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European Journal of Cancer 38 (2002) 57–63

European Journal of Cancer

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A randomised trial of oral versus intravenous topotecan in patients with relapsed epithelial ovarian cancer

M. Gore[a,*], A. Oza[b], G. Rustin[c], J. Malfetano[d], H. Calvert[e], D. Clarke-Pearson[f], J. Carmichael[g], G. Ross[h], R.A. Beckman[i], S.Z. Fields[i]

[a]*Royal Marsden Hospital, Fulham Road, London SW3 6JJ, UK*
[b]*Princess Margaret Hospital, Toronto, Canada*
[c]*Mount Vernon Hospital, Northwood, Middlesex, UK*
[d]*Albany Medical College of Union University, Albany, NY, USA*
[e]*Newcastle General Hospital, Newcastle-Upon-Tyne, UK*
[f]*Durham, NC, USA*
[g]*City Hospital, Nottingham, UK*
[h]*SmithKline Beecham Pharmaceuticals, Harlow, UK*
[i]*SmithKline Beecham Pharmaceuticals, Collegeville, USA*

Received 26 March 2001; accepted 3 April 2001

Abstract

A multicentre, randomised study was carried out in Europe, South Africa and North America to compare the activity and tolerability of oral versus intravenous (i.v.) topotecan in patients with relapsed epithelial ovarian cancer. Patients who had failed first-line therapy after one platinum-based regimen, which could have included a taxane, were randomised to treatment with either oral (p.o.) topotecan, 2.3 mg/m^2/day or i.v. topotecan 1.5 mg/m^2/day for 5 days every 21 days. Patients were stratified by prior paclitaxel exposure, interval from previous platinum therapy and tumour diameter. 266 patients were randomised. Response rates were 13% orally (p.o.) and 20% (i.v.) with a complete response in 2 and 4 patients, respectively. The difference in the response rates was not statistically significant. Median survival was 51 weeks (p.o.) and 58 weeks (i.v.) with a risk ratio of death (p.o. to i.v. treatment) of 1.361 (95% confidence interval (CI): 1.001, 1.850). Median time to progression was 13 weeks (p.o.) and 17 weeks (i.v.). The principal toxicity was myelosuppression although grade 3/4 neutropenia occurred less frequently in those receiving oral topotecan. Toxicity was non-cumulative and infectious complications were relatively infrequent. Non-haematological toxicity was generally mild or moderate. The incidence of grade 3/4 gastrointestinal events was slightly higher for oral than i.v. topotecan. Oral topotecan shows activity in second-line ovarian cancer and neutropenia may be less frequent than with the i.v. formulation. A small, but statistically significant, difference in survival favoured the i.v. formulation, but the clinical significance of this needs to be interpreted in the context of second-line palliative treatment. Oral topotecan is convenient and well tolerated and further studies to clarify its role are ongoing.

Keywords: Ovarian cancer; Topotecan

1. Introduction

The incidence of ovarian cancer is highest in women in North Eastern Europe and North America with 1 in 70 in the United States developing the disease. Ovarian malignancies in the Western world are of the epithelial type in almost 90% of cases [1]. Systemic chemotherapy following maximum surgical cytoreduction is the mainstay of treatment for advanced ovarian cancer and objective response rates to combination chemotherapy range from 60 to 80% in previously untreated patients [2]. However, the majority of women with advanced disease ultimately relapse and overall 5-year survival remains less than 30% [3]. Response rates to second-line single agent therapy for patients who relapse within 12 months of finishing their initial treatment are generally 15–20% and all patients who relapse will eventually die from their disease. In the early 1990s, paclitaxel was

* Corresponding author. Tel.: +44-207-808-2198; fax: +44-207-808-2475.
E-mail address: martin.gore@rmh.nthames.nhs.uk (M. Gore).

0959-8049/02/$ - see front matter
PII: S0959-8049(01)00188-5

developed and response rates of 20–30% were initially reported [4], although a subsequent larger European–Canadian study showed response rates of 15% [5]. Paclitaxel was considered the most active agent for this patient group during this period.

The topoisomerase-1 inhibitor, topotecan, showed activity in single agent phase II studies in patients with recurrent ovarian cancer [6–8] and a subsequent randomised trial demonstrated that topotecan (1.5 mg/m^2/day×5 every 21 days) had equivalent activity to paclitaxel at standard dosing (175 mg/m^2/3 h every 21 days [9]. The principal toxicity of topotecan is myelosuppression particularly neutropenia, but non-haematological toxicity is generally only of grade 1/2.

Recently, an oral formulation of topotecan has been developed which removes the need for daily physician visits. A phase I study identified 2.3 mg/m^2/daily for 5 days as the maximum tolerated dose (MTD) for oral topotecan [10]. A phase II non-randomised study of oral topotecan in patients with ovarian cancer that had relapsed within 12 months of finishing their first-line chemotherapy, showed a response rate of 22%, a median survival of 63 weeks and a lower incidence of grade 4 neutropenia compared with that seen with the intravenous (i.v.) formulation [11]. The current study was designed to compare the efficacy, safety and tolerability of oral topotecan compared with the standard i.v. regimen in a similar group of patients with relapsed ovarian cancer.

2. Patients and methods

2.1. Patients

The study was an open-labelled multicentre trial which was carried out in Europe, South Africa and North America. 79% of patients were enrolled in Europe or South Africa and 21% of patients were accrued in North America. Patients were eligible for the study if they had a histological diagnosis of epithelial ovarian cancer, originally International Federation of Gynecology and Obstetricians (FIGO) stage III or IV disease and had either progressed on first-line chemotherapy or had relapsed within 12 months of completing their initial treatment. First-line chemotherapy must have included a platinum compound, which could have been combined with a taxane. Patients were only allowed to have had one previous line of chemotherapy.

Patients were required to be at least 18 years of age, to have measurable disease with one lesion $\geqslant$2 cm in diameter (or $\geqslant$1 cm for skin lesions), an European Cooperative Oncology Group (ECOG) performance status $\leqslant$2 and a life expectancy of at least 3 months. Patients must not have received surgery, radiotherapy, chemotherapy or hormone therapy for 4 weeks prior to study entry, or 60 days in the case of prior immunotherapy. Patients were required to have adequate bone marrow, renal and hepatic function defined as haemoglobin $\geqslant$90 g/l, white blood cell (WBC) $\geqslant 3.5\times10^9$/l, neutrophils $\geqslant 1.5\times10^9$/l, platelets $\geqslant 100\times10^9$/l, creatinine $\leqslant$132.6 μmol/l (or creatinine clearance $>$1 ml/s) serum bilirubin $\leqslant$34.2 μmol/l and liver enzymes $\leqslant$2 times the upper limit of normal (or $\leqslant$5 times the upper limit of normal if liver metastases were present). Patients were excluded from study entry by the presence of malignancies at other sites (except for basal and squamous cell carcinoma of the skin and carcinoma *in situ* of the cervix), brain or leptomeningeal metastases, uncontrolled infection or other severe medical problems. Patients with peptic ulcers or other gastrointestinal conditions affecting absorption or motility, or patients receiving concomitant treatment for gastric or duodenal ulcers, were also excluded because one arm of the trial involved an oral medication.

The study was carried out in accordance with the Declaration of Helsinki, all patients gave written, informed consent to participation and separate approvals were obtained from all the Institutional Review Boards/Ethics Committees of participating centres.

2.2. Treatment

Randomisation to treatment with oral or i.v. topotecan (Hycamtin®, SmithKline Beecham Pharmaceuticals) was by telephone. Patients were stratified according to the patient's response to previous platinum chemotherapy, tumour size ($<$ or $\geqslant$5 cm in diameter) and whether or not the previous regimen had included a taxane. Response to previous therapy was categorised as platinum-refractory (patients with progressive or stable disease during initial chemotherapy), platinum-resistant (patients who responded and subsequently relapsed within 6 months of discontinuing initial chemotherapy) and platinum-sensitive (patients who had responded to initial therapy, but subsequently relapsed after more than 6 months).

Patients received either oral topotecan at a dose of 2.3 mg/m^2/day or i.v. topotecan, 1.5 mg/m^2/day for 5 days every 21 days. Dose reductions, in increments of 0.4 mg/m^2/day, orally (p.o.) or 0.25 mg/m^2/day, i.v., were made for grade 4 neutropenia associated with fever/infection or lasting $\geqslant$7 days, grade 3 neutropenia lasting beyond day 21, grade 3/4 thrombocytopenia or any non-haematological toxicity of grade 3/4 (excluding grade 3/4 nausea and vomiting). The daily dose could be increased in similar increments if, during the previous course, there had been no toxicity greater than grade 2.

The duration of treatment depended upon the response to therapy and was at the discretion of the investigator, although it was recommended that patients with stable disease should receive at least four courses of

treatment. In responding patients, treatment for at least two cycles beyond best response was recommended.

2.3. Evaluation of response

Tumours were evaluated by abdominal/pelvic computed tomography (CT) or magnetic resonance scan (MRI) scan, chest X-ray or photography. Lesions which had been evaluated at baseline by CT or MRI scan were re-assessed at the end of each alternate treatment course, and those evaluated by chest X-ray or photography were re-assessed at the end of every course. Response to treatment was evaluated using World Health Organization (WHO) criteria such that a complete response (CR) was the complete disappearance of all known measurable and evaluable disease determined by two measurements not less than 4 weeks apart, and a partial response (PR) was defined as a greater than 50% decrease in measurable lesion size for at least 4 weeks, with no simultaneous increase in a known lesion or appearance of new lesions or increase in evaluable disease. All claimed complete and partial responses were subjected to an independent, blinded radiological review.

Time to response, time to progression and survival were all measured from the time of the first dose of topotecan, and response duration was measured from the time of the first documented CR or PR to the first sign of disease progression.

Response rate was also evaluated by measurement of serial CA125 values. Response was defined by a 50% decrease in two samples, confirmed by a further sample, or a serial decrease over three samples of greater than 75%. The final sample had to be at least 28 days after the previous sample [12].

2.4. Toxicity assessment

Adverse events were collected throughout the study. Blood samples were taken for laboratory testing on days 1, 8 and 15 of each course and prior to the start of the following course. A complete blood count was performed on each occasion and blood chemistry tests were carried out on all but the day 8 samples. Toxicity was graded according to Common Toxicity Criteria (CTC) and subjective toxicities were assessed before each treatment cycle and 3–4 weeks after the last course of therapy.

2.5. Statistical analysis

The response rate for each treatment group was calculated, as well as the estimated percentage difference in response rates between the two groups with two-tailed 95% confidence intervals (CIs). Time-to-event data (time to response, response duration, time to progression and survival) were plotted by the Kaplan–Meier method. Cox's regression analysis was used to estimate the relative likelihood of an event occurrence. Patients for whom an event (relapse, progression or death) had not occurred at the cut-off date for inclusion in the analysis were censored at the time of last contact.

3. Results

3.1. Patient characteristics

A total of 266 patients were randomised to treatment; 135 received oral topotecan and 131 received i.v. topotecan (Fig. 1). The median age was 60 years in each group, approximately 60% of patients originally had FIGO stage III disease and more than 90% were of performance status 0 or 1. In each group, 30% of patients were platinum-refractory and 70% were either platinum-resistant or platinum-sensitive. Details of demographic and baseline characteristics are shown in Table 1.

3.2. Response

17 patients (13%) (95% CI: 7.6%, 19.1%) in the oral topotecan group and 26 (20%) (95% CI: 13.0%, 26.7%) in the i.v. topotecan group were confirmed by independent radiological review as having responded to treatment (Table 2). 2 patients in the oral group and 4 in the

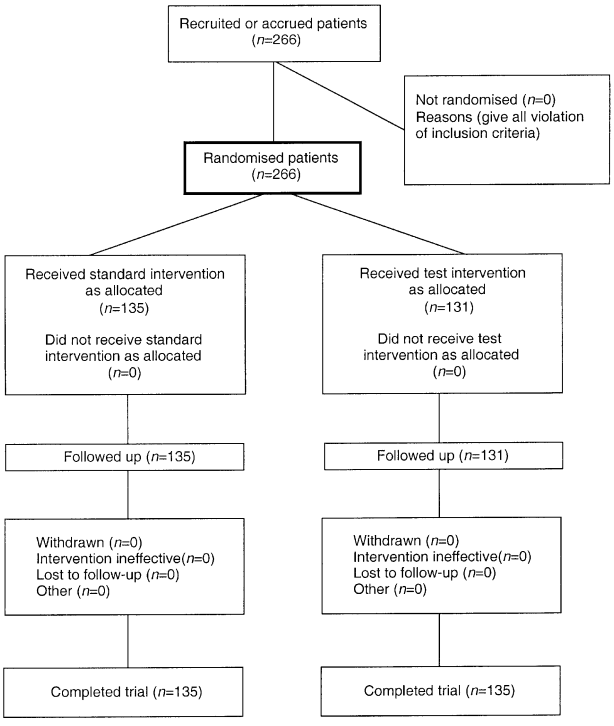

Fig. 1. Flow chart of the progress of patients through the trial (adapted from Ref. [17]).

Table 1
Demographic and baseline characteristics

	Treatment group	
	Oral topotecan ($n=135$)	i.v. topotecan ($n=131$)
Age (years): median (range)	60 (23–80)	60 (27–80)
FIGO Stage *n* (%):		
III	84 (62)	82 (63)
IV	43 (32)	42 (32)
Missing data	8 (6)	7 (5)
Performance status *n* (%):		
0	59 (45)	47 (35)
1	60 (46)	77 (57)
2	12 (9)	11 (8)
Tumour size (cm) *n* (%):		
<5	66 (49)	65 (50)
5–10	58 (43)	50 (38)
>10	10 (7)	11 (8)
Missing data	1 (1)	5 (4)
Classification of relapse *n* (%):		
Platinum-refractory	40 (30)	39 (30)
Platinum-resistant	37 (28)	36 (28–27)
Platinum-sensitive	58 (43)	56 (43)

FIGO, International Federation of Gynecology and Obstetricians; i.v., intravenous.

i.v. group obtained a complete response; none of these differences as statistically significant. Stable disease for 8 weeks or more was reported in a similar proportion of patients in each group (29% oral; 27% i.v.).

Response rates to oral and i.v. topotecan were similar in patients with platinum-refractory or -resistant disease. In platinum-sensitive patients, i.v. topotecan had a higher response than the oral formulation, 36% versus 19% (Table 3), which was not statistically significant. There was no clear correlation between largest tumour diameter at baseline and response to treatment in either group, although none of the complete responders had a tumour larger than 5 cm in diameter (tumour diameter data from 1 patient was missing). For both the oral and i.v. groups, the activity was similar in the sub-group of patients who had received paclitaxel in combination with platinum as first-line line therapy.

Table 2
Response to topotecan (number (%) of patients)

Response	Treatment group	
	Oral topotecan ($n=135$)	i.v. topotecan ($n=131$)
Complete response (CR)	2 (1%)	4 (3%)
Partial response (PR)	15 (11%)	22 (17%)
Overall response	17 (13%)	26 (20%)
95% CI	7.6–19.1%	13.0—26.7%
Stable disease (SD)	39 (29%)	35 (27%)
Progressive disease (PD)	65 (48%)	59 (45%)
Not evaluated	14 (10%)	11 (8%)

95% CI, 95% confidence interval; i.v., intravenous.

Table 3
Response to topotecan according to baseline stratifying factors

	Treatment group			
	Oral topotecan ($n=135$)		i.v. topotecan ($n=131$)	
	n	Response (%)	*n*	Response (%)
Platinum-sensitivity				
Refractory	40	3 (8)	39	2 (5)
Resistant	37	3 (8)	36	4 (11)
Sensitive	58	11 (19)	56	20 (36)
Tumour size				
<5 cm	66	10 (15)	65	15 (23)
⩾5 cm	68	7 (10)	61	10 (16)
First-line treatment				
Platinum/paclitaxel	53	8 (15)	54	12 (22)
All patients	135	17 (13)	131	25 (19)

i.v., intravenous.

A number of patients responded, but the response was not confirmed on subsequent scans for a variety of reasons. The response rate was 16% (p.o.) and 21% (i.v.) if these 'best responses' were taken into consideration.

Best response by CA125 for those patients who were evaluable according to CA125 was 28/99 (28%) for patients who received i.v. topotecan and 21/105 (20%) for patients who received oral topotecan. An intent-to-treat analysis reduced the response rate by CA125 to 28/131 (21%) for the i.v. arm and 21/135 (16%) for the oral arm.

Median time to response was 12 weeks following treatment with oral topotecan and 8 weeks following treatment with the i.v. topotecan, and the median response duration was 34 and 26 weeks, respectively (Table 4). Median time to progression was 13 weeks in the oral and 17 weeks in the i.v. arm, and median survival was 51 and 58 weeks ($P=0.033$), respectively.

3.3. Toxicity

The 135 patients treated with oral topotecan received a total of 729 courses of treatment with a median number of four courses (range: 1–23), and the 131 patients treated with i.v. topotecan received a total of 778 courses of treatment with a median number of six courses (range: 1–26). In the oral treatment group, 60% of courses were administered at the starting dose and 19% were at doses above the starting dose. In the i.v. topotecan arm, the percentage of courses at the starting dose was similar (58%), but the percentage of courses at an increased dose was lower (4%). Dose reductions occur-

Table 4
Time to response, response duration, time to progression and survival (weeks)

	Treatment group			
	Oral topotecan ($n=135$)		i.v. topotecan ($n=131$)	
	n	Median (range)	n	Median (range)
Time to response (weeks)	17	12 (5.6–18.1)	26	8 (5.1–25.4)
Response duration (weeks)	17	34 (13.1–62.3)	26	26 (6.6–52.7)
Time to progression (weeks)	135	13 (1.6–76.6)	131	17 (0.1–91.6)
Survival (weeks)	135	51 (1.6–109.0)	131	58 (0.3–120.0)

i.v., intravenous.

red in approximately 10% of courses in both treatment groups (9%, p.o.; 11%, i.v.).

Neutropenia and/or leucopenia were the principal haematological toxicities in both treatment groups, although grade 4 neutropenia occurred less frequently in the oral group (50% versus 84% of patients; 15% versus 51% of courses, (Table 5). The mean neutrophil nadir was 1.5×10^9/l following oral topotecan compared with 0.7×10^9/l in patients treated with i.v. topotecan. There was no clear evidence of cumulative toxicity in either treatment group. i.v. antibiotics were administered in fewer than 10% of courses with a slightly lower usage in the oral group (6% versus 8%). Infectious complications were not common and the proportions of courses with sepsis or with infection/fever of grade 2 were 5% in the oral group and 8% in the i.v. group. There were seven deaths in the study reported as being due to haematological toxicity, two in the oral group and five in the i.v. group.

Occurrence of grade 3/4 thrombocytopenia and anaemia was similar in the oral treatment group (thrombocytopenia; 15% of courses, anaemia; 13% of courses) as in the i.v. treatment group (thrombocytopenia; 15% of courses; anaemia; 11% of courses). Platelet transfusions were given in 3% of courses in the oral group and 3% of courses in the i.v. arm and red blood cell (RBC) transfusions in 21 and 20% of courses, respectively.

Gastrointestinal disturbances were the predominant non-haematological toxicities and there was a tendency for the incidence to be higher with the oral rather than the i.v. topotecan administration (Table 6). Most adverse events, however, were of mild to moderate severity and the incidence of grade 3/4 non-haematological toxicities generally occurred in less than 10% of patients. In the case of nausea, diarrhoea, vomiting and fever, grade 3/4 toxicities occurred in slightly more patients receiving oral topotecan than those receiving i.v. topotecan (nausea 9% versus 5%; diarrhoea 10% versus 5%; vomiting 7% versus 3%; fever 10% versus 5%, respectively).

Table 5
Grade 3/4 haematological toxicity, worst grade per patient and per course

	Treatment group			
	Oral topotecan		i.v. topotecan	
	Grade 3	Grade 4	Grade 3	Grade 4
Patients	($n=135$)		($n=131$)	
Neutropenia	40 (30%)	67 (50%)	15 (11%)	110 (84%)
Leucopenia	59 (44%)	28 (21%)	78 (60%)	40 (31%)
Thrombocytopenia	30 (22%)	27 (20%)	27 (21%)	23 (18%)
Anaemia	51 (38%)	5 (4%)	43 (33%)	10 (8%)
Courses	($n=729$)		($n=778$)	
Neutropenia	190 (26%)	106 (15%)	249 (32%)	393 (51%)
Leucopenia	163 (22%)	31 (4%)	371 (48%)	68 (9%)
Thrombocytopenia	70 (10%)	42 (6%)	90 (12%)	29 (4%)
Anaemia	85 (12%)	7 (1%)	78 (10%)	10 (1%)

i.v., intravenous.

4. Discussion

The response rate obtained in the current study with i.v. topotecan (20%) was very similar to the response rate of 21% shown in an earlier randomised, comparative study of i.v. topotecan versus paclitaxel [9]. This trial was carried out in a similar population of patients with ovarian cancer except they had not received prior

Table 6
Non-haematological toxicity, worse grade per patients

	Treatment group			
	Oral topotecan ($n=135$)		i.v. topotecan ($n=131$)	
	All grades	Grades 3/4	All grades	Grades 3/4
Nausea	92 (68%)	12 (9%)	80 (61%)	6 (5%)
Diarrhoea	76 (56%)	13 (10%)	40 (31%)	6 (5%)
Vomiting	74 (55%)	10 (7%)	52 (40%)	4 (3%)
Alopecia	72 (53%)	10 (7%)	68 (52%)	8 (6%)
Fatigue	50 (37%)	5 (4%)	50 (38%)	5 (4%)
Abdominal pain	49 (36%)	9 (7%)	39 (30%)	9 (7%)
Constipation	47 (35%)	4 (3%)	42 (32%)	2 (2%)
Fever	38 (28%)	14 (10%)	31 (24%)	7 (5%)

i.v., intravenous.

paclitaxel and a response rate of 14% was achieved in the patients treated with paclitaxel in that study [9]. That study [9] and the current report have demonstrated similar toxicities in patients treated with i.v. topotecan. These were mainly haematological, principally neutropenia, which was generally manageable and non-cumulative. The response rate obtained in the oral arm of the current study was lower than that for i.v. topotecan (13% versus 20%), but was not statistically significant. A small, but statistically significant, difference in survival between formulations was also observed.

Of those patients who responded in the current study, 50% on the oral arm and 46% on the i.v. arm responded after four cycles of treatment. Exceptionally, responses have been noted at cycle 8. It is therefore recommended that patients receiving therapy with topotecan receive at least four cycles, provided that there is no progression of the tumour and that the therapy is tolerated. There is circumstantial evidence that some patients in this study, particularly on the oral arm (5 oral, 2 i.v.), might have been removed from study before they had received the optimal number of cycles of therapy with topotecan.

In a phase II study of oral topotecan in a similar population, the response rate in 116 patients was 22% [11] which is comparable to the response rate seen with the i.v. arm of the current study, and the median survival was 63 weeks. Oral topotecan was also shown to have similar activity (23%) to i.v. topotecan (15%) in a phase II study in small cell lung cancer patients [13].

The CA125 response rate seen in this study was higher than the clinical response rate in both the oral and i.v. arms of the study. When the same CA125 criteria were used to study 14 different drugs including topotecan in 19 other trials, a similar trend was noted [12]. This difference can be partly explained by only counting patients evaluable according to CA125 in the denominator for calculating the CA125 response rate. The only bias that might cause concern is if a higher than expected number of patients came off study before they had three CA125 samples and were thus counted as not evaluable. However, an intention-to-treat analysis reduces the CA125 response rates to 21% with i.v. and to 16% for oral topotecan, closer to the clinical response rates. The conclusions regarding the efficacy of topotecan are identical whether standard or CA125 criteria are used.

In the current study, toxicity in both the oral and the i.v. topotecan treatment groups was mainly haematological, principally neutropenia with grade 4 neutropenia occurring in a higher proportion of i.v. courses (51%) than oral courses (15%). A lower incidence of grade 4 neutropenia with the oral formulation as opposed to the i.v. drug, has also been observed in phase II studies of the oral formulation in ovarian cancer [11] and in a randomised phase II comparison of the formulations in relapsed, potentially chemosensitive small cell lung cancer patients [13]. These differences in the severity of the haematological toxicity are consistent with the major pharmacokinetic differences between oral and i.v. topotecan that have been reported, namely, a lower Cmax and area under the curve (AUC) for oral topotecan. In particular, the lower Cmax may correlate with the reduced neutrophil toxicity, in that neutrophil killing may require a higher peak level to overcome the activity of surface efflux pumps [14,15].

The relative reduction in toxicity associated with oral topotecan and its ease of administration suggests a potential for prolonged treatment with this compound. Such a strategy might improve survival in these patients because there have been reports of longer duration of therapy being associated with a reduction in mortality [16]. Obviously, however, only further randomised studies can resolve this issue.

Oral topotecan is active as second-line therapy in ovarian cancer and well tolerated. The observed response rate was numerically lower than that for i.v. topotecan and a small, but statistically significant, survival difference in favour of the i.v. formulation was seen. However, second-line therapy in patients with relapsed ovarian cancer is always palliative and oral topotecan is well tolerated and convenient. Studies are currently underway to investigate oral topotecan in other tumour types and novel schedules and combinations are being studied. In addition, studies are now exploring the possibility of prolonged oral dosing because of the cell cycle-specific mechanism, convenience of administration and favourable toxicity profile. Finally, ongoing studies with i.v. topotecan will address its utility as consolidation after standard induction therapy for ovarian cancer, an approach for which oral topotecan would be well suited.

Acknowledgements

The authors wish to acknowledge the numerous individuals whose contributions made this study possible. This study was supported by a grant from SmithKline Beecham Pharmaceuticals.

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