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Phase I/II clinical trial of concurrent radiochemotherapy in combination with topotecan for the treatment of brain metastases

K. Grüschow*, G. Klautke, R. Fietkau

Klinik und Poliklinik für Strahlentherapie der Universität Rostock, Südring 75, 18059 Rostock, Germany

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Abstract

The prognosis of patients with brain metastases is very poor. In this phase I/II study we tested the feasibility, dosage, toxicity and tumour efficacy of a concurrent radiochemotherapy regimen including topotecan. Twenty patients were recruited between July 1998 and February 2000 (9 women, 11 men) and treated with a whole-brain irradiation of 40 Gy (some patients were also given a boost) in combination with topotecan given as a 21-day continuous infusion in a dosage of 0.4 to 0.6 mg/m^2/day. The median survival was five months (95% Confidence Interval (CI): 2–8 months). In 13 of 20 patients, it was possible to evaluate the remission with computed tomography (CT) scans or magnetic resonance scans. We detected four complete responders (CRs), two partial responders (PRs), and one progressive disease (PD). 6 patients had stable disease (SD). An intracerebral recurrence was experienced in 3 patients, 3 patients experienced spinal lesions. Systemic progression of cancer outside the central nervous system (CNS) was dominant in 9 of 20 patients. A reversible, non-cumulative haematological toxicity mainly occurring from a dose of 0.5 mg/m^2/day and above was dose-limiting for this type of therapy. Combined concurrent radiochemotherapy with topotecan is feasible in spite of various pretreatments. Myelosuppression was the dominant toxicity, which was reversible and manageable. We recommend a dose of 0.4 mg/m^2/day of topotecan as a 21-day continuous infusion therapy in combination with radiotherapy.

Keywords: Brain metastases; Radiotherapy; Chemotherapy; Topotecan

1. Introduction

The prognosis of patients with brain tumours is rather bad. Without therapy, most of the patients die within 1 or 2 months. Anti-oedematous therapy with glucocorticoids can prolong the survival time to 2–3 months. After a conventionally fractioned radiotherapy with single doses of 2.2 or 3 Gy in combination with steroids, survival time generally ranges from 2 to 4 months, with a maximum of 6 months [1]. It is true that this treatment alleviates the neurological symptoms quickly; however, up to 50% of the patients experience an intracerebral recurrence. A patient collective that is selected to include patients with brain metastases only and a maximum of three intracranial lesions operated upon or given stereotactic irradiation followed by whole-brain irradiation if necessary, exhibits a survival time of up to 12 months [2–4].

Brain metastases, however, are mostly a sign of a generalised disease. In 50% of cerebrally irradiated patients, systemic progression outside the central nervous system (CNS) is the main cause of death. Theoretically, the introduction of chemotherapy offers an advantage for these cases. A chemosensitive primary tumour is a precondition for the efficacy of the chemotherapy. Since most patients are already pretreated with cytostatic agents, the selection of adequate cytostatics is limited. Moreover, the patients are in poor general condition due to the advanced stage of their disease and that also limits the remaining therapeutic options.

Topotecan is a semi-synthetic camptothecin derivative that selectively inhibits topoisomerase I in the S-phase of the cell cycle. It interferes with the replication and transcription processes in the tumour cell introducing single-strand nicks in the DNA, thereby holding the DNA in a relaxed state and leading to apoptosis of the

* Corresponding author. Tel.: +49-381-494-9001; fax: +49-381-494-9002.

E-mail address: kathleen.grueschow@med.uni-rostock.de (K. Grüschow).

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cells. Topotecan also penetrates the cerebrospinal fluid and has radiosensitising abilities [5–7].

In this phase I/II clinical trial, we investigated the feasibility, toxicity and efficacy of a concurrent radiochemotherapy with topotecan.

2. Patients and methods

The ethical commission of the University of Rostock approved the study protocol. Patients were eligible for the study if the following criteria were fulfilled: (1) age $\geqslant 18$ years; (2) histologically and computed tomography (CT) confirmed primary tumour; (3) diagnosis of brain metastases using CT or nuclear magnetic scans; (4) at least one bidimensionally measurable brain metastasis; (5) Karnofsky index $\geqslant 60\%$; (6) adequate bone marrow function, normal renal and liver function; (7) life expectancy $\geqslant 12$ weeks; (8) written informed consent of the enrolled patients. A hormonal therapy and dexamethasone in parallel were allowed, but no other concomitant chemotherapies. As a rule, histological assurance of brain metastases was not done since some of the patients were very ill.

Patients with brain metastases derived from a malignant melanoma, hypernephroma or testicular tumour and with other primary cancers, except cone biopsied cervical cancer and non-melanoma skin cancer, were excluded.

In cases with solitary metastases, the possibility of surgical treatment or stereotactical irradiation of the lesions was first checked. Patients primarily treated by irradiation were not recruited into the study unless they had a recurrent tumour that was detected upon imaging analysis.

2.1. Irradiation

The neurocranium was irradiated with lateral opposed isocentric and coplanar portals. In conventional fractionation with a single dose of 2.0 Gy, a total dose of 40 Gy was applied, mainly with a tele-cobalt unit, otherwise with 9 MV photons. In cases of good general condition and a maximum of two lesions or one big lesion among multiple small lesions, a boost of up to 16 Gy was applied after primary CT planning. It was thought that the patients might benefit from a higher local dose without an increase in the late toxicity. The volume consisted of the contrast enhancing areas, including surrounding oedema plus a 2-cm margin.

2.2. Chemotherapy

Topotecan was given systemically via a port system as a continuous infusion over 21 days without any breaks for the weekends. A dose of 0.4–0.6 mg/m^2/day in cohorts of 3–5 patients was applied to determine the optimal dosage. Grade 4 toxicities as dose-limiting toxicities (DLT) determine the maximum tolerated dose (MTD). The first chemotherapy course was started between days 1 and 5 of the beginning of radiotherapy depending on the availability of the port system. A maintenance therapy with topotecan was given, with a maximum of four courses, if there was no need to change the therapy because of the progression of extracerebral manifestations. This was possible, either as a further continuous infusion over 21 days with 0.5 mg/m^2/day or as a single 30-min short infusion 5 days per week with 1.0–1.5 mg/m^2/day repeated every 21 days. During therapy, blood counts were regularly undertaken, at least once per week. In the case of a decrease in leucocytes to fewer than 1.8×10^9/l or a decrease in thrombocytes to fewer than 49×10^9/l, chemotherapy was interrupted. Upon normalisation of parameters, leucocytes $>3.0\times10^9$/l, thrombocytes $>100\times10^9$/l), the therapy was resumed.

2.3. Follow-up statistics

Four to six weeks after the termination of the radiochemotherapy, remission of brain metastases was checked by CT or magnetic resonance scans. Responses were determined according to the World Health Organization (WHO) criteria by CT or magnetic resonance imaging (MRI) scans. Further efficacy controls followed in intervals of 3–6 months. Side-effects were rated by Radiation Therapy Oncology Group (RTOG)/WHO scores.

The data file was closed on 1 July 2001. At present, the follow-up period is up to 19 months (mean 5.5 months, median 6.5 months, range 1–19 months). Survival was determined using Kaplan–Meier curves and the Statistical Package for the Social Sciences (SPSS) statistics program.

3. Results

3.1. Patients' characteristics

20 patients with brain metastases were recruited consecutively between July 1998 and February 2000 (9 women, 11 men) into this phase I/II clinical trial for concurrent radiochemotherapy with topotecan. Patients' characteristics are listed in Table 1. The age of the patients at the beginning of the therapy was between 37 and 75 years (median 53 years).

5 patients had solitary brain metastases measuring over 40 mm; the other patients had more than one lesion (1× two, 2× three, 1× four, 11× five or more metastases). In 12 patients, the primary tumour site was bronchocarcinomas—five non-small cell cancers

Table 1
Characteristics of all patients

No.	Age/sex	Tumour type	Metastases	No. of brain lesions	Topo-doses (mg/m^2/day)	Topo-courses/ modus	Radiation (Gy)	Response	Comment
1	47/m	SCLC	hep	>5	0.4	1	2→40	CR	Syst. PD CNS recurrence
			pulm				2→6		
			cerebr						
2	43/f	Ovarian cancer	periton	2	0.4	3 civ	2→40	ND	Syst. PD
			hep				2→14		
			cerebr						
3	59/f	Breast cancer	pulm	>5	0.4	4 bolus	2→40	CR	Syst. PD
			cerebr						
			lymph node						
4	46/m	SCLC	hep	1	0.4	3 civ	2→40	ND	Syst. PD
			pulm				2→16		
			adrenal						
			cerebr						
5	55/f	NSCLC	cerebr	1	0.4	1	2→36	PD	Previous cranial radiation
			oss						
6	39/m	NSCLC	cerebr	>5	0.5	2 civ	2→40	NC	
							2→16		
7	52/f	NSCLC	pulm	1	0.5	4 bolus	2→40	CR	Syst. PD
			cerebr				2→16		
8	48/f	Breast cancer	pulm	>5	0.5	2 civ	2→40	PR	Spinal recurrence
			cerebr						
9	57/m	SCLC	lymph node	>5	0.5	4 bolus	2→40	NC	Gliosis
			cerebr						
10	54/f	Breast cancer	pulm	>5	0.6	4 bolus	2→40	CR	Spinal recurrence
			hep						
			oss						
			lymph node						
			cerebr						
11	66/m	SCLC	oss	>5	0.6	2 bolus	2→40	PR	Syst. PD
			hep						
			pulm						
			cerebr						
12	57/m	Colorectal cancer	hep	1	0.6	2 civ	2→40	ND	Syst. PD
			pulm				2→10		
			cerebr						
13	61/m	NSCLC	cerebr	3	0.6	4 civ	2→40	NC	Gliosis
14	47/f	Breast cancer	pulm	1	0.5	1	2→40	NC	Syst. PD
			hep						
			cerebr						
15	44/m	SCLC	cerebr	>5	0.5	2 bolus	2→40	NC	Spinal recurrence CNS recurrence
16	62/f	Breast cancer	pulm	>5	0.5	1	2→26	ND	Related intracerebral bleeding death
			hep						
			oss						
			cerebr						
17	75/m	SCLC	cerebr	>5	0.5	1	2→24	ND	Wish of patient Related intracerebral bleeding
18	37/m	NSCLC	pulm	3	0.5	1	2→26	ND	Pulmonary embolism death
			cerebr						
19	41/f	Breast cancer	pulm	>5	0.5	4 civ	2→40	NC	Syst. PD still alive
			hep						
			pleural						
			lymph node						
			oss						
			cerebr						
20	58/m	SCLC	cerebr	4	0.4	1	2→40	ND	

m, male; f, female; SCLC, small-cell lung cancer; NSCLC, non-small cell lung cancer; hep, hepatic; pulm, pulmonary; cerebr, cerebral; periton, peritoneal; oss, osseous; civ, continuous infusion; CR, complete remission; PR, partial remission; NC, no change; ND, no data; syst, systemic; topo, topotecan; PD, progressive disease; CNS, central nervous system.

(NSCLC), seven small-cell cancers (SCLC); 6 patients had a mammary carcinoma. One patient suffered from an ovarian carcinoma and 1 patient from sigmoid cancer. 19 of 20 patients were pretreated with a mean number of 1.6 regimens (1×0, 11×1, 5×2, 1×3, 2×4 regimens) of cytostatics (2–39 courses, median six courses). 14 of 20 patients had already received radiotherapy in the region of their primary tumours or other metastases. A female patient had a recurrence after surgical intervention and irradiation of a solitary brain metastasis. 10 of 20 patients had had an operation for their primary tumours or for other metastases.

6 patients received a boost irradiation (range 6–16 Gy, median 15 Gy, mean 13 Gy) because of their good general condition, small number or the location of metastases.

3.2. Dose-finding study

In the first 13 patients, i.e. dose-finding study; the topotecan dosage was increased from 0.4 to 0.5 to 0.6 mg/m^2/day. Grade 4 toxicities developed from 0.6 mg/m^2/day onwards. The toxicities were exclusively leucopenia (leucocytes $<1.0\times10^9$/l) and thrombocytopenia (thrombocytes $<25\times10^9$/l) as DLT which rapidly normalised upon withdrawal of topotecan. The MTD seemed to be 0.6 mg/m^2/day. Therefore, we decided to continue with the dose of 0.5 mg/m^2/day and treated a further 6 patients with this dose. One patient received an incorrect dose with 0.4 mg/m^2/day. However, we included this patient in the analysis because of the small number of patients available. A renewed evaluation of toxicity also revealed leucopenia and thrombocytopenia grade 3 and 4 at these doses (Table 2).

3.3. Survival

The mean and median survival in all 20 patients were 6 and 5 months (95% Confidence Interval (CI) for mean survival 4–8 months, limited to 19; for median survival 2–8 months). If we analyse the data taking into account metastases of additionally affected organ systems, the median and mean survival decreased in conjunction with an increase in the number of sites with metastases in the various organ systems. 13 of the 19 deceased patients died of cerebral or systemic progression. 2 patients died during or shortly after therapy of a related intracerebral bleeding. Intercurrent death occurred in 4 patients suffering from bronchocarcinomas. In 3 cases, the cause of death was pneumonia or a septic abscess in the lung, in 1 case pulmonary embolism. Pneumonia or septic abscess occurred 1–3 months following the end of topotecan treatment. No leucopenia was present at that time and, therefore, no connection with the treatment was assumed.

Table 2
Analysis of toxicity of all patients ($n=20$), shown is haematological toxicity only as no other organ toxicities appeared

Dosage (mg/m^2/day)	WHO-grade III	WHO-grade IV
Leucopenia		
0.4	1/6	0/6
0.5	6/10	0/10
0.6	1/4	1/4
Thrombocytopenia		
0.4	1/6	1/6
0.5	3/10	2/10
0.6	0/4	1/4

WHO, World Health Organization.

3.4. Response rates

In 13 of 20 patients, one follow-up CT or MRI scan could be obtained at least 1 month after the end of the combined treatment. In the remaining 7 patients, we were unable to do diagnostics due to the systemic progression of the disease or because of the generally poor condition of the patient. One patient had a progression of brain metastases. In 6 patients, we detected no change of disease; 2 patients achieved a partial remission. 4 patients displayed a complete remission with no detectable cerebral metastases. The characteristics of the patients who developed a partial or complete remission are shown in Table 3.

Only 2 of the responding patients, 1 with multiple lesions and 1 with a single lesion, received a boost. For 3 other patients with boost irradiation, we have no diagnostic information. One patient showed no change of the metastases.

13 of 20 patients received maintenance therapy with topotecan, either as a further continuous infusion (8 of 20) over 21 days with 0.5 mg/m^2/day or as a single 30-min short infusion (5 of 20) 5 days per week with 1.0–1.5 mg/m^2/day repeated every 21 days. The maintenance therapy was administered over a maximum of four courses.

4 of the responding patients (3 CR, 1 PR) had maintenance chemotherapy administered as a bolus with one to four courses. In patients with continuous infusion of topotecan, one partial remission was achieved. One complete remission patient had no topotecan maintenance chemotherapy.

3.5. Analysis of recurrence

CT or MRI scans were performed at 3–6-monthly intervals following irradiation and repeated at the time of neurological deterioration.

An intracerebral recurrence or progression was seen in 2 patients after 4 and 9 months, respectively. In 3 patients, spinal recurrence occurred 2, 5 and 6 months, respectively, after the initial treatment. In these cases,

Table 3
Characteristics of responders

No.	Tumour type	Pretreatment	Prior response	Metastases	No. of brain metastases	Radiation (Gy)	Topotecan (mg/m^2/day)	Brain response
1	SCLC	5×Carbo/Eto/(Vin) pulmonary radiation	PD lung PD hepar	Brain Hepar Lung	>5	2→40 2→6	0.4	CR CNS-recurrence
2	Breast cancer	Surgery radiation of breast hormonal therapy 6×paclitaxel/Epi	 CR lymph node PR lung	Brain Lung Lymph node	>5	2→40	0.4	CR
3	NSCLC	Simultaneous chemotherapy+ pulmonary radiation (2×Campto/Cis)	PR lung	Brain Lung	1 cerebellar	2→40 2→16	0.5 3×1.25 bolus	CR
4	Breast cancer	Surgery 3× CMF hormonal therapy 6×paclitaxel/Epi Axillary radiation	 CR lung PR hepar SD bone PR lymph node CR lymph node	Brain Lung Hepar Bone Lymph node	>5	2→40	0.6 3×1.0 bolus	CR Spinal recurrence
5	Breast cancer	Surgery hormonal therapy 6x Taxotere pulmonary radiation mammary radiation 6×Cyclo/MTX hormonal therapy 6×docetaxel pulmonary radiation	 CR lung NC lung PR lung	Brain Lung	>5	2→40	0.5 1×0.5 civ	PR Spinal recurrence
6	SCLC	6×AC(O)	CR lung PR bone	Brain Bone Lung Hepar	>5	2→40	0.6 1×1.5 bolus	PR

SCLC, small-cell lung cancer; NSCLC, non-small cell lung cancer; Carbo, carboplatin; Eto, etoposide; Vin, vincristine; Epi, epirubicin; Campto, camptothecin; Cis, cisplatin; Cyclo, cyclophosphamide; MTX, mitoxantron; AC(O), doxorubicin + cyclophosphamide(+ vincristine); CR, complete response; PR, partial response; NC, no change; civ, continuous infusion; PD, progressive disease; CNS, central nervous system; CMF, cyclophosphamide + methotrexate + 5-fluorouracil; hepar, hepatic.

no intracerebral progression was detected by MRI scans, and the neurological symptoms of brain metastases had completely receded. In 1 patient who initially had an intracerebral complete remission, an intraspinal recurrence was detected. This lesion was irradiated. Two months later, an intracerebral recurrence was observed. As a result of this, and the fact that the patient's poor general condition allowed for no further therapeutic options, the patient died shortly thereafter. The other patients underwent an irradiation of the spinoaxis after a regimen of intrathecal chemotherapy with mitoxantrone/cyclophosphamide or local cerebral irradiation. All of these patients have died in the meantime, 1 female patient under therapy for recurrent disease, the others 1, 2 or 4 months after the start of the secondary therapy. The patient who was irradiated after a relapse after surgery, was afflicted by a progression of brain metastases.

The systemic progression of tumours outside the CNS in our patients was dominant. 9 of 20 patients had a proven progression of further distant metastases. In 8 patients surviving longer than 3 months, no progress of systemic disease was detectable. The remaining 3 patients were not evaluable in this respect, partly because of their short survival time.

3.6. Toxicity and feasibility of therapy

Treatment-related death did not occur. Leucopenia and thrombocytopenia according to WHO-grade 4 (Table 2) were dose-limiting for the therapy. These toxicities increased with increasing dosage, they were however reversible upon termination of chemotherapy. An interruption of radiotherapy was therefore not necessary. Acute neurological toxicities during concurrent radiochemotherapy were not observed. In 2 patients, we observed a reactive gliosis detected by a nuclear magnetic resonance technique as a late neurological complication 5 months after the end of the therapy. Clinically, there was no correlation between the gliosis and any symptoms of the patients.

Table 4
Feasibility of chemotherapy is dependent on dosage

Dosage (mg/m^2/day)	Termination of therapy		
	After 1 week	After 2 weeks	After 3 weeks (regularly)
0.4	0/6	1/6	5/6
0.5	2/10	4/10	4/10
0.6	0/4	2/4	2/4

In 11 of 20 patients, the chemotherapy could be carried out according to plan. With increasing topotecan dosage, the number of early therapeutic terminations (Table 4) increased. In 1 case at a dose of 0.5 mg/m^2/day, the therapy was terminated after two weeks because of a pulmonary embolism followed by death of the patient. The actual mean/median dose intensities were 7.9/8.4 mg/m^2 at the 0.4 mg/m^2/day level, 8.4/8.3 mg/m^2 at the 0.5 mg/m^2/day level and 11.4/12.0 mg/m^2 at the 0.6 mg/m^2/day level.

In 17 of 20 patients, the radiotherapy could be completely applied as planned. 3 patients terminated radiotherapy early, in 1 case upon the request of the patient. 2 patients died while under radiotherapy due to increasing deterioration of the patient's general condition together with bleeding in brain metastases and in 1 case due to lung embolism.

In 19 of 20 patients, the therapy had to be started in the hospital due to the patients' bad general condition or due to neurological symptoms. With improvement of situations and conditions, at least 10 of the 20 patients terminated the therapy as outpatients. One patient remained in hospital solely because of his adverse social conditions. The cortisol doses were reduced from a mean of 16 mg/day (median 12 mg/day) dexamethasone at the beginning to 3 mg/day (median 0 mg/day) at the end of therapy.

4. Discussion

The results of total brain irradiation alone in the case of brain metastases are hardly encouraging. The neurological symptoms can be controlled very quickly, however, more than 50% of the patients experience an intracerebral recurrence. The median survival times of these patients are accordingly low around 3–4 months [8–10]. As in many patients, systemic metastases are dominant in addition to metastases in the brain; primary chemotherapy has been increasingly requested for these patients [11,12]. Only a few years ago, it was generally assumed that only inadequate amounts of cytostatics penetrate the blood–brain barrier into the cerebrospinal fluid and thus reach the brain metastases. Recent investigations, however, showed that this is not true for some substances as well as for bigger lesions [13]. Published data on survival fluctuate greatly and range from a median of 3.2–6.5 months for the SCLC and a median of 4–6.5 months for the NSCLC (reviews in Refs. [11,14].

Many authors described the feasibility of concurrent radiochemotherapy in patients with glioblastoma multiforme. Fisher and colleagues reported the results of a phase I study of topotecan plus cranial radiation. In contrast to our trial, they administered topotecan as a short infusion daily for 5 days at 21-day intervals. They also observed haematological toxicity alone as the dose-limiting toxicity increased as the dose of topotecan increased. There was no statistically significant difference in the median survival between different doses of topotecan. They discussed the possible superiority of continuous infusion over bolus injection [15].

We therefore tried to combine topotecan with a total brain irradiation to improve the treatment, taking into consideration the specific problems of patients with brain metastases:

- Brain metastases are mostly a sign of a generalised disease. Therefore, the cytostatic agent should achieve a systemic level of concentration, which was shown for a 21-day continuous-infusion for ovarian cancer by Hochster and colleagues [16].
- Brain metastases occur very late in the history of a patient. Most patients are pretreated with a variety of cytostatic agents. In the patient group investigated, topotecan was not used in the first-line therapy and thus was available as a second- or third-line cytostatic [17] because of its non-cross-resistance. In various investigations, topotecan has showed activity in SCLC [18–20]. as well as in NSCLC [21,22]. At the same time, good experiences with mammary carcinoma have been described [23].
- A cumulative acute and late toxicity of radiotherapy and chemotherapy must be avoided. Topotecan is interesting because this drug is active only on proliferating cells and thus a non-specific radiosensitising effect [5,24] in somatic brain cells cannot be assumed.
- In contrast to the parent substance camptothecin, topotecan also penetrates the intact blood–brain barrier offering therapeutic levels of the drug in the cerebrospinal fluid so that even small lesions can be treated [7]. First case reports have shown that a monotherapy with topotecan may be effective in cases of mammary carcinoma, [25] as well as for bronchocarcinomas [13,26].
- The haematological toxicity of the combined treatment must be kept under control, since most of our patients had already been given many regimens of chemotherapy with various cytostatic agents. This meant that the bone marrow reserve

cannot be estimated properly; however, it had to be assumed to be highly reduced. This control was achieved by using continuous infusion protocol. Following the advice for stopping the treatment (see Material and methods), we had to stop the cytostatic treatment in 6/10 patients treated with 0.5 mg/m^2/day after 1 or 2 weeks of topotecan. Only 2 of these patients had reversible grade IV-haematological toxicity and neither of these 2 patients had a neutropenia-induced fever. Using 0.4 mg/m^2/day, complete topotecan treatment was possible in 5/6 patients: none of these 5 had a grade IV leucopenia. Therefore, we propose using 0.4 mg/m^2/day topotecan in further studies.

- The continuous application of radiotherapy should not be influenced by the administering of the cytostatic drug. This was achieved in our study, since in 17/20 patients the radiotherapy could be completely applied as planned. In the 3 remaining patients, chemotherapy was not the reason for interrupting radiotherapy.
- The treatment should be performed as soon as possible in an out-patient manner. We achieved this in 11/20 patients. Moreover, we were able to reduce the dose of cortisol very quickly in order to avoid further immunosuppression of the patients.

Experiences with concurrent radiochemotherapy of brain metastases are rare. The French authors Reboul and colleagues reported in 1996 for example on a phase I trial of the combination of cisplatin, carmustine and etoposide with whole brain irradiation (36 Gy in 15 fractions) in patients with lung carcinomas [27]. In this trial, a 41.6% complete remission rate with a median survival time of 7.4 months was achieved. Robinet and colleagues reported in 1998 on a phase III trial with patients who had cerebral metastases of a broncho-carcinoma [28]. These patients were treated either concurrently with cisplatin and vinorelbine or sequentially with chemotherapy with a total brain irradiation after two courses. The median survival of both sets did not significantly differ and varied between 15 and 20 weeks (3–4 months).

Two other working groups published various experiences with concurrent radiochemotherapy with topotecan and brain metastases as abstracts. In 2000, Morris and colleagues [29] terminated their investigation after the first 6 patients at the first dose-escalation level. They treated the patients with total brain irradiation with single doses of 2 Gy up to a total dose of 40 Gy and concurrently infused with 0.5 mg/m^2/day of topotecan over 5 days. Their explanation for the failure of the therapy was the pretreatment of their patients. In contrast to these experiences, in 1999 Kocher and colleagues published [30] comparatively positive experiences to our study. Apart from a total brain irradiation (3 Gy to a total of 36 Gy, or 2 Gy to a total of 46 Gy), they treated patients with a short infusion of topotecan (5–8 days 0.5 mg/m^2/day or 12 days 0.5 mg/m^2/day). The median survival was 4 months. In 4 of 7 patients, they demonstrated an objective response for the brain metastases.

Our experiences show that a combined concurrent radiochemotherapy with topotecan can be safely applied in spite of various pretreatments. Side-effects developed exclusively in the haematological system. They were reversible and well manageable. Long-term toxicity could not be demonstrated except for two morphologically-described glioses 5 months after radiochemotherapy. However, they were of no clinical importance. Retrospectively, we assume that the median survival with 5 months is at least as good as sole radiation therapy as reported in the literature. We recommend parallel to radiation a dose of 0.4 mg/m^2/day topotecan as a 21-day infusion therapy repeated on day 29 for four cycles of chemotherapy or a prolongation of maintenance therapy until clinically-documented progression of the disease occurs.

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