	8/16	1/16	2/16	0/16
Transaminase	6/16	3/16	2/16	1/16
Bilirubin	2/16	–	1/16	–

[a] γ-Glutamyl transpeptidase toxicity of grades 1 (1 patient) and 2 (1 patient) recorded prior to treatment

[b] Alkaline phosphatase grade 1 toxicity recorded in 1 patient prior to treatment

with grade 1 neutropenia prior to treatment – and 1 case of grade 2 (neutrophils, 2.0–2.9 × 10⁹/l). No thrombocytopenia was encountered. Methaemaglobin toxicity is shown in Fig. 2. Methaemaglobinaemia was usually mild, but two patients did require methylene blue for breathlessness due to this toxicity. Toxicity was recorded as the cumulative incidence according to WHO grade, but analysis of individual courses showed no evidence of any cumulative haematological toxicity. WHO grade 1 (1.26–2.5 times the normal value) elevations of liver enzymes occurred in 8/16 cases (Table 2). Two patients were withdrawn from the study because of liver toxicity, which reverted to normal on cessation of the drug. Patients experienced no nausea, vomiting or alopecia. One subject developed a deep venous thrombosis during sulofenur therapy and required treatment with warfarin; the prolongation of the prothrombin time suggested an interaction between these drugs, as would be expected for two highly protein-bound compounds.

Plasma levels of sulofenur and its hydroxy and keto metabolites during treatment are illustrated in Fig. 3a, 3b, and 3c, respectively. Responses to sulofenur are also shown in the last column in Table 1. There was no complete or partial response, but two minor responses were observed after two courses of sulofenur as documented by CT scans and falling CA 125 levels; however, these responses were not sustained with continued treatment. All of the other patients had progressive disease.

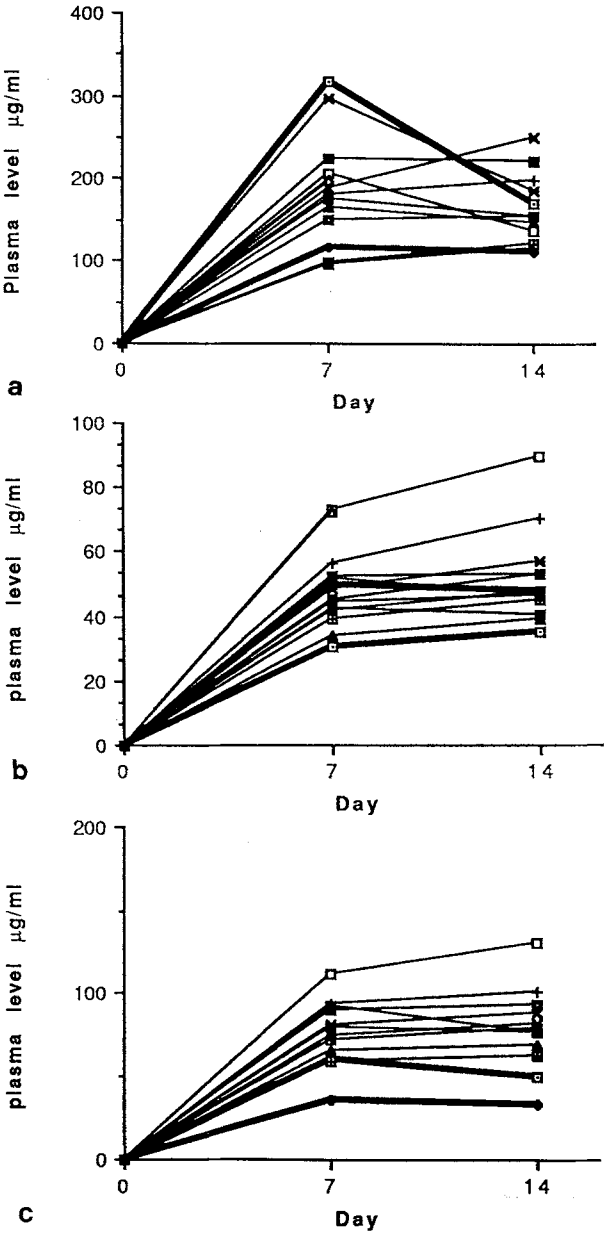

Fig. 3. a Trough plasma levels of the parent drug sulofenur. **b** Plasma levels of the hydroxy metabolite of sulofenur. **c** Plasma levels of the keto metabolite of sulofenur. *Bold lines* represent minor responders

Discussion

Sulofenur is a drug with an interesting preclinical data profile. Responses were obtained in phase I studies [4]. Phase II studies in a number of solid tumours are nearing completion in Europe and the United States. In the present phase II study of patients who had previously been treated with cisplatin but exhibited a good performance status, sulofenur was not active.

The most prevalent subjective toxicity was fatigue, which occurred in 14/16 patients; in all cases this could be ascribed to anaemia and/or methaemaglobinaemia. The abnormalities in liver function were a cause for concern, but from the patients' characteristics, we could not predict which subjects would be predisposed to this toxicity.

Among the 16 patients treated, 3 showed initial responses to cisplatin that lasted longer than 18 months and 14 displayed an initial documented response to cisplatin, including 5 who achieved a complete remission; both of these factors are thought to be useful in predicting the response to second-line therapy in ovarian cancer [2]. The two patients who showed initial minor responses eventually developed progressive disease on continuing treatment. Both of these subjects showed a symptomatic response in addition to the documented <50% reduction in tumour bulk; as both had initially exhibited >5 cm residual disease after surgery and had achieved only partial re-

sponses of short duration during treatment with cisplatin (symptom-free interval, 5 and 7 months, respectively), it would be considered unlikely that they would show a further useful response to other known chemotherapeutic agents. The 12 patients whose disease progressed during sulofenur treatment underwent further chemotherapy, but no response was documented; however, this is not surprising, as the anti-tumour activity of the regimen of choice at that time was low (Wiltshaw, personal communication).

In in vitro studies, Houghton et al. [5, 6] used 10% foetal bovine serum and demonstrated anti-tumour activity for sulofenur the order of found in the present clinical study; these authors also found that decreasing the level of foetal bovine serum resulted in increased cytotoxicity in vitro [6]. Sulofenur is known to be highly protein-bound [7], and the plasma levels were probably affected in vivo by human serum. In addition, plasma drug levels (Fig. 3) were considered to be insufficient to result in anti-tumour activity as extrapolated from animal data – a level of 400 μg/ml would have been required (Worzalla, personal communication). The plasma drug levels of the two patients who showed minor responses did not differ from those of the rest of the group, nor did these two individuals experience toxicity more severe than that encountered in the other patients.

This drug, which caused mild methaemaglobinaemia but no nausea, vomiting or alopecia, will not be tested further in patients with relapsed ovarian cancer. However, since the animal data indicated anti-tumour activity for sulofenur, further studies that attempt to increase the bioavailability and improve the therapeutic index are warranted.

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