ONKOLOGIE

Onkologie 2000;23(suppl 3);9–12

Topotecan in Second-Line Therapy of SCLC: Impact on Survival?

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Introduction

Small-cell lung cancer (SCLC) accounts for about 25% of lung cancer at initial diagnosis. It is a highly chemosensitive disease, but despite high initial response rates, the median survival time is only 9–16 months in limited disease and 6–12 months in extensive disease [1, 2]. About 70% of the patients who have limited disease and over 90% of patients who have extensive disease will develop recurrent or progressive disease. There is no standard second-line therapy following first-line treatment, and the prognosis after relapse is poor [3]. CAV (cyclophosphamide, doxorubicine, vincristine) is often used after first-line treatment with etoposide and cisplatin. In two studies, CAV produced second-line response rates of 13 and 28% [4, 5], but duration of response to second-line chemotherapy is short, with a median survival time of 10–20 weeks [6].

Thus the identification of new, more active drugs is clearly crucial. Among several new drugs investigated during the last few years, topotecan has demonstrated significant activity. It is a semi-synthetic, water-soluble derivative of the alkaloid camptothecin, a specific inhibitor of the topoisomerase I. Inhibition of this enzyme results in cell-killing DNA damage during the course of DNA replication. It proves to be effective in patients with brain metastases and it may be effective in preventing brain metastases.

Topotecan passes the intact blood-brain barrier, and two phase II studies have already been performed in patients with relapsed or refractory SCLC with topotecan as a single agent at a dosage of 1.5 or 2 mg/m^2/day on 5 consecutive days [7, 8]. In a phase III comparison, the monotherapy with topotecan resulted in the same responses and survival as the combination of CAV, symptoms relief was significantly better with the topotecan treatment [9]. Additionally, Lane et al. [10] reported a significant longer survival for patients with stable disease after topotecan treatment compared to those with disease progression. Although in all studies topotecan therapy was well tolerated by the patients, the percentage of grade 3 and 4 hematological toxicities is high. Other clinical complications are rare, but dose reductions and treatment delays are required. In a study with a topotecan dosage of 1.25 mg/m^2/day published by Perez-Soler et al. [11], hematological toxicities such as granolocytopenia and thrombocytopenia grade 4 were observed in 28 and 11% of cycles, respectively.

As it became apparent by the analysis of Armstrong and O`Reilly [12] that the hematological toxicities are highest during the 1st cycle, the SOABB study group conducted a phase II study with an initial topotecan dose of 1.25 mg/m^2/day to reduce the hematological toxicities. In the following cycles the doses were increased or decreased depending on toxicities by a standard operational procedure.

Primary interest of this phase II study was median survival time of the patients, other objectives were the evaluation of the response rate and response duration of topotecan monotherapy in the second-line therapy of SCLC after platinum-based or non-platinum-based first-line therapy. The assessment of hematologic and non-hematologic toxicities and the assessment of the dose intensity were further objectives.

Patients and Methods

Eligibility Criteria

All patients were required to have a histologically or cytologically confirmed diagnosis of SCLC. They had to have first-line therapy and were categorized according to a platinum-based or non-platinum containing first-line therapy. At least one tumor lesion had to be measurable two-dimensionally. Other eligibility criteria included an Eastern Cooperative Oncology Group (ECOG) performance status of less than or equal to 2,

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corresponding to a Karnofsky index > 60%, a sufficient bone marrow and renal function and for women with childbearing potential an adequate contraception. All patients gave written informed consent before study entry.
Patients were ineligible if they had a history of first-line therapy with any topoisomerase I inhibitor, a history of other neoplasms than SCLC, surgery within the last two weeks prior to inclusion, or a history of hypersensitivity to topotecan. Also ineligible were pregnant or lactating women and patients with severe infections.

Pretreatment and Follow-up Studies
At the beginning and at the end of the study, all patients underwent a complete medical history. An assessment of performance status and staging were done at the beginning of the study, at the beginning of each cycle and at the end of the study. Blood counts were done at the beginning and at the end of the study, at the beginning of each cycle and during each cycle at day 8 and 15; blood chemistry was obtained at the beginning and the end of the study and at the beginning of each cycle.

Stratification
Patients were stratified in 2 groups based on first-line therapy, either failure after platinum-based chemotherapy or failure after non-platinum containing chemotherapy.
Retrospective strata include patients with sensitive or refractory disease as well as the duration of the remission of the first-line therapy.

Treatment Schedule
Topotecan was administered as a starting dose of 1.25 mg/m^2/day for 5 consecutive days every 21 days. Patients could receive a maximum of 6 cycles. Dose modifications were performed in steps by 0.25 mg/m^2/day based on hematological toxicity.
Grades of toxicity that occurred during the first treatment course will be reviewed and the dose for the next treatment course will be escalated by one step if only toxicities of NCIC CTCG grade 2 occurred.
The dose could be reduced in one of the following cases:
- NCIC CTCG grade 3 leukopenia (neutrophils 1.0×10^9/l) ≥ 7 days
- febrile neutropenia (T ≥ 38.2 °C and neutrophils < 0.5 and necessity of antibiotics)
- NCIC CTCG grade 3 thrombocytopenia (thrombocytes < 25×10^9/l)
- neutrophils < 1.5×10^9/l and thrombocytes < 100×10^9/l on day 22

The lowest dose level was 1.0 mg/m^2/day.
Re-escalation after dose reduction was not allowed.

Statistical Analysis
Data were analyzed by descriptive statistical methods.

Results

From March 1998 to January 1999 a total of 171 patients with recurrent SCLC were entered into the study from 43 German centers. The present evaluation is based on 100 patients, for whom complete data sets were available.
Main patient characteristics are listed in table 1. There were only 5% of the patients with limited disease, all other patients were extensive disease. Two thirds of the patients had a platinum-based first-line therapy, one third had mostly CAV or a modification of CAV as first-line therapy. Refractory patients was one third, and two thirds of the patients were considered sensitive with relapses between 3 and 6 months after first-line therapy. In first-line therapy patients had 23% complete remission (CR), 53% partial remission (PR), 5% stable disease (SD) and 19% progressive disease (PD).

Table 1. Main patient characteristics

	n	%
Eligible	171	
Evaluable	100	
Sex		
Male		75
Female		25
Age		
Median, years	60	
Range, years	38–76	
ECOG performance status		
0 (Karnofsky 100%)	16	16
1 (Karnofsky 80–90%)	59	59
2 Karnofsky 60–70%)	25	25
Extent of disease at study entry		
Limited disease	5	5
Extensive disease I	18	18
Extensive disease II	77	77
Brain metastases present	24	24
First-line therapy		
Platinum-based	66	66
Non-platinum-based	34	34
Time to relapse after first-line therapy		
< 3 months (refractory)	34	34
≥ 3 months to < 6 months (sensitive)	66	66
Best response to first-line therapy		
CR		23
PR		53
SD		5
PD		19

Dose Intensity

A total of 295 courses was given, the mean dosage was 1.28 mg/m^2/day. About 29% of the cycles could be increased to 1.5 mg/m^2/day, only 8.3% of the cycles had to be reduced to 1.0 mg/m^2/day. The mean dose density was (mg/m^2/day of a 21-day cycle) 0.26 in cycle 1, 0.3 in cycle 3, and 0.27 in cycle 5 (table 2).

Evaluation of Efficacy

The overall response rate was 14%. There were 14 patients (14%) with partial remission. 40 patients (40%) had stable

Table 2a. Mean dosage

	Total	Cycle					
		1	2	3	4	5	6
N	295	100	83	44	32	20	16
Mean dosage, mg/m^2/day	1.28	1.25	1.29	1.33	1.39	1.38	1.39

Table 2b. Dose intensity

Dosage mg/m^2/day	Patients		Cycles	
	n	%	n	%
1.0	13	13	24	8.3
1.25	59	59	180	62.5
1.5	28	28	84	29.2

Table 2c. Dose density

	Cycle				
	1	2	3	4	5
N	83	44	32	20	16
Dose density mean (mg/m^2/day of a 21-day-cycle)	0.26	0.29	0.3	0.28	0.27

and 46 patients (46%) had progressive disease. We observed the same partial remission rate in platinum-based and non-platinum containing first-line therapy. There were little differences in the percentage of stable and progressive disease categories between platinum-based and non-platinum containing first-line therapy, this was also evident for performance status ECOG 0–1 and ECOG 2 (table 3). In 46% of the 24 patients with brain metastases, disease was arrested and 54% progressed.

The median time to progression for all patients was 8 weeks. Although there was a statistically significant difference regarding time to progression in those patients who could be increased with their dose (14 weeks time to progression), the median survival was equal. The 14 patients who responded had a median duration of response of 9 weeks.

The median survival time of all patients was 25 weeks. There were no differences between the type of first-line therapy or sensitive versus refractory. There was a difference in median survival time between the performance status: 25 weeks ECOG 0–1, 22 weeks ECOG 2.

Toxicity

The hematological side effects were remarkably rare with grade 4 neutropenia in 11.5% and thrombocytopenia grade 4 in 4.7% of the courses.

Table 3. Response rates

Response, %	All patients (n = 100)	Platinum (n = 66)	Non-platinum (n = 34)	ECOG 0–1 (n = 75)	ECOG 2 (n = 25)
CR	0.0	0.0	0.0	0.0	0.0
PR	14.0	14.0	15.0	12.0	20.0
SD	40.0	36.0	47.0	40.0	40.0
PD	46.0	50.0	38.0	48.0	40.0

Table 4. Comparison of time to progression and survival in relation to neutropenia and thrombocytopenia from the German multicenter study and the von Pawel study

	SOABB	Von Pawel et al. [9]	
Study drug	topotecan	topotecan	CAV
Median time to progression, weeks	8	13	12
Median survival, weeks	25	25	22
Neutropenia grade 4 (% of all courses)	11.5	38	52
Thrombocytopenia grade 4 (% of all courses)	4.7	10.3	1.5

At the dose levels of 1.25 mg/m^2/day, there was grade 3 neutropenia in 12% and grade 4 neutropenia in 8%. Concerning the thrombocytes, there was grade 3 thrombopenia in 7% and grade 4 thrombopenia in 4%. The toxicities were not increased in those patients who could be increased during the course of their therapy, but they were lower in the dose levels of 1.0 mg/m^2/day. There were no statistically significant differences concerning toxicities between the type of first-line therapy. Hematological toxicities were not cumulative during the course of the therapy.

There were few non-hematological side effects (fever: 2 patients, pancreatitis: 2 patients, dyspnoea, pneumonia, gastritis, erythema: 1 patient each).

Discussion

Prognosis in terms of response and survival of patients with recurrent SCLC still remains poor. Among several new drugs investigated during the last few years topotecan, a water-soluble analogue of camptothecin which acts as an inhibitor of topoisomerase I, has demonstrated significant activity. A phase II study conducted by the EORTC reported a 21.7% overall response (38% among sensitive, 6.4% among refractory patients) and a median duration of response of 33 weeks [7]. In that study the dose of topotecan was 1.5 mg/m^2/day for 5 consecutive days, every 3 weeks. The remission rate observed in another study with topotecan as a single agent with 1.5 mg/m^2/days 1–5 was 19% in sensitive patients and 3% in patients with refractory response to first-line therapy [8].

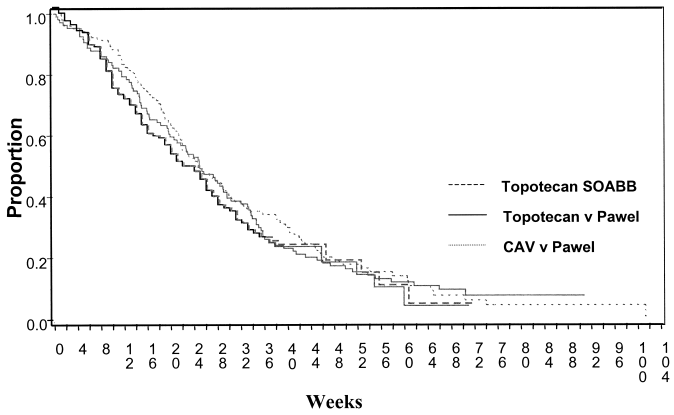

Fig. 1. Kaplan-Mayer plot for survival of both trials, German multicenter SOABB and von Pawel's study.

Perez-Soler et al. [11] already conducted a study with a topotecan dosage of 1.25 mg/m^2/day. They recorded a remission rate of 11% (only partial remissions), 17% had stable disease and the median survival was 20 weeks.

Due to the promising results observed in these studies, a randomized phase III trial of topotecan as single agent versus CAV was performed [9]. In that multicenter trial, a total of 211 evaluable patients were included. As the patient characteristics are very similar to each other, a comparison of both studies is interesting (table 4). In the German multicenter trial the response rate achieved so far is 14% partial remission, the topotecan arm of von Pawel's study had 24%, the CAV arm 16%. The progression rate was 46% in the German multicenter trial versus 44.5 and 53% in the two arms of von Pawel's study. Although there were differences in the median time to progression (German multicenter study: 8 weeks, topotecan arm: 13 weeks, CAV arm: 12 weeks), the median survival time so far is 25 weeks for both topotecan arms, the dose adjustment for each patient in the German multicenter study and the standard dose of 1.5mg/m^2/day in von Pawel's study, compared to 22 weeks in the CAV arm (fig. 1).

A comparison of the results regarding survival and myelotoxicity is summarized in table 4.

The topotecan dose modification could reduce myelotoxicity to half that of the standard treatment.

Thus in the German multicenter study presented here, there was the same efficacy and survival compared to a combination of 3 drugs with markedly less toxicity due to the lower starting dose of topotecan of 1.25 mg/m^2/days 1–5 and subsequent dose modifications. Therefore topotecan has clearly an impact on survival in second-line therapy of small-cell lung cancer.

Appendix

The following institutions participated in this study:
Städtische Klinik Leipzig West, Krankenhaus Großhansdorf, Zentralkrankenhaus Gauting, Klinikum Schillerhöhe, Gerlingen, St. Vincentius-Krankenhaus, Karlsruhe, Malteser KRH St. Franziskus-Hospital, Flensburg, Clemenshospital, Münster, Fachklinik Kutzenberg, Ebensfeld, Med. Einrichtungen der Rhein. Friedrich-Wilhelms-Universität, Bonn, Krankenhaus Donaustauf, Klinikum Rechts der Isar, München, Medizinische Fakultät der Univ. Magdeburg, Diakoniekrankenhaus Halle, Klinikum der Albert Ludwigs-Universität, Freiburg, Krankenhaus Zschadraß, Zentral-Krankenhaus Bremen Ost, Zentralklinikum Augsburg, Mutterhaus der Borromäerinnen, Trier, Krankenhaus Nordwest, Frankfurt, Fachkrankenhaus Coswig, Klinikum der Hansestadt Stralsund GmbH, Allgem. Krankenhaus Hamburg-Harburg, Klinikum St. Marien Amberg, Universitätskliniken des Saarlandes, Homburg-Saar, Fachkrankenhaus für Lungen- und Thoraxchirurgie, Berlin, Krankenhaus Düren, Augusta-Krankenanstalt, Bochum, Kliniken Essen-Mitte , Klinikum Innenstadt, Ludwig-Maximilians-Universität, München, Klinikum Neubrandenburg, Klinikum Nürnberg, Krankenhaus der Barmherzigen Brüder, Regensburg, Städtisches Krankenhaus Bogenhausen, München, Städt. Krankenanstalten Krefeld, Klinikum der J. W. Goethe-Universität, Frankfurt, Universitätskrankenhaus Eppendorf, Hamburg, Städtisches Krankenhaus Heidehaus, Hannover, Städt. Klinikum Karlsruhe, Klinik Bad Trissel, Oberaudorf, Lungenfachklinik Philippstiftung e. V. , Immenhausen, Klinikum Chemnitz GmbH, Universitätsklinik, Jena, Universität Leipzig, Medizinische Universitätsklinik, Rostock

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