Eur Respir J 2006; 27: 1183–1189
DOI: 10.1183/09031936.06.00015605

Efficacy of a toxicity-adjusted topotecan therapy in recurrent small cell lung cancer

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ABSTRACT: The present prospective multicentre trial investigated whether topotecan, given at a starting dose of 1.25 mg·m^{-2} with individual dose adjustment, can improve safety in patients with relapsed/refractory small cell lung cancer without loss of efficacy.

Patients received topotecan intravenously on days 1–5, every 21 days, for up to six courses. In the absence of relevant haematotoxicities, topotecan was increased to 1.5 mg·m^{-2} and reduced to 1.0 mg·m^{-2} in case of severe haematotoxicities.

Of 170 recruited patients, 73.2% had stage IV disease and 63.4% had platinum-containing pre-treatment. Patients received a total of 521 courses. In 72.6% of those courses, the dose remained at 1.25 mg·m^{-2}; in 9.1% it was reduced and in 18.3% it increased. Overall response rate was 14.1% including one complete response; 28.8% had stable disease. Median duration of response was 13.6 weeks and median survival was 23.4 weeks. Clinical benefit was obvious for sensitive as well as for refractory patients. Haematotoxicity of grade 3 or 4 was clearly lower compared with the standard dose of 1.5 mg·m^{-2}.

In conclusion, topotecan at a dose of 1.25 mg·m^{-2} appears to be as effective as the dose of 1.5 mg·m^{-2}, but with reduced toxicity. Since patients with recurrent small cell lung cancer have a poor prognosis, they benefit especially from good tolerability.

KEYWORDS: **Second-line therapy, small cell lung cancer, topotecan**

Small cell lung cancer (SCLC) is considered to be among the most chemosensitive solid tumours [1]. With combination chemotherapy, such as platinum/etoposide or cyclophosphamide/doxorubicin/etoposide, objective response rates of 20–90% are observed, with a median survival of ~10 months. However, the majority of patients will experience tumour recurrence after successful therapy [2–4]. The prognosis with second-line treatment was analysed by HUISMAN *et al.* [5] from 21 published phase II studies, including 1,749 patients showing response rates of 20%. Response to second-line therapy most likely depends on response to first-line treatment and length of the treatment-free interval. Patients developing disease progression within 3 months after first-line therapy are classified as refractory. Patients with disease progression >3 months after the last treatment of first-line therapy, which has induced an objective response, are classified as sensitive [3]. Since refractory patients have a smaller chance of responding to any drug than sensitive patients, stratification between sensitive and refractory patients is necessary to describe the efficacy of a tested regimen. Topotecan (Hycamtin®; GlaxoSmithKline, Munich, Germany) is a specific inhibitor of the nuclear enzyme topoisomerase I, which interferes with DNA replication and transcription. Inhibition of this enzyme produces lethal DNA damage [6]. Topotecan was reported to be effective as second-line treatment for SCLC [7]. In a randomised phase III study, topotecan (1.5 mg·m^{-2} *i.v.*, days 1–5, every 21 days) was at least as effective as the three-drug regimen of cyclophosphamide 1,000 mg·m^{-2}, doxorubicin 45 mg·m^{-2} and vincristine 2 mg (CAV). Response rate was 24.3% in the topotecan arm and 18.3% in the CAV arm. Median survival was 25 weeks for topotecan and 24.7 weeks for CAV. The present study demonstrated that topotecan has significant advantages in controlling disease-related symptoms [8]. In three studies, a total of 264 evaluable patients with recurrent SCLC were stratified as either refractory (126 patients) or sensitive (138 patients), according to their response to first-line therapy. All patients received *i.v.* topotecan 1.5 mg·m-$^{-2}$ on days 1–5, every 21 days. The efficacy is summarised in table 1 [9–11]. The most frequent adverse event of the 1.5 mg·m^{-2}·day^{-1} regimen in all studies was neutropenia grade 3/4. VON PAWEL *et al.* [12] reported an incidence of grade 4 neutropenia in 67.3% of patients (32.5% of

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Received:
February 10 2005
Accepted after revision:
January 29 2006

SUPPORT STATEMENT
The present study was supported by an unrestricted grant from GlaxoSmithKline, Munich, Germany.

European Respiratory Journal
Print ISSN 0903-1936
Online ISSN 1399-3003

courses) in their phase II study [12] and 70.2% (38.7% of courses) of patients in their phase III study [8]. ARDIZZONI *et al.* [11] reported grade 4 neutropenia in 46.9% of courses. Grade 4 thrombocytopenia was also shown in 8–11% of courses [11, 12]. Infection associated with grade 4 neutropenia occurred in 28% of patients and 8.7% of courses in the topotecan arm of a previous comparative phase III trial, along with four treatment-related deaths (3.7% of patients) [8]. ARDIZZONI *et al.* [11] observed infection in 6% of courses and one treatment-related death. PEREZ-SOLER *et al.* [13] reported a lower incidence of haematological toxicity when topotecan was administered in a dose of 1.25 mg·m^{-2} *i.v.* on days 1–5 in patients with SCLC refractory to etoposide/platinum. In 28% of courses, grade 4 neutropenia was observed, but there were no episodes of neutropenic fever and no treatment-related deaths [13].

The objective of this multicentre phase II trial was to evaluate prospectively the efficacy and safety of topotecan starting with a starting dose of 1.25 mg·m^{-2} and with dose adjustment in accordance with toxicity. Patients with recurrent or refractory SCLC were stratified according to pre-treatment with a platinum-containing or platinum-free regimen and their response to pre-treatment.

PATIENTS AND METHODS

Patient eligibility

Patients with histologically and/or cytologically documented SCLC, which has recurred or progressed after first-line chemotherapy, were eligible. Further inclusion criteria were: bi-dimensional measurable disease (minimum size of lesion= 2×2 cm); male or female patients aged 18–75 yrs; Eastern Cooperative Oncology Group (ECOG) performance status ⩽2; written informed consent according to the local institutional ethics committee requirements; leukocyte count ⩾4,000 cells·μL^{-1}; platelet count ⩾100,000·μL^{-1}; haemoglobin concentration ⩾9.0 g·dL^{-1}; and creatinine clearance ⩾60 mL·min^{-1}.

TABLE 1 Efficacy of *i.v.* topotecan (1.5 mg·m^{-2}·day^{-1}, on days 1–5) in second-line small cell lung cancer

First author [ref.]	Subjects n	CR	PR	OR %	SD %	Survival weeks#
ECKHARDT [9]						
Refractory	38¶		1	2.6	45	20.4
Sensitive	36+	3	4	19.4	36	26.6
Total	74			10.8	40.5	NR
VON PAWEL [10]						
Refractory	41¶		1	2.4	NR	16.3
Sensitive	57+	1	7	14.0	NR	25.7
Total	98			9.2	27	21.6
ARDIZZONI [11]						
Refractory	47¶	1	2	6.4	40	18.8
Sensitive	45+	6	11	37.8	31	27.6
Total	92			21.7	35.9	21.6

CR: complete response; PR: partial response; OR: odds ratio; SD: stable disease; NR: not reported. #: median. ¶: patients who failed to respond or progressed within 90 days of first-line therapy were termed refractory; +: patients who relapsed after 90 days after first-line therapy were termed sensitive.

Exclusion criteria included: pre-treatment with a topoisomerase I inhibitor; more than one pre-treatment; pregnant or lactating females; history of neoplasm other than SCLC; serious concomitant medical conditions; dementia; surgery within 2 weeks before study entry; and participation in any other clinical study within 30 days before study entry.

The present study was approved by the ethical committee of each participating centre.

Descriptive statistical methods were used to assess response evaluation, dose intensity, time to progression and toxicity data. Survival estimates were performed using the Kaplan–Meier method.

Treatment

Topotecan was administered as a 30-min *i.v.* infusion at a starting dose of 1.25 mg·m-$^{-2}$ for 5 consecutive days, repeated every 21 days for six cycles. One topotecan dose escalation of 0.25 mg·m^{-2} was to be performed in the second cycle in the absence of haematological toxicities grade 3 or 4. Further dose escalations of 0.25 mg·m^{-2} in the absence of haematological toxicities grade 3 or 4 was left to the discretion of the investigator.

A topotecan dose reduction of 0.25 mg·m^{-2} was to be performed in case of the following: 1) grade 4 neutropenia lasting 7 days or longer, or complicated by fever or infection; 2) platelet count <25,000·μL^{-1}, or neutrophil count <1,500 cells·μL^{-1} and platelet count <100,000·μL^{-1} on day 22; and 3) in case of grade 3 or 4 nonhaematological toxicity (except for nausea, vomiting and alopecia). In any case, the minimum topotecan dose had to be 1.0 mg·m^{-2}·day^{-1}. No dose re-escalation was allowed.

Use of granulocyte colony-stimulating factor (G-CSF) was left to the discretion of the investigator. Duration of the treatment was based on response evaluation which was performed after a minimum of two courses. In case of complete response, treatment was continued for two additional courses. In case of partial response, or stable disease, treatment was continued until disease progression or severe toxicity was observed or for the planned treatment of six cycles. Patients were withdrawn from the current study in case of disease progression or incomplete haematological recovery 2 weeks after scheduled treatment or for other generally accepted reasons. Response and toxicity were evaluated according to the World Health Organization and National Cancer Institute-Common Toxicity Criteria (revised version, 1994) [14].

Study design

The objectives of the present study were to evaluate response rates, response duration, toxicities, dose-intensity, and median survival of relapsed SCLC treated with topotecan at a starting dose of 1.25 mg·m^{-2}·day^{-1}. Patients were stratified according to pre-treatment with or without platinum, and according to response to pre-treatment (sensitive *versus* refractory).

According to given treatment, patients were grouped to a ''safety'', ''survival'' or ''response'' collective. The objectives of the current study were analysed within the corresponding groups. Patients (n=170) who received at least one dose of study drug were evaluated by safety analysis. Patients (n=164)

TABLE 2 Patients characteristics[#]

Patients registered	
Assessable for response intention to treat	170 (100)
Assessable for survival	164 (96.5)
Assessable for toxicity	170 (100)
Age	
Median 61 yrs	
<60 yrs	66 (40.3)
⩾60 yrs	98 (59.7)
Sex	
Male	128 (78.0)
Female	36 (22.0)
ECOG performance status	
0 Karnofsky 100%	34 (20.7)
1 Karnofsky 80–90%	92 (56.1)
2 Karnofsky 60–70%	37 (22.6)
Extent of disease	
Limited disease	4 (2.4)
Extensive disease without distant metastasis	38 (23.2)
Extensive disease with distant metastasis	120 (73.2)
No data	2 (1.2)
Liver metastases	
Present	59 (36.0)
Absent	105 (64.0)
Brain metastases	
Present	46 (28)
Absent	118 (72)
Best response to first-line treatment	
Complete response	31 (18.9)
Partial response	95 (57.9)
Stable disease	9 (5.5)
Progression	29 (17.7)
Time to relapse after first-line therapy	
<3 months refractory	57 (34.8)
⩾3–<6 months sensitive	107 (65.2)
Time to progression after first-line therapy	
Median days	191
Prior anticancer treatment	
Prior radiotherapy	85 (51.8)
Prior surgery	17 (10.4)
First-line therapy	
Platinum-based	104 (63.4)
Nonplatinum-based	60 (36.6)
First-line chemotherapy regimen	
Carboplatin, etoposide, vincristin	48 (29.3)
Platinum cisplatin or carboplatin, etoposide	36 (21.9)
Carboplatin, taxol, etoposide	7 (4.3)
Adriamycin, cyclophosphamide, vincristine	20 (12.2)
Epirubicin, cyclophosphamide, vincristine	20 (12.2)
Cyclophosphamide, etoposide, adriamycin	12 (7.3)
Other regimes	21 (12.4)
Number of measurable lesions	
1	69 (42.1)
2	50 (30.5)
3	33 (20.1)
>3	12 (7.2)

Data are presented as n (%), unless otherwise stated. ECOG: Eastern Cooperative Oncology Group. [#]: n=170.

who had received at least one course of study medication and did not show any serious study deviation (*i.e.* no measurable disease) were evaluated for survival, demographic data, dose intensity and time to progression. Objective response evaluation was performed in patients (n=120) who received at least two courses of the study drug and had a tumour baseline status with re-evaluation (response collective). In 41 patients, clinical progressive disease or death was observed prior to response re-evaluation after the end of the second cycle. Clinical progressive disease, death or missing response data were regarded as progressive disease, according to a worst-case scenario (intention-to-treat).

Tumour response was judged by each individual centre. Median time to progression and survival were calculated according to the Kaplan-Meier product limit method.

RESULTS

Patient characteristics

A total of 170 patients were enrolled from 44 participating centres between February 1998 and June 1999. The last follow-up was performed in December 2002. It was possible to evaluate all patients for safety analysis. In total, 164 patients were evaluated for survival analysis (two patients did not complete a full course and four patients did not have a bi-dimensionally measurable lesion). Tumour response, as the primary end-point of the present study, was evaluated in all patients who received at least one dose of the study drug (n=170; intention-to-treat). Of these, 37 patients received less than two courses and seven patients were lost to follow-up. A total of 76.8% of patients had performance status ECOG 0–1. The majority of patients (73.2%) had distant metastatic disease and 63.4% of patients had received a platinum-based primary therapy. The overall response rate to primary therapy was 76.8%. In total, 34.8% of patients were refractory, whereas 65.2% of patients were sensitive to prior therapy. The median time to progression after first-line therapy was 191 days (table 2).

Dosing

A total of 514 topotecan courses were received by 164 patients. Of these, 22.6% of patients (n=37) received only one course of therapy, 2.4% (n=4) of patients received eight courses and 52 patients (31.7%) received two courses. The first cycle was administered to 164 patients and the sixth cycle to 36 patients. In 58.2% of courses (n=299), the starting dose was maintained. The topotecan dose had to be reduced to 1.0 $mg \cdot m^{-2} \cdot day^{-1}$ in 8.9% (n=46) of courses. The targeted dose of topotecan (1.5 $mg \cdot m^{-2} \cdot d^{-1}$) was reached in 32.9% (n=169) of courses. In the first course, the topotecan dose was administered as a starting dose of 1.25 $mg \cdot m^{-2} \cdot day^{-1}$ to 98.2% of patients (n=161). This starting dose was maintained in 46.5% of patients (n=59) in course two. Dose escalation to 1.5 $mg \cdot m^{-2} \cdot day^{-1}$ of topotecan was performed in 37.8% of patients (n=48), whereas in 15.7% (n=20) it was reduced to 1.0 $mg \cdot m^{-2} \cdot day^{-1}$. Protocol deviations, according to dose modification in the second cycle, were noticed in 13.1% (no dose escalation to 1.5 $mg \cdot m^{-2}$) and 17.0% (no dose reduction to 1.0 $mg \cdot m^{-2}$) of patients, respectively. While the number of patients who received subsequent courses decreased, the percentage of patients who received an escalated dose rose from 46.7% (third cycle) to 58.3% (sixth

cycle). At the same time, the percentage of patients who received a reduced dose decreased from the third cycle (13.3%) to the sixth cycle (8.3%), with the exception of the fifth cycle (14.0%). The percentage of patients within the third to sixth cycles receiving the starting dose was between 30.2% (fifth cycle) and 40.0% (third cycle). Median dose intensity of all administered cycles was 1.25 $mg \cdot m^{-2} \cdot day^{-1}$ (table 3).

Efficacy

Response to treatment

A total of 170 patients were evaluated for their response (intention to treat). The overall response rate was 14.1% with one complete response and 23 (13.5%) partial responses. Stable disease was observed in 25.9% and progressive disease in 60% of patients. No difference in response rates was seen between patients with or without platinum-containing pre-treatment, with overall response rates of 14.9 and 12.7%, respectively. However, patients who had been refractory to primary therapy achieved a lower response rate and a higher rate of disease stabilisation to topotecan therapy. The overall response rate was 8.6% in refractory patients *versus* 17.1% in sensitive patients and stable disease was observed in 36.2 and 20.7% of patients, respectively (table 4). Among all responding patients, the median time to response was 7.2 (range 2.9–14.7) weeks. There was no significant difference between patients with platinum-containing and platinum-free pre-treatment at 8.1 *versus* 6.6 weeks ($p=0.8952$), respectively. In refractory patients, time to response was significantly longer at 12.4 weeks *versus* 6.4 weeks ($p=0.0260$). As shown in table 5, median duration of response was 13.6 (3.0–47.9) weeks and was not significantly different among the subgroups. Median time to progression for all patients was 8.0 (0.1–53.6) weeks. An analysis according to stratification parameters showed no significant differences between sensitive *versus* refractory patients.

Survival

It was possible to evaluate 164 patients for survival. The median survival time was 23.4 weeks (95% confidence interval (CI) 19.0–27.0 (0.9–92.4) weeks) and mean survival was 28.3 weeks (fig. 1). Median survival time for patients with a complete and partial response, stable disease or progressive disease was 43.4, 28.6 and 26.0 weeks, respectively. Stratified according to pre-treatment and response to pre-treatment, no differences in median survival time could be detected. Median survival time of 62 weeks was found in patients with an objective response to topotecan and nonplatinum-containing pre-treatment.

After 1 yr 25 patients were alive according to a 1-yr survival rate of 15.2%.

TABLE 3 Dose intensity and administered courses in the study patients

Course	Administered dose $mg \cdot m^{-2}$			
	1.00	1.25	1.5	>1.5
1	2 (1.2)	161 (98.2)	1 (0.6)	0 (0.0)
2	20 (15.7)	59 (46.5)	48 (37.8)	1 (0.8)
3	10 (13.3)	30 (40.0)	35 (46.7)	1 (1.3)
4	5 (8.2)	22 (36.1)	34 (55.7)	2 (3.3)
5	6 (14.0)	13 (30.2)	22 (55.8)	2 (4.7)
6	3 (8.3)	12 (33.3)	21 (58.3)	1 (2.8)
7	0 (0.0)	1 (25.0)	3 (75.0)	0 (0.0)
8	0 (0.0)	1 (25.0)	3 (75.0)	0 (0.0)

Data are presented as n (%).

Toxicity

A total of 170 patients received at least one dose of topotecan and were evaluable for toxicity. Treatment delays of >14 days due to haematological toxicity were observed in five patients. Delays of >7 days due to toxicity or management reasons were performed in 11.7% of courses. Therapy had to be stopped in nine patients. All cases were associated with myelosuppression. One treatment-related death was observed. This patient, with poor performance status, declined hospitalisation despite grade 4 neutropenia and thrombocytopenia. Major side-effects were neutropenia and leukopenia, whereas anaemia and thrombocytopenia were less common. Grade 3 and 4 neutropenia occurred in 27.7 and 27.6% of patients, and in 31.5 and 6.9% of treatment courses, respectively. G-CSF was administered in 21.2% of patients in 11.5% of treatment courses. Febrile neutropenia was observed in 0.8% of courses. The incidence of grade 3 and 4 thrombocytopenia was 10.3% and 5.0% of treatment courses (23.5 and 13.5% of patients), respectively. In total, 10% of patients received a platelet substitution in 3.3% of treatment courses. Anaemia grade 3 and 4 was less common (5.5% and 0.6% of all courses, respectively); in 3.6% of courses, erythrocytes had to be substituted. No evidence of cumulative haematological toxicity was observed. Haematological toxicity among the subgroups is presented in table 6 demonstrating lower rates of neutropenia and thrombocytopenia in refractory patients. In patients without platinum-containing pre-treatment, grade 3 and 4 anaemia was more frequent. Nonhaematological toxicities of grade 3 and 4, which were observed in >1% of patients, included: pain (5.9%), infection (4.7%), nausea (1.8%) and fever (1.8%).

DISCUSSION

Despite the high chemosensitivity of SCLC, the majority of patients have a relapse after induction chemotherapy. The prognosis of patients with recurrent disease remains poor. The goals of chemotherapy in this patient population were to obtain maximum control of disease symptoms, prevent serious complications and increase survival without diminishing quality of life [1, 4, 5]. The current prospective study is the first trial in which an individual dose adjustment strategy with a reduced topotecan starting dose was evaluated in order to reduce toxicity, a procedure which is in close relationship to the clinical practice in relapsed SCLC.

A prospective analysis of the haematological toxicity profile of topotecan, administered at a dose of 1.25 $mg \cdot m^{-2} \cdot day^{-1}$ on days 1–5 to pre-treated patients with ovarian cancer, revealed that the severity of topotecan-induced thrombocytopenia is maximal after the first cycle, but significantly decreases after the second cycle without dose reductions [15]. FIELDS *et al.* [16] performed a retrospective analysis of second-line patients with

TABLE 4 Responses according to stratification

	All patients	Platinum pre-treatment		Response to pre-treatment[#]	
		Yes	No	Sensitive	Refractory
Subjects n	170	107	63	111	58
Complete response	0.6	0.9	0.0	0.9	0.0
Partial response	13.5	14.0	12.7	16.2	8.6
Overall response	14.1	14.9	12.7	17.1	8.6
Stable disease	25.9	25.2	27.0	20.7	36.2
Progressive disease	60.0	59.8	60.3	62.2	55.2
95% CI for response		30.8–50.1	27.6–52.8	28.8–47.5	31.7–58.5

Data are presented as %, unless otherwise stated. CI: confidence interval. [#]: missing data (n=1).

SCLC treated with the standard topotecan dose. In 110 patients, the dose was reduced to $\leqslant 1.25$ mg·m^{-2}·day^{-1} due to haematological toxicity. Response rates and survival in the reduced dose population were similar to the results of the standard dose population [16].

The presented results demonstrate that treatment with the reduced topotecan starting dose of 1.25 mg·m^{-2}·day^{-1} and an individual dose adjustment is equi-effective to the efficacy of the standard dose of 1.5 mg·m^{-2}·day^{-1}. VON PAWEL and co-workers [8, 16] reported a median survival of 25 weeks for 98 patients receiving the *i.v.* regimen of 1.5 mg·m^{-2}·day^{-1} in the phase II and 107 patients in the phase III study; in the present study, the median survival was 23.4 weeks. Of note, in these trials, mostly sensitive patients were included [8, 12].

The greater tolerability of this regimen is also reflected in the reduced rate of haematological toxicities compared with recently reported trials, where topotecan was given at a standard dose. In the current trial, grade 4 neutropenia and thrombocytopenia occurred in 6.9 and 5% of courses, respectively, and febrile neutropenia was observed in only 0.8%. In other studies using the standard *i.v.* dose of topotecan in relapsed SCLC, grade 4 neutropenia and thrombocytopenia were observed in 32.5–46.9% and 7.7–11.9% of courses, respectively [8, 11]. Febrile neutropenia occurred in 3.3–6% of *i.v.* topotecan courses. Nonhaematological toxicities were mild and did not influence patients' well-being. Notably, grade 3 and 4 neutropenia and thrombocytopenia is less frequent in refractory compared with sensitive patients. This is very important for refractory patients, since the clinical benefit does not seem to be associated with a higher toxicity and justifies therapy in this special patient group.

TABLE 5 Response duration, time to progression and survival

	Patients	Weeks
Response duration		
All	24	13.6 (3.0–47.9)
Platinum +PT	16	12.1 (3.0–47.9)[#]
Platinum -PT	8	19.4 (7.3–40.9)
Sensitive	19	15.0 (3.0–47.9)[¶]
Refractory	5	13.0 (4.7–27.1)
Time to progression		
All	164	8.0 (0.1–53.6)
Platinum +PT	104	7.9 (2.1–53.6)[+]
Platinum -PT	60	9.6 (0.1–48.0)
Sensitive	107	8.0 (2.1–53.6)[§]
Refractory	57	9.6 (0.1–41.3)
Survival		
All	164	23.4 (0.9–92.4)
Platinum +PT	104	23.4 (0.9–92.4)[ƒ]
Platinum -PT	60	22.9 (1.1–83.1)
Sensitive	107	22.4 (0.9–92.4)[##]
Refractory	57	23.7 (1.1–85.7)

Data are presented as n or median (interquartile range). Platinum +PT: platinum-containing pre-treatment; Platinum -PT: platinum-free pre-treatment. [#]: p=0.372 platinum +PT *versus* platinum -PT; [¶]: p=0.339 sensitive *versus* refractory; [+]: p=0.017 platinum +PT *versus* platinum -PT; [§]: p=0.472 sensitive *versus* refractory; [ƒ]: p=0.878 platinum +PT *versus* platinum -PT; [##]: p=0.82 sensitive *versus* refractory.

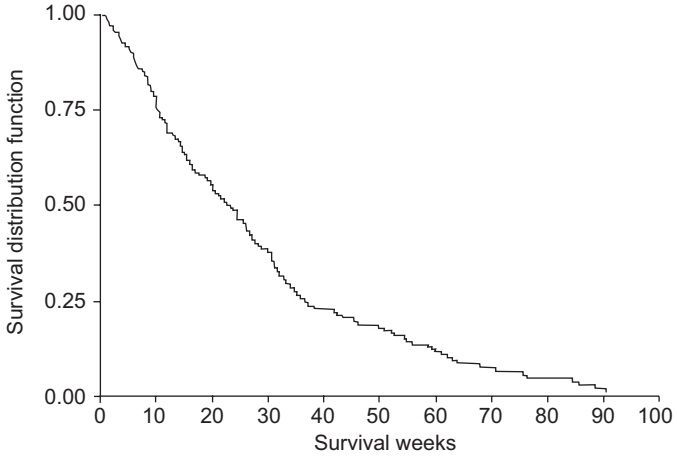

FIGURE 1. Kaplan–Meier plot of overall survival (n=164). Median survival: 23.4 weeks.

TABLE 6 Haematological toxicity

	All	Platinum pre-treatment		Response to pre-treatment	
		Yes	No	Sensitive	Refractory
Subjects	170	104	60	107	57
Leukopenia	44.1/17.6	44.3/16.3	45.5/21.2	47.7/22.4	38.6/10.5
Neutropenia	27.7/27.6	28.9/31.7	38.4/23.3	35.6/31.7	26.3/22.8
Thrombopenia	23.5/13.5	25.0/12.5	20.1/16.6	12.2/16.8	15.8/8.8
Anaemia	16.0/1.7	14.4/1.9	18.4/1.6	14.0/2.8	19.3/0

Data are presented as n or % of patients with grade 3/4 toxicity.

Median dose intensity of all administered cycles was 1.25 $mg \cdot m^{-2} \cdot day^{-1}$. In 58.2% of all courses, the starting dose was maintained and in 32.9% of courses the dose was escalated to 1.5 $mg \cdot m^{-2} \cdot day^{-1}$. Only 8.9% of courses had to be reduced due to haematological toxicity compared with phase II studies with a standard topotecan dosage, where dose reductions of 16–19% were reported [11, 12].

The overall response rate of 14.1% obtained in the present study is comparable to recently published reports using *i.v.* topotecan in the standard dosage (table 1). As expected, the response rate was higher in sensitive patients (17.1%) than in refractory patients (8.6%), and median time to response was longer for refractory patients (12.4 weeks) than for sensitive patients (6.4 weeks). This is in accordance with reports by ARDIZZONI *et al.* [11] and PEREZ-SOLER *et al.* [13]. In contrast, no difference was seen between patients with or without platinum-containing pre-treatment indicating the lack of cross-resistance to platinum. PEREZ-SOLER *et al.* [13] reported the responses to topotecan in etoposide-refractory patients and concluded that it may overcome etoposide resistance. Interestingly, in 36.2% of refractory patients and 20.7% of sensitive patients, stabilisation of disease was observed. As shown by CESANO *et al.* [17], stable disease represents a potential clinical benefit, since stable disease has the same survival benefit as a partial response *versus* progressive disease. Primary progression rate also provides support for a clinical benefit; it shows no difference between the four subgroups and is not higher in refractory patients.

Median duration of response was 13.6 weeks and median time to progression was 8.0 weeks for all patients. Patients with platinum-free pre-treatment had an advantage in median time to progression compared with patients with platinum-containing pre-treatment. Median time to progression was 9.6 weeks *versus* 7.9 weeks in these groups (table 5). The results concerning pre-treatment are difficult to compare with other studies, as the distinction between platinum-containing and platinum-free pre-treatment is not reported.

The median survival was 23.4 weeks and 1-yr survival was 15.2% without any differences between the subgroups. The survival data for all patients are comparable to reports using the standard topotecan dosage in phase II and III trials [9–11]. ARDIZZONI *et al.* [11] reported longer survival data for sensitive than for refractory patients (6.9 *versus* 4.7 months). In the present study, survival data of refractory patients are similar to survival in sensitive patients (23.7 *versus* 22.4 weeks). High rate of disease stabilisation, especially in the refractory patients' group, may contribute to better median survival of refractory patients in the current study. This is in agreement with previous reports in which survival of patients with partial response was comparable with survival of patients with stable disease following topotecan therapy of SCLC and ovarian cancer [17]. Stable disease is a valid end-point provided that symptom palliation is achieved and treatment-related toxic side-effects are mild.

A meta-analysis of four multicentre trials treating patients with relapsed SCLC with topotecan at a starting dose of 1.5 $mg \cdot m^{-2} \cdot day^{-1}$ suggests that dose reductions due to haematological toxicity ($\leqslant 1.25$ $mg \cdot m^{-2} \cdot day^{-1}$) are not correlated with decreased efficacy. The response rate and median survival in the reduced dose population was 17.3% and 29.9 weeks, respectively, compared with 18.1% and 28.6 weeks in the standard dose population. These results support those of the present study, indicating that moderate topotecan dose reductions can counterbalance the haematological toxicity but are not associated with reduced efficacy [16].

To the best of the present authors' knowledge, this is the first prospective trial in relapsed small cell lung cancer which shows a positive impact on safety parameters of topotecan therapy at a reduced starting dose with an individual dose adjustment strategy. It is of special interest that this impact is in association with the same efficacy compared with standard topotecan regimens. These results demonstrate that patients with sensitive and refractory relapsed small cell lung cancer can benefit from chemotherapy and that treatment-related side-effects are manageable by individual dose titration.

ACKNOWLEDGEMENTS

The authors would like to thank the clinical research organisation GKM Gesellschaft für Therapieforschung (Munich, Germany) for the monitoring and statistical analysis performed in the current study.

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