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Phase II trial of temozolomide and cisplatin followed by whole brain radiotherapy in non-small-cell lung cancer patients with brain metastases: a GLOT-GFPC study

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Background: Brain metastases (BM) considerably worsen the prognosis of non-small-cell lung cancer (NSCLC) patients. The usefulness and choice of chemotherapy remain uncertain in this indication since these patients are excluded from most clinical trials. We conducted a phase II study to determine the efficacy and tolerability of up-front chemotherapy with association of temozolomide and cisplatin in NSCLC patients with BM.

Patients and methods: Fifty NSCLC patients with BM received temozolomide (200 mg/m^2/day for 5 days every 28 days) and cisplatin (75 mg/m^2 at day 1 of each cycle), up to six cycles, followed by whole brain radiotherapy (WBRT). An evaluation was carried out every two cycles and after WBRT. WBRT was performed earlier in case of progressive disease at any time or stable disease after cycle 4.

Results: Eight objective responses were achieved (16%). Overall median survival was 5 months. Median time to progression was 2.3 months. Ten patients (20%) presented a grade 3/4 neutropenia and 11 patients (22%) presented a grade 3/4 thrombopenia.

Conclusion: This study demonstrates a lack of efficacy of up-front chemotherapy with association of temozolomide and cisplatin in these patients. Nevertheless, it supports the feasibility of chemotherapy before brain radiotherapy in NSCLC patients with BM.

Key words: brain metastases, cisplatin, NSCLC, temozolomide

introduction

Brain metastases (BM) occur in 20–30% of patients with non-small-cell lung cancer (NSCLC) and their presence considerably worsen the prognosis. In absence of surgical excision, the median survival is less than 3 months [1]. Whole brain radiotherapy (WBRT) is the standard of treatment for these patients but even so, the median survival is less than 5 months [2].

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Chemotherapy is considered as the main treatment of disseminated NSCLC, but it remains controversial in patients with BM since they are excluded from most clinical trials, the blood-brain barrier (BBB) being regarded as preventing the passage of chemotherapy into the brain. Nevertheless, data suggest that the BBB is disrupted when BM are present, and some reports show that the concentration of chemotherapy drugs, including platinum, is similar in cerebral and extracerebral sites of the disease [3].

Temozolomide (TMZ) is an oral, new alkylating agent that has demonstrated a preclinical activity against a variety of solid tumors [4]. It is an active drug in the treatment of patients with high-grade gliomas [5] and melanomas [6]. It readily crosses the BBB, achieving therapeutic concentrations in the brain, which makes it an attractive agent against BM [7, 8]. Two phase II studies tended to show activity of TMZ in heavily pre-treated patients with BM from different solid tumors [9, 10]. In NSCLC, a phase II study failed to show any activity of TMZ alone in patients with or without BM [11], whereas

a recent study showed promising cerebral response rate [12]. In all cases, TMZ was safe and well-tolerated.

Cisplatin (CDDP) is an active cytotoxic drug in NSCLC. It has been shown to reduce the activity of the DNA repair enzyme O^6-alkylguanine-DNA alkyltransferase (AGT), the same enzyme that mediates resistance to TMZ [13]. Preclinical, *in vitro* data have demonstrated that TMZ and CDDP are synergistic when used in combination [14, 15] and a phase I pharmacokinetic study of TMZ and CDDP in patients with advanced solid tumors demonstrated the safety of this combination and some activity in NSCLC patients [16].

Based on these data, we undertook a multicenter phase II study on the association of TMZ and CDDP in chemotherapy-naïve NSCLC patients with inoperable BM in order to assess the efficacy and safety of this combination.

patients and methods

eligibility criteria

Patients with histologically or cytologically-confirmed NSCLC and inoperable brain metastase(s) were eligible for the study. BM needed to be more than 20 mm in the largest diameter and assessable by contrast-enhanced computed tomographic scan (CT) or gadolinium-enhanced magnetic resonance imaging (MRI). Patients needed to be aged between 18 and 75 years old, to have a World Health Organization (WHO) Performance Status of 0–2, a life expectancy of more than 12 weeks and good hematological function (absolute neutrophil count >1500/mm^3, platelet count >100 000/mm^3), hepatic function (total bilirubinemia <1.25 × upper limit of normal (ULN, 2.5 × ULN in case of liver metastases), aspartate amino transferase (AST) and alanine amino transferase (ALT) < 2×ULN (3 × ULN in case of liver metastases)) and renal function (serum creatinine < 110 μmol/l). No previous malignancies were allowed except for adequately treated *in situ* carcinoma of the cervix or squamous carcinoma of the skin. Patients with uncontrollable angina, heart failure or infectious disease were not eligible.

Any patient who had received prior chemotherapy or radiotherapy for BM, or had not stabilized neurological symptoms despite antiedematous treatment was also ineligible. Previous surgery or radiotherapy in order to control an extracerebral tumor site was tolerated. Written informed consent was required. This trial was approved by the local ethical committee.

treatment plan

TMZ was administered orally at the dose of 200 mg/m^2/d for five consecutive days. Anti-emetics were given systematically before TMZ. CDDP was administered intravenous at 75 mg/m^2 over 1 hour on day 1, with sufficient hydration and anti-emetics (setrons and corticosteroids). Treatment cycles were repeated every 28 days. Antiedematous treatment (including corticosteroids and mannitol) was adapted to neurological symptoms.

WBRT was administered systematically after cycle 6, or in case of stable disease (SD) after cycle 4 or progressive disease (PD) at any time. Planned conventional WBRT was administered with two opposed lateral fields. The dose was 3 Gy by fraction, 1 fraction per day, for 10 days. Patients were irradiated with high energy photons (photons X).

Study design is summarized in Figure 1. Initial treatment consisted of two cycles of association of CDDP and TMZ. The first evaluation of the disease was made after two cycles. In the case of global objective response (OR, including cerebral and extracerebral response), continuation of the chemotherapy was proposed up to six cycles with an evaluation every two cycles, followed by WBRT. In the case of SD after cycle 2, chemotherapy was continued for two more cycles. In the case of SD after cycle 4 or PD at any time, or because of unacceptable toxicity or patient refusal, chemotherapy was discontinued and the patient received WBRT.

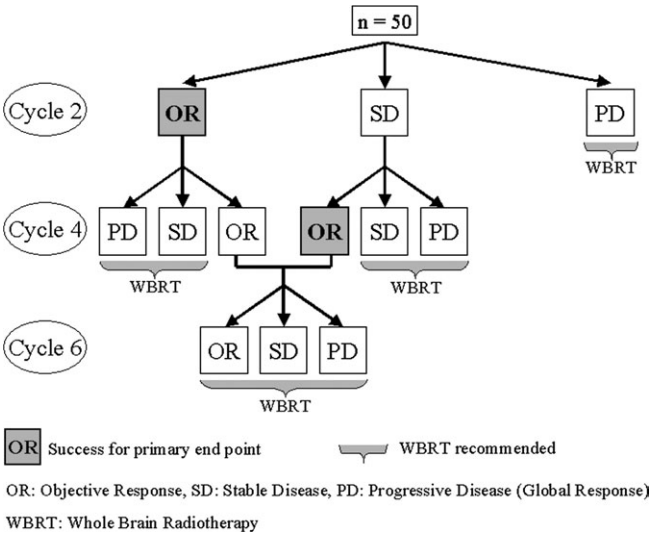

Figure 1. Study design.

Chemotherapy was administered if absolute neutrophil count was >1500/mm^3, platelet count >100 000/mm^3 and serum creatinine <150 μmol/l. Otherwise, chemotherapy was delayed for a week. The patient discontinued the study if treatment had to be delayed for more than two consecutive weeks. Doses of CDDP were decreased of 50% if serum creatinine was between 110 and 150 μmol/l with a creatinine clearance >45 ml/min despite sufficient hydration. The patient discontinued the study if serum creatinine was >150 μmol/l or creatinine clearance <45 ml/min despite sufficient hydration, or in case of grade 3 neurological toxicity. Doses of TMZ were decreased by 25% in case of febrile grade 4 neutropenia for more than five consecutive days, or non-febrile grade 4 neutropenia or grade 4 thrombopenia for more than seven consecutive days during the previous cycle.

baseline evaluation and follow-up studies

Baseline evaluation included a complete medical history, physical examination, determination of WHO Performance Status, biologic evaluation, chest X-ray, chest CT scan, bronchic endoscopy, abdominal ultra-sounds or CT scan, and bone scintigraphy. Detection of BM was carried out by brain CT scan systematically associated with MRI in case of a single lesion potentially amenable to surgical resection. Clinical, biologic and toxicity evaluations were assessed at each cycle. Brain CT scan (or RMI, in accordance with the baseline imaging technique), chest CT scan and other exams if needed (according to the extracerebral disease) were repeated every two cycles and every 2 months after cycle 6.

response and toxicity criteria

Tumor response was graded according to the RECIST criteria. Primary endpoint was the global response (calculated using cerebral and extracerebral measurable lesions). Success for primary endpoint was defined as global OR after cycle 2, or after cycle 4 in case of SD after cycle 2 (Figure 1). The analysis was conducted on an intention-to-treat basis which included all patients. Secondary endpoints were cerebral and extracerebral responses; best global response (including evaluation after WBRT); duration of response for responders; overall survival (OS); time to progression (TTP). Toxicity was evaluated according to the Common

Toxicity Criteria of the National Cancer Institute (http://ctep.cancer.gov:reporting:CTC-3.html) [17].

statistical methods

The total number of patients included was determined according to a Fleming plan consisting of two steps of 25 patients each, with global response probability p0 and p1 of 0.10 and 0.30 respectively, for a 5% α-risk and a 5% β-risk that were recalculated according to the Fleming plan. p0 = 0.10 was chosen as the probability of success under the null hypothesis H0 : $p \leq p0$. p1 = 0.30 (probability of success under the hypothesis H1 : $p \geq p1$) was calculated so that the power $1-\beta = 1-\alpha$. H1 was tested at the first step to stop the study earlier if efficacy was already shown. At the first step, threshold values were respectively 1 and 8. If the number of successes was below or equal to one, the study was discontinued because of inefficacy. If the number of successes was above or equal to eight, the study was discontinued because of efficacy. If two to seven successes occurred, 25 new patients were included. The threshold value for the second step was nine. If nine successes or more were observed, treatment was considered as efficient. Recalculated α-risk and β-risk after these two steps were respectively 5.7% and 1.9%. The inferior boundary of the one-tailed global response 95% confidence interval (CI) was calculated taking into account the two-steps design.

OS was estimated from enrolment to the date of last follow-up or until the patient's death. TTP was deemed as the time between initiation of treatment and progression. The Kaplan-Meier method was used to calculate TTP and survival rates. Secondary endpoints 95% CI (two-tailed) were calculated ignoring the two-steps design, using the binomial exact method.

results

patient characteristics

A total of 50 patients were included in the study from September 2001 to December 2002. Patient demographics and baseline disease characteristics are shown in Table 1. The median age was 57 years. Thirty patients (60%) had adenocarcinoma, 10 patients (20%) had squamous cell carcinoma and 10 patients (20%) had large cell carcinoma. All patients had BM and 40 patients (80%) had two or more BM. Thirty-eight patients (76%) had at least one other metastatic site. Four patients (8%) had undergone surgery before the study. Three patients (6%) had been previously irradiated. No patient had received prior chemotherapy.

efficacy of chemotherapy

primary endpoint. Global response evaluated every two cycles is summarized in Table 2. After cycle 2, three patients had discontinued the study (one patient due to early death, two patients due to early toxicity) and were considered as a failure for primary endpoint, seven patients had global OR, 29 patients had PD and 11 patients had SD, of whom one patient had global OR after cycle 4. Finally, eight patients achieved success for primary endpoint after inclusion of 50 patients, giving an overall response rate of 16% (one-tailed 95% CI inferior boundary: 8%).

Median duration of OR in case of success was 60.5 days (range 48–214). All the global OR were partial responses. Four of the eight global OR were confirmed two cycles later.

According to the initial Fleming plan, eight global OR were not enough to conclude to efficacy of the treatment.

Table 1. Patient demographics and baseline disease characteristics

n = 50	*n*	%
Age (in years)		
Median	57	
Range	38–71	
Sex		
Male	40	80
Female	10	20
Histological subtype		
Squamous cell	30	60
Adenocarcinoma	10	20
Large cell	10	20
WHO Performance Status		
0	12	24
1	31	62
2	7	14
Site of metastases		
Brain	50	100
Lung	14	28
Adrenals	13	26
Bone	11	22
Lymph nodes	10	20
Liver	10	20
Other	2	4
Number of brain metastases		
1	10	20
2	13	26
3	3	6
4	5	10
5	1	2
>5	18	36
Prior surgery		
Right pneumonectomy	1	2
Left pneumonectomy	1	2
Lobectomy	1	2
Vertebra consolidation	1	2
Prior radiotherapy		
Primary tumor	1	2
Bone metastase	2	4

Table 2. Cerebral response, primary tumor response, extracerebral metastatic sites response and global response after cycle 2

	Cerebral response (%)	Primary tumor response (%)	Extracerebral metastatic sites response (%)	Global response (%)
CR	2	0	0	0
PR	10	12	12	14
SD	42	40	32	22
PD	40	34	22	58
NA	6	14	34	6

CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; NA, not available.

secondary endpoints. An evaluation was made every two cycles for all patients who had begun the series of two cycles, i.e. 47 patients after cycle 2, 18 patients after cycle 4 and six patients after cycle 6. Best global response was PR in

eight patients (16%), SD in nine patients (18%) and PD in 30 patients (60%). Cerebral response, primary tumor response, extracerebral metastatic sites response and global response after cycle 2 are summarized in table 2. Cerebral response after cycle 2 showed 1 CR (2%), 5 PR (10%), giving a cerebral response rate of 12% (95% CI 4.5–24.3%), 21 SD (42%) and 20 PD (40%). Primary tumor response after cycle 2 was assessable in 43 patients and showed 6 PR (12%), 20 SD (40%) and 17 PD (34%). Extracerebral metastatic sites response after cycle 2 was assessable in 33 patients and showed 6 PR (12%), 16 SD (32%) and 11 PD (22%).

Thirty-four patients (68%) received WBRT. Cerebral response after WBRT was assessable in 24 cases and showed 1 CR, 3 PR, 14 SD and 6 PD.

Twenty patients (40%) had second-line chemotherapy, one of whom had PR. Five patients had a third-line treatment (two patients received gefitinib) but no OR was observed.

Forty-five patients (90%) had PD at the end of the study. The median TTP was 2.3 months (Figure 2). Forty-three patients (86%) died; one because of pulmonary embolism and the others because of cancer. The median OS was 5 months (Figure 3). One-year survival rate was 16% (95% CI 5% to 26%).

toxicity

A total of 129 cycles of chemotherapy were administered to 50 patients. One patient died before cycle 2 because of pulmonary embolism. Two patients presented early toxicity: one patient had febrile aplasia for 10 days complicated by septicaemia caused by *Escherichia coli*. The other one had severe pneumonia caused by *Aspergillus fumigatus* without prolonged aplasia.

The maximum hematologic and non-hematologic toxicity experienced by patient is listed by grade of severity in Table 3. Ten patients (20%) presented a grade 3 or 4 neutropenia, lasting more than seven consecutive days in two cases. Two patients (4%) had febrile neutropenia, lasting 10 days in one case. Eleven patients (22%) presented a grade 3 or 4 thrombopenia.

Non-hematologic toxicity occurred in 33 patients (66%), mostly due to vomiting, nausea and fever. Dose reduction was required in three cases. Treatment delay (median 6.96 days, range 3 to 8 days) due to toxicity occurred in 14 patients (28%).

discussion

This phase II study demonstrates the lack of efficacy of up-front chemotherapy with association of TMZ and CDDP in NSCLC patients with BM. Nevertheless, it supports the feasibility of chemotherapy before brain radiotherapy in these patients.

The usefulness of chemotherapy as initial treatment for BM in NSCLC is debatable. WBRT is regarded as the standard treatment for inoperable metastases, although long-term results are disappointing with median survival ranging from 3 to 5 months.

Robinet et al. recently conducted a phase III study showing that chemotherapy has a level of activity against BM which is not different from that achieved in other metastatic sites [18]. Therefore the presence of inoperable BM should not alter the treatment approach to patients with disseminated NSCLC, who require chemotherapy. The same study evaluated optimal timing for WBRT when given in association with chemotherapy, and failed to demonstrate any significant difference between early and delayed WBRT. These results allow the use of a sequential regimen of chemotherapy followed by WBRT, which enables treatment of the systemic disease and, if local failure occurs in the brain, the use of brain radiation.

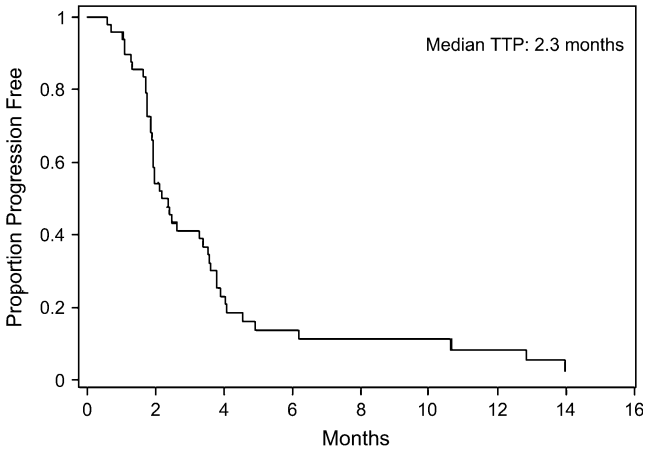

Figure 2. Kaplan-Meier progression-free survival curve.

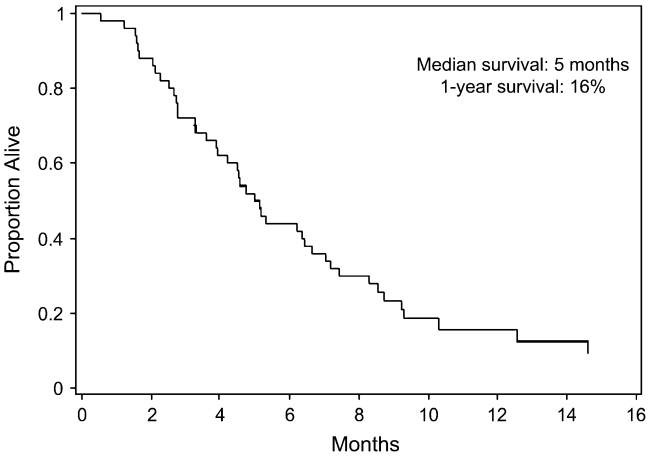

Figure 3. Kaplan-Meier overall survival curve.

Table 3. Maximum hematologic and non-hematologic toxicity all cycles

$n = 50$	Grade 1 (%)	Grade 2 (%)	Grade 3 (%)	Grade 4 (%)	All grade (%)
Neutropenia	4	0	8	12	24
Thrombo-cytopenia	14	16	10	12	52
Anemia	8	18	10	0	36
Nausea	4	6	6	0	16
Vomiting	10	8	6	0	24
Fever	2	6	2	6	16
Renal toxicity	2	2	0	0	4

The choice of effective drugs on BM from NSCLC is limited. Some data suggest that the BBB is disrupted in the presence of BM, allowing activity of chemotherapy. However, some agents that can readily cross the BBB may have greater potential in the treatment of BM. TMZ readily crosses the BBB and achieves therapeutic concentrations in the brain [7, 8]. Its efficacy has been established for high-grade glioma and BM from melanoma [5, 6], but is still being investigated for NSCLC. A phase II study conducted on pre-treated patients with recurrent or progressive BM from different solid tumors treated with TMZ 150 mg/m^2/d for 5 days, every 28 days, showed one PR in 12 NSCLC patients [10]. Another phase II study was conducted on patients with recurrent or progressive BM from different solid tumors, treated with TMZ 150 mg/m^2/d (200 mg/m^2/d if no prior chemotherapy) for 5 days, every 28 days. In 22 NSCLC patients enrolled, there were two PR and eight SD [9]. Dziadziuszko et al. performed a phase II study to evaluate the activity of TMZ 200 mg/m^2/d for 5 days, every 28 days, in two groups of chemotherapy-naïve NSCLC patients, with (n =12) and without (n = 13) BM [11]. No objective response was noted. A recent phase II study conducted on heavily pre-treated NSCLC patients (with prior chemotherapy and WBRT) showed a 10% cerebral response rate but global response rate was not reported [12]. A randomised phase II study evaluated the efficacy of concurrent TMZ (75 mg/m^2/d during radiation treatment, followed by 200 mg/m^2/d for 5 days, every 28 days) and radiotherapy versus radiotherapy alone in 58 patients with previously untreated BM from different solid tumors (31 patients had NSCLC) [19]. Results showed significant cerebral response rate improvement (96% versus 67%) in the TMZ group.

These trials demonstrated a good tolerability of TMZ that permits its use in combination with other cytotoxic agents. Association of TMZ with gemcitabine in a NSCLC patient and with oral etoposide in a small-cell lung cancer patient have been reported, resulting in a dramatic cerebral response in both cases [20].

CDDP, an active cytotoxic drug in NSCLC, might enhance the antitumor activity of TMZ by reducing the activity of the DNA repair enzyme AGT. A phase I study of TMZ and CDDP combination defined recommended doses for each drug and demonstrated good tolerability [16]. Phase II studies in patients with advanced melanoma showed promising results, even in patients with BM, and a good safety profile [21, 22]. In a phase II trial conducted by the HeCOG, 32 patients with BM from solid tumors (including mostly breast and lung cancers and melanoma) received TMZ 150 mg/m^2 or 200 mg/m^2 for 5 days in 28-day cycles (depending on whether they had been previously treated or not with chemotherapy) combined with CDDP 75 mg/m^2 on day 1 of each cycle. In 11 NSCLC patients, one CR and one PR were observed. The median survival for this subgroup was not reported but overall survival was 5.5 months [23].

The 16% global response rate observed in our study is quite similar to that observed in the HeCOG trial (18%). However, although association of CDDP provides better results than TMZ alone, response rates were not better than those achieved with other regimen. In their phase III study, Robinet *et al.* found a 21% global response rate in 86 patients treated by CDDP and vinorelbine in the delayed WBRT arm [18]. The median survival in this arm was 24 weeks and median TTP was 13 weeks. A phase II study with a combination of CDDP and etoposide in NSCLC patients with BM found 13 cerebral OR on 30 patients (cerebral response rate: 30%) [24]. Another phase II study enrolled 23 NSCLC previously untreated patients with BM to evaluate the efficacy of an association of CDDP and VM-26 [25]. Eight cerebral OR were observed (34%) with a median OS of 21 weeks.

Our study is one of the largest prospective studies in which chemotherapy was administered as an up-front treatment for NSCLC patients with BM. It is worth noting that the objective response rate for BM is not different from that achieved for extracerebral lesions, which confirms the possibility of treating BM like any other metastatic site. WBRT was administered to 68% of patients, a similar result to the one in the delayed WBRT arm in the study reported by Robinet et al. [18]. Patients who did not have WBRT died early, mostly because of progression of the disease. Whether these patients required early WBRT remains uncertain.

Toxicity of association of TMZ and CDDP was not mild. Grade 3 or 4 neutropenia and thrombopenia occurred in respectively 20% and 22% of patients. Non-hematologic adverse events were rare. No toxic death was recorded but two patients discontinued the study because of early toxicity.

conclusion

We undertook a phase II prospective trial on the association of TMZ and CDDP in NSCLC patients with BM. Response rates and OS were not better than those usually achieved with other regimen. However, this study supports the feasibility of chemotherapy before brain radiotherapy in NSCLC with BM. Further drugs need to be chosen for their intrinsic activity against cancer rather than for their ability to cross the BBB.

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