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Response to topotecan of symptomatic brain metastases of small-cell lung cancer also after whole-brain irradiation: a multicentre phase II study

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Abstract

The purpose of this multicentre phase II study was to evaluate the efficacy and toxicity of topotecan in pretreated patients with small-cell lung cancer (SCLC) who relapsed with symptomatic brain metastases. 30 patients with a median age of 62 years were entered into the study. 22 patients received the initially planned dose of 1.5 mg/m^2 topotecan as a 30-min intravenous (i.v.) infusion for 5 consecutive days every 3 weeks. Due to the observed thrombocytopenia, the dose was reduced to 1.25 mg/m^2 in the last 8 patients. All 30 patients were pretreated with chemotherapy: 14 with one and 16 with at least two protocols. 8 patients had prior whole-brain iradiation (WBI): 7 in the prophylactic and 1 in the palliative setting. Concomitant systemic metastases were recorded in 24 patients at the time of brain relapse. Cerebral metastases responded in 33% of patients (10/30; three complete responses (CR) and seven partial responses (PR)). Noteworthy is the fact that response was achieved in 4 of 8 patients pretreated by WBI (3 in prophylactic and 1 in palliative setting). The systemic response rate was 29% (7/24). Median time to progression was 3.1 months (range 0.25–14.2+ months), median survival from the beginning of this study was 3.6 months (range 0.25–14.2+ months). Therapy was generally well tolerated, with myelotoxicity being the most common adverse event. Grade 3 leucocytopenia according to the Common Toxicity Criteria (CTC) occurred in 28% (23/83) of the courses and grade 4 in 22% (18/83). Grade 3 thrombocytopenia was observed in 17% of the courses (14/83) and grade 4 in 11% (9/83). 17% of patients (5/30) had a documented grade 3 infection. These results using topotecan are promising in heavily pretreated patients with SCLC brain metastases and merit further evaluation.

Keywords: Topotecan; Whole-brain irradiation; Brain metastases; Small-cell lung cancer; Phase II study

1. Introduction

Lung cancer is the most common primary source of Central Nervous System (CNS) metastases accounting for 40–60% of all brain deposits [1]. Brain metastases are observed in 20% of the patients with small-cell lung cancer (SCLC) at the time of first diagnosis and in 80% at autopsy [2].

The benefit of whole-brain irradiation (WBI) in these patients is local control, but most of them die from the systemic disease after a median survival of less than 6 months [2]. Neurosurgery may offer some advantage over radiotherapy, but the benefit is restricted to patients with resectable CNS metastases, limited systemic disease and good performance status.

In contrast, an effective systemic chemotherapy (CHT) would have the advantage of simultaneous

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treatment of systemic spread. Despite the need for advances in the therapy of brain metastases, systemic chemotherapy has rarely been considered an important treatment option since it was not believed to cross the blood–brain barrier (BBB). However, it is now well established that brain metastases cause a disruption of the BBB, rendering it permeable for agents unable to penetrate it under physiological circumstances. Moreover, some chemotherapeutic agents possess the ability to cross even an intact BBB. These observations led to the development of an alternative hypothesis: that a lack of therapeutic activity, and not the BBB itself, may be the obstacle to successful treatment of brain metastases with systemic chemotherapy.

Topotecan (Hycamtin TM, SmithKline Beecham Pharma München, Germany), a semi-synthetic analogue of the alkaloid camptothecin, is a specific topoisomerase-I inhibitor. Topoisomerase-I is intimately involved in DNA replication and relieves the torsional strain introduced ahead of the moving replication fork. The activity of topoisomerase-I is higher in the S phase and topoisomerase-I inhibitors are usually S phase-specific. Topotecan was shown to be effective against a number of solid tumours including SCLC. Preclinical and clinical studies revealed that topotecan produces cerebrospinal fluid (CSF) concentrations exceeding 30% of the corresponding plasma concentrations [3–6]. Activity of topotecan against SCLC brain metastases was observed in a retrospective analysis of patients with refractory or relapsing SCLC [7,8]. The aim of this multicentre phase II study was a prospective evaluation of the efficacy of topotecan in patients with symptomatic SCLC brain metastases.

2. Patients and methods

2.1. Patients eligibility

Eligibility criteria for this study included: relapse of an initially histologically or cytologically confirmed SCLC and symptomatic brain metastases after CHT, age $\geqslant 18$ years, performance status $\leqslant 2$ (European Cooperative Oncology Group (ECOG scale)), life expectancy $\geqslant 3$ months, and written informed consent. There had to be at least one two-dimensionally measurable CNS lesion defined by contrast-enhanced diagnostic studies including Computed Tomography (CT) or Magnetic Resonance Imaging (MRI) scans. The same diagnostic imaging method had to be used throughout the study to evaluate the lesions. Any previous cranial radiotherapy had to be completed more than 2 months before entrance into the study. Concomitant steroid therapy for oedema control was permitted. All patients enrolled were required to have adequate neutrophil ($\geqslant 2.0\times10^9$ g/dl) and platelet ($\geqslant 100\times10^9$ g/dl) counts, haemoglobin ($\geqslant 10.0\times10^9$ g/dl), renal function (serum creatinine $\leqslant 1.5\times$upper limit of institutional normal) and hepatic function (serum bilirubin $\leqslant 1.5\times$upper limit of institutional normal and serum albumin $\geqslant 3$ g/l).

Exclusion criteria were occlusive hydrocephalus, medical or psychiatric contraindications to chemotherapy, history of allergic reaction to compounds chemically related to topotecan, pregnancy, lactation or no contraception in potentially reproductive patients, and history of malignancy within 5 years before study entry (except for adequately treated non-melanoma skin cancer or *in situ* cervical carcinoma).

The study was good clinical practice (GCP)-controlled, conducted according to the Declaration of Helsinki and with the approval of the local Review Board.

2.2. Treatment plan

Topotecan (Hycamtin™, SmithKline Beecham) was given at a dose of 1.5 mg/m^2/day as a 30-min intravenous (i.v.) infusion for 5 consecutive days and repeated every 21 days provided there was adequate resolution of haematological and non-haematological toxicity. The dose was reduced to 1.25 mg/m^2/day in the last 8 patients to reduce myelotoxicity. Nausea prophylaxis was given at the discretion of the treating physician. Therapy was continued until progression or for six courses past the maximal response. Further continuation of treatment was also allowed in patients with progressive extracranial disease if it appeared to be beneficial to the patient. CHT doses in subsequent courses were reduced by 0.25 mg/m^2/day if one of the following occurred: neutropenia $<0.5\times10^9$/l associated with fever/infection or lasting $\geqslant 7$ days, neutropenia 0.5–0.9×10^9/l lasting beyond day 21 of the treatment course, thrombocytopenia $<25\times10^9$/l or non-haematological toxicity Common Toxicity Criteria (CTC) grade 3–4. Treatment was discontinued in patients requiring a dose reduction of >0.5 mg/m^2/day or >2 weeks of treatment delay.

2.3. Response, survival and toxicity evaluation

Responses of the brain lesions were assessed after the first and second treatment courses and then after every two courses. The systemic response was evaluated after every two courses. Primary endpoints were response of brain metastases and time to progression, secondary endpoints were improvement of neurological symptoms, systemic response, toxicity and overall survival.

Complete response (CR) was defined as the complete resolution of the indicator lesion documented by two measurements taken at least 4 weeks apart. Partial response (PR) was defined as a $\geqslant 50\%$ decrease in the product of the greatest length and perpendicular width of the indicator lesion documented by two measurements

taken at least 4 weeks apart. Progression (PD) was defined as a >25% increase in the product of the indicator lesion or appearance of any new lesion. Areas of oedema were not included in the measurements. Toxicity was graded according to the CTC system and evaluated after each course. Time to progression was evaluated from the first day of therapy to documented progression, last follow-up or death. Survival was evaluated from the first day of therapy with topotecan to death or last follow-up.

2.4. Statistical methods

The main objective was to assess whether topotecan is sufficiently active with regard to the response rate, defined as the ratio between the number of patients with CR or PR and the total number of patients. A minimum response rate of 20% was considered to be of clinical interest in this patient population. If none of the first 14 evaluable patients had responded, the treatment would have been rejected as being less than 20% effective with only a 5% chance of a false rejection. All patients were evaluated on an intent-to-treat basis. All patients who had received at least one application were considered evaluable for safety/toxicity. Survival and time to progression were estimated by the product limit Kaplan–Meier method.

3. Results

3.1. Patient characteristics

A total of 30 patients at five institutions entered the study between August 1997 and January 2000. Patients' characteristics are shown in Table 1. Most patients suffered from widespread systemic disease in addition to cranial metastases. 16 patients (53%) were pretreated by platinum-containing protocols. 14 patients (47%) previously received one CHT protocol and 16 patients (53%) were pretreated by at least two protocols. 8 patients were pretreated with WBI: 7 in a prophylactic and 1 in a palliative setting.

3.2. Response and survival

The total response rate for CNS lesions based on CT scans was 33% with three CR (10%) and seven PR (23%). The CNS metastases stabilised in 8 patients (27%). 7 patients (23%) progressed. 5 patients (17%) died before evaluation and were not assessable for response: 1 died of toxicity, and 4 of PD. 2 of 8 patients treated with 1.25 mg/m^2 topotecan responded in the brain compared with 8 of 22 patients treated with 1.5 mg/m^2. Clinical symptoms improved or resolved in all patients with objective responses.

Table 1
Patients' characteristics

No. of patients entered	30
Age (years): median/range	62/37–76
Symptoms and signs	
Dizziness	20
Headache	12
Seizures	4
Hemiparesis	4
Ataxia	4
Paresthesia	3
Visual disturbance	3
Mental disturbance	3
No. of patients with extracranial metastases	24
Metastatic sites	
Liver	11
Lung	11
Adrenal gland	6
Bone	4
Pancreas	2
Kidney	1
Skin	1
No. of patients with meningeal carcinomatosis[a]	3
Previous whole brain irradiation	8
Prophylactic/palliative	7/1
Disease-free interval between WBI and CNS relapse (months): median/range	9.5/2–19
Interval between WBI and study entry (months):	
Median/range	10.5/2.5–19
Previous chemotherapy:	30
One/⩾two chemotherapy protocols	14/16
Best response to previous chemotherapy	
CR	9
PR	18
NC	3

CR, complete remission; PR, partial remission; NC, no change; WBI, whole-brain irradiation; CNS, Central Nervous System.
[a] Diagnosed by magnetic resonance imaging (MRI).

4 of 8 patients with previous WBI responded in the brain (1 CR, 3 PR): 3 of these patients were irradiated in prophylactic and one in palliative setting. The disease was stable in 3 patients with previous WBI and the other patient progressed. 7 of 10 patients with a response of cerebral metastases were evaluable for systemic response: 4 patients responded, 2 showed systemic disease stabilisation and 2 progressed. 2 cerebral responders did not have systemic disease and in the other patient the evaluation was not performed.

Disease stabilisation was observed in 3 patients with meningeal carcinomatosis. Their survival (at 1.4, 5.3 and 11 months, respectively) appeared to be comparable to that of patients without meningeal involvement.

Median time to progression was 3.1 months (range 0.25–14.2+ months) in all patients and 3.9 months (range 1.4–6.7 months) in responders. Median survival was 3.6 months (range 0.25–14.2+ months; Fig. 1) in all

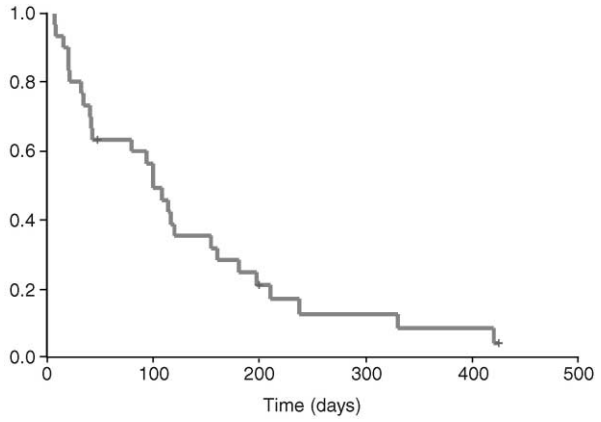

Fig. 1. Overall survival.

patients and 5.9 months (range 1.4–7.9 months) in responders. 8 patients (27%) survived at least 6 months after the initiation of treatment.

3.3. Toxicity

A total of 83 treatment courses were given (a median of three per patient; range 1–6), with 10 delays and eight dose reductions (in patients treated with 1.5 mg/m^2 topotecan). Reasons for dose reductions included haematological toxicity in seven (8%) courses and reduced performance status in one (1%) course. Therapy was delayed due to infection, haematological toxicity and generalised seizures in one course each and other non-treatment-related events in seven courses (8%). Haematological toxicity was the reason for treatment discontinuation in 2 patients.

Myelosuppression was the most common therapeutic side-effect. CTC grade 3 leucocytopenia was observed in 23/83 courses (28%) and grade 4 in 18/83 courses (22%). Grade 3 thrombocytopenia occurred in 14/83 courses (17%) and grade 4 in 9/83 courses (11%).

5 patients (17%) had documented grade 3 infection. Other less frequent high-grade toxicities included grade 3 alopecia (2 patients), grade 3 diarrhoea, grade 3 constipation and grade 3 nausea (1 patient each).

CTC grade 3 thrombocytopenia developed in 6 and grade 4 in 8 of 22 patients treated with 1.5 mg/m^2 topotecan. Thus, topotecan dose was reduced to 1.25 mg/m^2 in the last 8 patients. Here, thrombocytopenia was less severe with 3 cases of CTC grade 3 and no cases of CTC grade 4. Grade 3 alopecia, diarrhoea, constipation and nausea only occurred in the patients treated with 1.5 mg/m^2 topotecan (Table 2).

There was one treatment-related death. The patient who presented with pre-existing thrombocytopenia (110/nl, normal range 150–300/nl) and petechial bleeding before treatment died of a brain haemorrhage during thrombocytopenia 20 days after the first course was started.

Table 2
Treatment toxicity (according to CTC) (patient numbers are given)

	1.25 mg/m^2 Topotecan	1.5 mg/m^2 Topotecan
Leucopenia		
Grade 2	2/8	0/22
Grade 3	3/8	6/22
Grade 4	3/8	9/22
Thrombocytopenia		
Grade 2	2/8	4/22
Grade 3	3/8	6/22
Grade 4	0/8	8/22
Infection		
Grade 2	2/8	1/22
Grade 3	2/8	3/22
Alopecia		
Grade 2	2/8	3/22
Grade 3	0/8	2/22
Nausea		
Grade 2	0/8	3/22
Grade 3	0/8	1/22
Diarrhoea		
Grade 3	0/8	1/22
Constipation		
Grade 3	0/8	1/22

CTC, Common Toxicity Criteria.

4. Discussion

Several new compounds have recently become available for treating SCLC. Among these drugs, camptothecins represent an important class of chemotherapeutic agents with a unique mechanism of action inhibiting the nuclear enzyme topoisomerase-I. An interesting aspect of the topoisomerase-I inhibitor topotecan is its ability to cross the intact BBB. Thus, topotecan activity was assumed in brain metastases of SCLC. In two phase II studies of second-line treatment with 1.5 mg/m^2 topotecan days 1–5 every 3 weeks, patients with asymptomatic brain metastases were also accepted for enrollment. In a study by von Pawel and colleagues [8], 4 of 9 patients responded partially and 1 (concomitantly treated with WBI) completely. In a study conducted by the European Organization for Research and Treatment of Cancer (EORTC), there were three complete responses and one partial response in 11 patients with brain metastases [7]. These retrospective data required confirmation in a prospective study.

We have demonstrated that systemic CHT with topotecan can induce objective regression of metastatic brain lesions in patients with SCLC in relapse. Noteworthy is the fact that a response was also obtained in 50% of patients with previous WBI. This is important, since no effective therapy options are available for patients previously submitted to cranial irradiation. Responses were

also obtained in 2 of 8 patients treated with 1.25 mg/m^2 topotecan.

In general, topotecan was subjectively well tolerated. This finding is of major importance for severely ill and heavily pretreated patients. Especially in patients with previous WBI, there was no late neurological toxicity during the observation time. However, in patients with limited bone marrow reserve after previous CHT, topotecan applied in the given dose can induce substantial myelotoxicity. When the dose was reduced to 1.25 mg/m^2, no grade 4 thrombocytopenia occurred.

WBI is an effective treatment of brain metastases with a response rate up to 77% [9] and symptomatic improvement in more than 50% of patients. However, its efficacy is restricted to the brain. Systemic CHT has the advantage of simultaneous treating prognostically relevant systemic disease. In this study, the 29% response rate of extracranial metastases was similar to the response rate in the brain. Extracranial disease was evaluable in 7 of 10 patients with a response of cerebral metastases; 4 of these patients responded, 2 stabilised and only 1 patient progressed. Interestingly, brain metastases regressed in 1 patient with systemic progression, and progressed in 2 patients who responded extracranially.

The response of SCLC brain metastases to systemic CHT has already been demonstrated in several studies (Table 3; [10–19]). Data pooled from five studies indicated a 66% response rate in 64 evaluable patients with brain metastases treated with first-line CHT [9]. Comparable response rates of cerebral metastases and systemic disease were achieved even using cytostatics unable to penetrate the intact BBB. Interestingly, adding BBB-penetrating drugs such as procarbazine, nitrosoureas and high-dose methotrexate to a standard combination regimen against SCLC did not improve the CNS relapse frequency [2,20]. Treatment of both extensive and microscopic disease at first diagnosis with drugs like topotecan that combine better activity against SCLC with the ability to cross the intact BBB may possibly result in a more effective prevention of CNS relapse. Topotecan was found to be ineffective in preventing CNS metastases after cisplatin plus etoposide in advanced-stage SCLC [21]. However, it is possible that topotecan would have been more effective if it had been administered with the first cycle of therapy. In a recent phase III Japanese trial, enhanced survival was observed when another topoisomerase inhibitor irinotecan was combined with cisplatin as 'up-front' first-line therapy [22]. Optimally designed randomised studies comparing topotecan-based regimens with standard CHT in first-line treatment are needed to clarify the role of topotecan in the prevention of CNS relapse in SCLC.

When used to treat SCLC in relapse, CHT can induce a response in 30–40% of the cases [14–19]. Again, the response rate is the same for cranial as for extracranial manifestations. The response rate of 33% plus an additional 27% disease stabilisation and the median time to progression of 3.1 months achieved in our study are comparable with the results reported in the literature. Some of the studies reported considerable toxicity with a mortality rate of up to 18% [11,13,15,17]. The low rate of septicaemia and toxic deaths in our study compares favourably with these data and makes the regimen suitable for routine palliative treatment.

The results of this study are promising for single-agent treatment and severely pretreated patients. The drug is a reasonable option for patients after WBI, particularly in the presence of progressive extracranial disease. However, this demonstrates again that patients with brain metastases of SCLC in relapse have a poor

Table 3
Chemotherapy for treatment of cerebral metastases of SCLC: clinical studies

Author [Ref.]	Regimen (%)	Previous therapy (months)	Response (months)	Survival	Remission duration
Kristjansen, 1988 [10]	CCNU, CTX, VCR, VP16 or CDDP, VM26, VCR	None	7/10 (70)	3.9	NR
Lee, 1989 [11]	CTX, DX, VCR	None	9/14 (64)	8.5	6
Twelves, 1990 [12]	CTX, VP16, VCR	None	10/19 (53)	7	4.8
Kristjansen, 1993 [13]	CDDP, VM26, VCR CTX, CCNU, VP16, DX VDS, HEX	None	11/21 (52)	3.7	4.5
Giaconne, 1988 [14]	VM26	8 CHT, 4 WBI	3/8 (38)	3	NR
Postmus, 1989 [15]	VP16	27 CHT, 16 WBI	10/28 (36)	8 (responders) 1 (non-responder)	3.5
Groen, 1993 [16]	Carboplatin	17 CHT, 13 WBI	8/20 (40)	3.7	2
Postmus, 1995 [17]	VM26	69 CHT, 27 WBI	26/82 (32)	9.2 (CR)/4.2 (PR)	5.4 (CR)/4.2 (PR)
Malacarne, 1996 [18]	Carboplatin, VP16	4 CHT	7/12 (58)	5.7	NR
Kaba, 1997 [19]	THG, PRC, DBR, CCNU, 5-FU, HU	7 CHT, 9 WBI	6/9 (67)	8	NR

CHT chemotherapy; WBI, whole-brain irradiation; NR, not reported; CTX, cyclophosphamide; VCR, vincristine; VP16, etoposide; CDDP, cisplatin; VM26, teniposide; DX, doxorubicin; VDS, vindesine; HEX, hexamethylmelamine; THG, thioguanine; PRC, procarbazine; DBR, dibromodulcitol; 5-FU, fluorouracil; HU, hydroxyurea; CCNU, lomustine; SCLC, small-cell lung cancer; CR, complete remission; PR, partial remission.

outcome. It was found that topotecan enters into a synergy with many other anticancer agents like cisplatin, temozolomide [23] and vincristine [24]. In addition, initial treatment with topotecan was associated with increasing responsiveness to subsequent doses of etoposide [25] or doxorubicin [26]. Furthermore, studies have demonstrated that topotecan potentiates the effects of radiation on human and animal tumour cell lines *in vitro* and *in vivo* [27]. Thus, improved results can be expected with combined treatment. Future research should address the possible synergistic effect of combined CHT and WBI in the treatment and prevention of brain metastases in SCLC.

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