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Temozolomide added to whole brain radiotherapy in patients with multiple brain metastases of non-small-cell lung cancer: a multicentric Austrian phase II study

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Summary
Background This multicentric randomized phase II study investigated the feasibility and toxicity of temozolomide (TMZ) added to whole brain radiotherapy (WBRT) followed by adjuvant TMZ in patients with multiple brain metastases of non-small-cell lung cancer (NSCLC).

Methods Patients with multiple brain metastases from NSCLC aged ≥18 years, classified according to recursive partitioning analysis class I or II and with adequate organ functions were eligible. Treatment consisted of WBRT + TMZ 75 mg/m^2 for 2 weeks followed at day 28 by TMZ 100 mg/m^2/day 2 weeks on/2 weeks off for up to 6 months (radiochemotherapy, RCT) or WBRT alone (radiotherapy, RT).

Results The study enrolled only 35 patients (22 patients in RCT and 13 in RT) and had to be closed prematurely due to poor accrual. The toxicity was mainly due to TMZ with WHO grade 3 and 4 thrombocytopenia in 3/22 versus 0/13, leucocytopenia in 1/22 versus 0/13 and lymphocytopenia in 7/22 versus 12/13 patients in RCT and RT respectively. Thirteen patients in RCT and six in RT progressed systemically and dropped out before first restaging of the response in brain. Median time to progression (TTP) was 2.4 months (95% CI: 2–2.6 months) and 2.0 months (95% CI: 0.5–3.5 months), median overall survival (OAS) was 3 months (95% CI: 1.7–3.1 months) and 6.3.months (95% CI: 0.2–7.6 months) in RCT and RT, respectively.

Conclusions Like other studies before on patients with brain metastases, insufficient number of recruited patients does not allow conclusions on efficacy and toxicity as the study closed prematurely.

Keywords Brain metastases · Non-small-cell lung cancer · Whole brain radiotherapy · Temozolomide · Trial design

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Radiochemotherapie mit Temozolomid für Patienten mit Hirnmetastasen bei nicht kleinzelligem Lungenkarzinom

Zusammenfassung
Grundlagen Wir berichten über die Ergebnisse einer multizentrischen randomisierten österreichischen Phase II Studie über Verträglichkeit und Toxizität der Zugabe von Temozolomid (TMZ) zur Ganzhirnbestrahlung (WBRT) bei PatientInnen mit multiplen Hirnmetastasen des nicht kleinzelligen Lungenkarzinoms (NSCLC):

Methodik Das Studienprotokoll sah vor, 92 erwachsene PatientInnen mit multiplen Hirnmetastasen bei NSCLC entweder mit WBRT alleine (RT) oder mit WBRT + TMZ 75 mg/m^2 konkomitant zur Bestrahlung und nach 28 Tagen Pause 100 mg/m^2, Tag 1–14/q28 (RCT) zu behandeln.

Ergebnisse Die Studie musste wegen fehlender Rekrutierung vorzeitig geschlossen werden. 35 PatientInnen wurden in die Studie aufgenommen, 22 in den RCT und 13 in den RT Arm. Die beobachteten Toxizitäten waren überwiegend auf TMZ zurückzuführen mit jeweils WHO Grade 3 und 4 Thrombocytopenie in 3/22 gegenüber 0/13, Leucocytopenie in 1/22 gegenüber 0/13 and Lymphocytopenie in 7/22 verglichen mit 12/13 PatientInnen im RCT Arm gegenüber dem RT Arm. Dreizehn PatientInnen des RCT Arms und sechs im RT Arm erreichten wegen systemischer Progression das erste Restaging zehn Wochen nach Therapiebeginn nicht. Die mediane Zeit bis zur Tumorprogression betrug 73 Tage (95 % CI: 63–80) im RCT Arm und 62 Tage im RT Arm, (95 % CI: 15–108), die mittlere Überlebenszeit 3 Monate in RCT (95 % CI: 1,7–3,1 Monate) gegenüber 6,3 Monate (95 % CI: 0,2–7,6 Monate) im RT Arm.

Schlussfolgerungen Diese Studie konnte ihr Rekrutierungsziel nicht erreichen. Wegen der zu geringen PatientInnenanzahl können auch keine Aussagen über die Wertigkeit der Zugabe von Temozolomide zur WBRT bei Hirnmetastasen von NSCLC gemacht werden.

Schlüsselwörter Hirnmetastasen · nicht kleinzelliges Bronchialkarzinom · Ganzhirnbestrahlung · Temozolomid · Studiendesign

Introduction

Patients with non-small-cell lung cancer (NSCLC) often develop brain metastases, but until recently have often been excluded from clinical trials in order to avoid the bias through neurological complications or death. Therefore, randomized controlled trials are rare despite the high prevalence of patients with brain metastases.

Treatment for patients with brain metastases consist mainly in surgical and radiotherapeutical approaches. Nevertheless, experience about the efficacy of chemotherapy in patients with brain metastases is accumulating. For most tumour entities, the response to cytotoxic drugs against brain metastases is comparable to the systemic response and reaches up to 25–35 % response rate in NSCLC [1–14].

Temozolomide (TMZ) is able to cross the blood–brain barrier and has shown activity against a broad range of cancers in vitro including NSCLC cell lines [15–17]. Thus, TMZ added to whole brain radiation therapy (WBRT) has been investigated and improved the response rate of patients with brain metastases of NSCLC [4]. In patients with multiple melanoma, Ridolfi et al. observed a less than expected brain metastases in patients treated with TMZ for systemic disease, suggesting the prevention of brain metastases by TMZ [18]. Furthermore, some salvage chemotherapy trials suggest activity of TMZ against brain metastases [1, 19]. However, it must be kept in mind that a phase II trial on the efficacy of TMZ against systemic NSCLC was stopped early because of lack of efficacy [9]. But efficacy of TMZ is enhanced by radiotherapy (RT) as shown by Kouvaris et al. and Addeo et al. [1, 6, 12, 19–22]. Moreover, in brain metastases, the cytotoxic effect of TMZ might be enhanced by its radiosensitizing during WBRT as in glioma cells [23, 24] (Table 1).

In order to test this hypothesis, we performed a national multicentric randomized phase II trial for patients with several brain metastases from NSCLC in Austria.

Patients and methods

Patient eligibility criteria included cytological or histological confirmed NSCLC and radiologically documented multiple brain metastases. At least one of the brain metastases had to be measurable by magnetic resonance imaging (MRI) scan. Resection or radiosurgery for brain metastases was allowed, when at least one measurable and untreated brain metastasis remained in the central nervous system (CNS). Other inclusion criteria were age of ≥ 18 years, World Health Organization (WHO) performance score of ≤ 2, adequate bone marrow function (neutrophil count > 1.5 G/l, platelets > 100 G/l, haemoglobin > 9 g/dl), as well as preserved renal and hepatic function (serum creatinine < 1.5 × and transaminases < 2.5 × of the upper limit of normal institutional normal values).

Study schedule and evaluations

The study was a national, open label, multicentric, randomized phase II trial. The primary aim of the study was to assess safety and toxicity of concomitant chemotherapy with TMZ at 75 mg/m^2 during WBRT and later on at the 2 weeks on/2 weeks off schedule in patients with cerebral metastases of NSCLC (radiochemotherapy, RCT) in comparison to patients treated with WBRT only (radiotherapy, RT). Additional parameters were progression-free survival at 6 months (PFS-6) and the duration of overall survival (OAS).

Screening assessments included medical history, physical examination, performance status, neurological function status, electrocardiogram, computed tomography (CT) scan of thorax and abdomen to assess systemic disease, MRI scan of the brain, as well as blood counts and serum chemistry. Patients were seen in weekly intervals during radiation therapy and every other week after radiation, or anytime when clinically indicated.

In both arms, a restaging was planned 6 weeks after completion of RT. At this time point, assessment of the therapeutic response of brain disease according to McDonald's criteria [25] was intended as well as restaging of the systemic disease allowing eventual changes in systemic therapy. Follow-up included laboratory procedures in monthly intervals for patients treated with chemotherapy and imaging procedures in 2 months intervals for all patients until progression. When clinically indicated, restaging was done anytime.

Table 1 Results of trials with chemotherapy with temozolomide in patients with brain metastases

Reference	TMZ conc	TMZ adj	*n*	CR (%)	PR (%)	SD (%)	PFS-6 (%)	PFS med (Months)	OAS med (Months)	ORR (%)
Abrey [1]	–	X	22		9	36				9
Antonadou [4]	X	X	24	38	58					96
Djiadjuisko [9]	–	X	12					<2		
Verger [13]	X	X	82				PFS-3: 72			
Antonadou [30]	X	X	103					7.5	7.9	48
Giorgio [19]	–	X	30	6	3	10				
Christodoulou [7]	–	X + CDDP	12	8	8			2.9		
Cortot [8]	–	Upfront + CDDP	50					2.3	5.4	16
Omuro [12]	–	+ vinorelbine	21			33		6		11
Choong [6]	–	75 mg/m^2, days 1–15, + irinotecan	46	–	8.7	37		1.8	9.8	
Kouvaris [11]	60 mg/m^2	X	33	36	43	7	50	11	12	78.6
Addeo [2]	X	75 mg/m^2, days 1–21	27	7.4	40.7			6	8	41
Kourroussis [10]	–	75 mg/m^2, days 1–21	31	–	6.5	10		2.4	3.4	

TMZ temozolomide, *TMZ conc* concomitant TMZ during WBRT: 75 mg/m^2 temozolomide concomitant to radiation therapy, *TMZ adj* adjuvant TMZ: 150–200 mg/m^2, days 1–5, repeated every 28 days, *CR* complete response, *PR* partial response, *SD* stable disease, *CDDP* cis-diamminedichloroplatinum(II), *PFS-6* progression-free survival at 6 months, *PFS med* median progression-free survival *OAS med* median overall survival, *ORR* overall response rate, *X* part of the treatment schedule in this study

Quality of life was assessed with the EORTC QLQ-C 30 + Brain Cancer module; (optional) evaluation of neurological functioning included the Mini Mental score and the EFIT test (Edinburgh Functional Impairment Test).

Treatment plan

The study protocol was approved by the ethical committees of the involved centres. This open label phase II study compared a radiotherapy arm (RT) to a radiochemotherapy arm followed by adjuvant chemotherapy (RCT). Whole brain radiotherapy (WBRT) administered according to the practice of the individual centre following two fractionation regimens consisting either of

- 20 fractions of 2 Gy each, administered 5 days a week or
- 10 fractions of 3 Gy each, administered 5 days a week

In the RCT arm TMZ 75 mg/m^2/day was administered daily during the last 2 weeks for the long radiation regimen and during the whole radiation for the short regimen. Two weeks after completion of WBRT, TMZ 100 mg/m^2 was continued for 14 days every 28 days until unacceptable toxicity or progression of disease for up to six cycles

Concomitant medications were recorded continuously and included anti-emetics, anti-epileptic drugs and corticosteroids and other medications at the discretion of the treating physician. Toxicities and adverse events were evaluated and monitored according to the National Cancer Institute Bethesda Common Toxicity criteria, NCI-CTC v.3.0 [26].

Statistical methods

The safety and efficacy analyses were based on the intent to treat population.

Demographic and background information was planned to be summarized and displayed using descriptive statistical techniques. The primary efficacy variable was defined as the rate of PFS at the first evaluation ten weeks after start of therapy. Statistical significance of the comparisons was assessed by a 5 % level two-sided log-rank test for the equality of the survival curves. The secondary efficacy variable was overall survival, defined as the time from randomization to death. The distributions for survival time was estimated with the Kaplan–Meier method and compared using the log rank test.

The assumptions for the calculation of the sample size were based on a PFS of 70 % in the RCT group B and of 40 % in the RT group (alpha = 5 %, power = 80 %) to account for dropouts, a total of 92 patients had to be recruited.

Results

Patient's characteristics

An elaborate consensus procedure on study design resulted in the option of 2 WBRT schedules and other provisions taken in order to facilitate recruitment of patients. Eighteen centres in Austria started participation in this study. However, only ten centres randomized patients and five of them enrolled only one patient each.

Patient's characteristics are listed in Table 2, 22 patients were randomized into the RCT arm and 13 in the RT arm. There were 14 female and 21 male patients, with

Table 2 Demographic data and patient's characteristics

Treatment arm		RCT arm		RT arm	
		n = 22	%	*n* = 13	%
Sex	Female	9	41	5	38.5
	Male	13	59	8	61.5
Age	Median (years)	69		64	
	Range	(36–85)		(54–78)	
RPA	Class I	5	22.7	3	23
	Class II	17	77.3	10	77
CNS metastasis resection	No	20	91	10	77
	Yes	2	9	3	23
Previous chemotherapy	No	12	55	7	47
	Yes	10	45	6	43
Previous RT (not CNS)	No	17	77.3	10	76
	Yes	2	13.6	3	23
KPS median		80		80	
WBRT schedule	10 × 3 Gy	16	72	9	69
	20 × 2 Gy	2	9	4	31
Progression	CNS	3	13.6	2	15.3
	Thorax	11	50	6	46
	Liver	7	32	2	15.3

RCT radiochemotherapy, *RT* radiotherapy, *RPA* recursive partitioning analysis, *CNS* central nervous system, *KPS* Karnofsky performance score, *WBRT* whole brain radiotherapy

a median age of 65 years (36–85 years). Their median Karnofsky performance score (KPS) at randomization was 80 (70–100). Eight patients were classified into recursive partitioning analysis (RPA) class I, 27 in RPA class II. Fifteen patients presented with synchronous brain metastases. The remaining 20 patients had already been treated with resection of the thoracic tumour ($n=8$), resection of brain metastases ($n=5$), with RT to the chest ($n=5$) and with one ($n=9$), two ($n=3$) or three lines ($n=4$) of systemic chemotherapy treatment.

Two patients in the RT arm and four RCT patients were treated with 20 × 2 Gy, all other patients were treated according to the 10 × 3 Gy WBRT regimen. A total number of 30 cycles of TMZ was administered to 18 patients within this study. Four patients got concomitant chemotherapy only and 14 patients a maximum of four cycles.

Treatment response

Ten weeks after completion of WBRT, an objective response of the CNS metastases was observed in seven patients: two complete responses (CR) and three partial responses (PR) (22 %) in the RCT arm and two PR (15 %) in the RT arm. Stable disease (SD) in CNS was observed in eight (36 %) RCT patients and one RT patient (7.6 %). However, PFS-6 was 27 % (6/22 patients) in RCT and 46 % (6/13 patients) in RT patients. PFS lasted in median 2.4 months in RCT (2–5.9 months) and 2.1 months in RT patients (1.2–6.2 months) (Fig. 1). Two RCT patients (9 %)

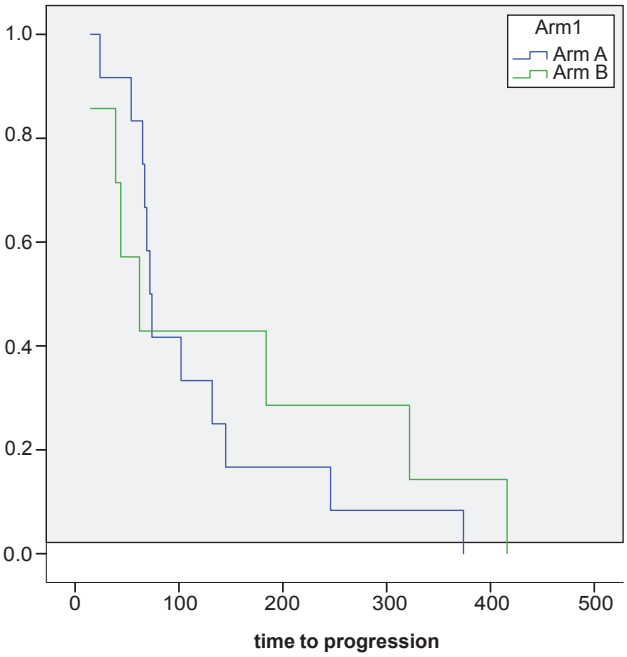

Fig. 1 Progression-free survival of patients with several brain metastases of non-small-cell lung cancer (NSCLC) in days from randomization. Arm A: radiotherapy (RT) + temozolomide (TMZ), $n=22$; Arm B: RT, $n=13$, $p>0.05$, not significant

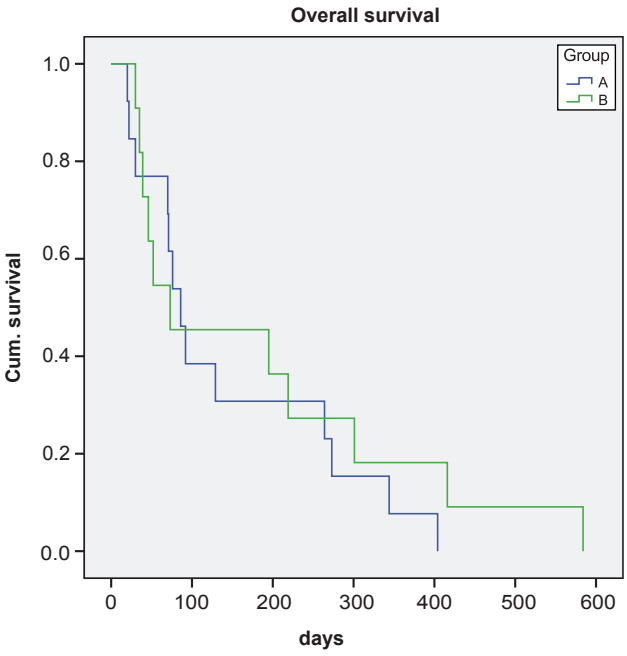

Fig. 2 Overall survival of patients with several brain metastases of non-small-cell lung cancer (NSCLC) in days from randomization. Arm A: radiotherapy (RT) + temozolomide (TMZ), $n=22$; Arm B: RT, $n=13$, $p>0.05$, not significant

and three RT patients (16.6 %) progressed in CNS. Nine RCT patients and five RT patients progressed either in lung or liver. The overall survival was 3 months in the RCT

Table 3 Haematological and non-haematological toxicity

Toxicity	RCT arm $n=22$ (%)		RT arm $n=13$ (%)	
	WHO Grade I and II	WHO Grade III and IV	WHO Grade I and II	WHO Grade III and IV
Haematological toxicity				
Red cells	55.6	0	46.2	0
Leucocytes	5.6	5.6	7.7	0
Neutrophils	0	5.6	0	0
Lymphocytes	33	16.7	7.7	30.8
Thrombocytes	33.4	16	38.5	0
Non-haematological toxicity				
Nausea and vomiting	50	16.7	30.8	7.7
Consciousness disturbance	16.6	22	31	7.7
Coordination	16.7	16.7	38.5	0
Mood disturbance	50	27.8	46	7.7
Headache	61	0	38.5	0
Change of behaviour	21.5	11	30	7.7
Vertigo	50	11	38.5	7.7
Sleep disturbance	39	22	38.5	22

RCT radiochemotherapy, *RT* radiotherapy, *WHO* World Health Organization

(0.7–13.2 months) and 6.3 months in the RT arm (1–25 months) (Fig. 2). The differences were not significant.

The quality of life data recorded were in accord with the high symptom burden and fatigue of advanced NSCLC patients. Due to the rapid progression of many patients, the follow-up was incomplete in most patients.

Toxicity

The toxicity recorded according to CTC-NIH v3.0 is listed in Table 3. Severe haematological toxicity occurred in four RCT patients, but was not observed in RT patients. No patient developed severe anaemia, 3/22 (13.6 %) of RCT patients developed severe thrombocytopenia and one patient developed severe leucocytopenia (Table 3). Five RCT patients and one RT patient developed infections that resulted in hospitalizations and in a fatal outcome for one of the RCT patients.

Of note, severe lymphocytopenia was observed in 30 % of RCT patients and in 17 % RT patients. Opportunistic infections were not observed.

The non-haematological toxicities were mainly mild and are listed in Table 3. The main complaints of the patients, such as nausea and vomiting, dizziness and asthenia, were mostly manifesting symptoms of the brain metastases, already present before the start of the treatment. A total of 91 adverse events were recorded in this study, 70 in the RCT arm and 21 the RT. Sixty-seven (73.6 %) adverse events were rated as unlikely related to treatment, 20 as possibly related and four events as probably related to study treatment. Most of them were related to the underlying disease.

Discussion

This study assessing the efficacy of TMZ added to WBRT against brain metastases of advanced NSCLC had to close prematurely due to poor accrual. Although there was a trend for increased response to with TMZ added to WBRT this endpoint could not be definitely assessed. Despite the preventive measures taken to facilitate the enrolment in this study, mainly co-morbid patients and patients with synchronous brain metastases not suitable for radiosurgery were recruited. Forty percent of the patients progressed very rapidly systemically. Therefore, a potential benefit of TMZ to CNS disease might have been missed in this study. However, the toxicity observed was fatal in a patient and twice as high as in glioma patients, underlining once again the vulnerability of patients with NSCLC.

Several trials with chemotherapy added to WBRT in lung cancer patients with brain metastases have yielded more favourable results reaching overall response rates (ORRs) from 40 % to up to 96 % and survival times up to 12 months [2, 4, 11, 27]. On the other hand, several phase II studies using TMZ alone or in combinations with cisplatin, irinotecan or vinorelbine as salvage therapy in patients with progressive lesions after WBRT yielded similar results [6, 7, 9, 10, 12, 13, 19, 21, 28].

The protocol of this study was designed for patients with multiple brain metastases—a population of patients that is frequent in real life, but underrepresented in studies—the results fit into what can and must be awaited in patients with RPA class II.

The 2 weeks on/2 weeks off regimen with a daily dose of 100 mg/m^2 of TMZ the present protocol provides 1.5 times higher dose intensity than the conventional 200 mg/m^2, 1–5 days regimen. Furthermore, the rationale for the 2 weeks on/2 weeks off regimen during the sequential chemotherapy treatment phase was based on considerations including patient's compliance. In the patient's view the gap of 2 weeks between treatment cycles compares favourably to the short 1-week rest of other dose-dense regimens. The study was not aiming at the highest possible dose of TMZ given during this regimen but intended to provide an active therapy for the CNS lesions and aimed at letting room for eventually adding drugs for systemic therapy after the assessment of response in the brain 6 weeks after WBRT.

Unfortunately, this endpoint could not be assessed—patients in the RCT arm showed a somewhat higher response rate in the brain. Only 14 % of patients included in this study progressed in CNS.

How could recruitment of patients with brain metastases into studies be improved? Allowing inclusion of patients with brain metastases in trials on NSCLC into a distinct stratum and reporting their results for systemic disease and brain disease separately appears as a feasible

strategy. Stratifying for brain metastases and providing the best available treatment with attentive assessment of the response in the brain and the recovery or preservation of quality of life appears a practicable and promising strategy [29].

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Conflict of interest
All authors declare that they have no conflict interest including any financial, personal or other relationships with other people or organizations that could inappropriately influence this work.

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