original article

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Pemetrexed and cisplatin as first-line chemotherapy for advanced non-small-cell lung cancer (NSCLC) with asymptomatic inoperable brain metastases: a multicenter phase II trial (GFPC 07-01)

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Background: Brain metastases (BM) occur in up to 40% of non-small-cell lung cancer (NSCLC) patients. This trial assessed the safety and efficacy of pemetrexed–cisplatin in this population.

Patients and methods: Chemonaive NSCLC patients with BM ineligible for (radio)surgery, performance status (PS) of 0 to 2, were eligible for up to six cycles of cisplatin 75 mg/m^2 and pemetrexed 500 mg/m^2 every 3 weeks. Whole -brain radiotherapy was given in case of disease progression or at chemotherapy completion. Primary end point was objective response rate (RR) on BM. Secondary end points included extracerebral and overall RR, safety profile and survival.

Results: Forty-three patients were enrolled. Initial characteristics were mean age 60.4 years; males 29; PS: 0 in 37.2%, 1 in 60.5% and 2 in 22.3% of patients; adenocarcinoma in 36 patients, large cell in 4 patients (nonsquamous, 93%) and squamous carcinoma in 3 patients. Functional classification of neurological status was stage I/II 86.0%, III 2.3% and IV 11.6%. Grade 3–4 hematological toxic effects were neutropenia, 11 patients (febrile neutropenia, 1 patient), and anemia, 6 patients. Non-hematological toxic effects were grade 2 urinary infection, one patient; grade 3 pneumonia, two patients; and grade 3 hypoacousia, one patient. Cerebral, extracerebral and overall RR by intent to treat analysis were 41.9%, 34.9% and 34.9%, respectively. Median survival time and time to progression were 7.4 and 4.0 months, respectively.

Conclusion: Pemetrexed–cisplatin is an effective and well-tolerated regimen as first-line therapy for NSCLC patients with BM who always suffer a poor prognosis.

Key words: brain metastases, chemotherapy, lung cancer, pemetrexed, prognosis, whole-brain radiotherapy

introduction

Non-small-cell lung cancer (NSCLC) patients present with brain metastases (BM) at diagnosis or later during the course of the disease in 10% and 40% of cases, respectively. Postmortem NSCLC studies show BM in up to 50% of cases. Unfortunately, in the vast majority of cases, BM from NSCLC are ineligible for a surgical approach and directly lead to the patient death in 30%–50% of cases [1, 2]. BM are therefore a challenge in NSCLC patients' management.

Whole-brain radiotherapy (WBRT) represents the standard of care for multiple symptomatic NSCLC BM [3]. The role of chemotherapy has been emphasized in few studies with a modest but demonstrated efficacy pending the combination of drugs used [4, 5].

Cisplatin plus pemetrexed has demonstrated efficacy in the first-line management of stage IV NSCLC patients with a 30.6% objective response rate (ORR), 4.8 months median progression-free survival (PFS) and 10.3 months median overall survival (OS). The survival benefit of the cisplatin plus pemetrexed combination was even greater in nonsquamous (NSQ) NSCLC when compared with standard cisplatin plus gemcitabine combination [hazard ratio = 0.81; 95% confidence interval (CI) 0.70–0.94; $P = 0.005$] [6].

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The objective of the present study was therefore to specifically assess the efficacy of the cisplatin plus pemetrexed combination as first-line treatment in the setting of multiple asymptomatic BM from NSCLC.

patients and methods

patients

Eastern Cooperative Oncology Group performance status of 0 to 2 chemonaive patients with cytologically or histologically proven NSCLC presenting with asymptomatic BM not amenable for a curative neuro- or radiosurgery with at least one unidimensionally measurable brain lesion according to the RECIST were eligible. The neurological status was defined using the Order's classification [7]. Patients had adequate bone marrow reserve and organ function including calculated creatinine clearance of 45 ml/min based on the standard Cockcroft and Gault formula. Patients with prior WBRT were not eligible. The protocol was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines and was approved by the Comité de Protection des Personnes Ouest IV (French institutional ethics review board) on 12 February 2008. All patients signed written informed consent before enrollment. The trial has been registered under the number NCT00744900.

treatment plan

Eligible patients received cisplatin 75 mg/m^2 plus pemetrexed 500 mg/m^2 on day 1. Chemotherapy was repeated every 3 weeks for four cycles with two additional cycles allowed for responding patients at investigator's discretion (unless there was earlier evidence of disease progression or intolerance of the study treatment). Patients received standard dexamethasone (or equivalent) prophylaxis of 4 mg orally twice per day on the day before, the day of, and the day after each day-1 treatment. All patients received oral folic acid (400 μg) daily and a vitamin B12 injection (1000 μg) every 9 weeks, beginning at least 1 week before the first dose and continuing until 3 weeks after the last dose of study treatment.

Patients requiring a day-1 dose reduction of pemetrexed or cisplatin received the reduced dose for the remainder of the study. Patients who had two dose reductions on day 1 and who experienced toxicity requiring a third dose reduction were discontinued from study therapy. Cycle delays of up to 42 days were permitted for recovery from adverse events (AEs). Concomitant supportive therapies, such as erythropoietic agents or granulocyte colony-stimulating factors, were allowed according to the American Society of Clinical Oncology guidelines.

After four to six cycles, or at disease progression or unacceptable toxicity, the patients received standard WBRT (30 Gy in 10 fractions or equivalent), at least 3 weeks after the completion of chemotherapy. The second-line therapy was left at the investigator's discretion (Figure 1).

baseline and treatment assessments

Before entering the study, patients underwent a medical history, physical examination, neurological status assessment [7], and tumor measurements of lesions assessed by computed tomography scan and/or magnetic resonance imaging for BM. The same baseline radiological assessment was repeated every two cycles, then 4 weeks after the completion of WBRT and then every 6 weeks after treatment discontinuation until disease progression. Disease status was assessed according to RECIST [8]. Enrolled patients who met the eligibility criteria and who had baseline imaging and at least one scan after starting chemotherapy were considered assessable for tumor response. All patients who received at least one dose of cisplatin plus pemetrexed were considered assessable for safety. Patients were assessed for toxicity according to the National Cancer Institute Common Toxicity Criteria, version 3.0 [9]. Efficacy analyses incorporated all enrolled patients on an intent-to-treat basis. The primary end point was overall cerebral response rate (RR) and all response evaluations were centrally reviewed by an independent committee. Secondary end points included OS, PFS, time to progressive disease, time to treatment failure, duration of response, and toxicity.

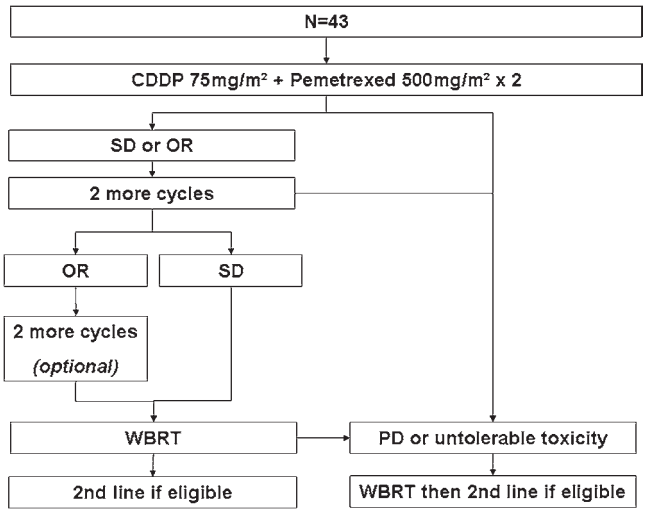

Figure 1. Flow chart of the trial. CDDP, cisplatin; SD, stable disease; OR, objective response; PD, progressive disease; WBRT, whole -brain radiotherapy.

statistical analyses

A single-arm, two-stage, sequential phase II design was used to test the null hypothesis (H0) that the true RR is ≥5% versus the alternative hypothesis (Ha) that the true RR is ≤20% [10]. At a risk alpha of 5% and a power of 90%, the study had to enroll 20 assessable patients in the first stage. If no patient responded to the therapy, this regimen will be deemed not worthy of any further investigation in this patient population, unless clinical considerations suggest otherwise. If at least 1 of the first 20 patients responded to therapy, accrual had to continue until 20 additional assessable patients have been recruited. If <5 of the 40 patients responded to therapy, this regimen will be deemed not worthy of any further investigation in this patient population, unless clinical considerations suggest otherwise. If responses are seen in ≥5 of the 40 patients, this regimen will be recommended for further study. Considering a 5%–10% rate of patients non-assessable for response, three additional patients have to be enrolled for a total of 43 patients. All tests on treatment effects were two sided unless otherwise stated.

results

patients

From September 2008 to May 2009, 43 patients have been enrolled included at 17 centers (Appendix 1). Patients' characteristics are summarized in Table 1. One patient was non-assessable as a result of early death before first tumor assessment.

treatment

All the patients received at least one cycle of chemotherapy. The total number of administered cycles was 165. The mean

Table 1. Patients' characteristics

	$N = 43$, n	%
Age (mean ± SD), years	60.4 ± 9	–
Gender		
Male	29	67.4
Female	14	32.6
ECOG PS		
0	16	37.2
1	26	60.5
2	1	2.3
Weight loss (mean ± SD), kg	3.3 ± 4	–
Histology		
SCC	3	7
ADC	36	83.7
LCC	4	9.3
Brain metastases		
Unique/multiple	7/36	16.3/83.7
Unilateral/bilateral	18/25	41.9/58.1
Neurological status		
I/II	37	85.9
III	1	2.3
IV	5	11.6
Primary lung tumor		
Controlled	3	7
Uncontrolled	40	93
Time from diagnosis (mean ± SD), days	14.2 ± 14	–

SD, standard deviation; ECOG PS, Eastern Cooperative Oncology Group performance status; SCC, squamous cell carcinoma; ADC, adenocarcinoma; LCC, large cell carcinoma.

number [±standard deviation (SD)] of cycles per patient was 3.84 ± 1.6. The dose intensity (±SD) was 132 ± 12 mg for cisplatin and 883 ± 79 mg for pemetrexed. The mean relative dose intensity (±SD) was 95.9% ± 9% for cisplatin and 98.1% ± 5.3% for pemetrexed.

Overall, 27 patients received the planned WBRT. Sixteen patients did not receive the WBRT because of early death in five cases, investigator decision for patients with brain objective response in six cases, and extracerebral progression that makes to the investigator's point of view another strategy preferable in five cases.

Data regarding second-line therapy are not available as it was not mandatory in the case report form and therefore not systematically reported by investigators.

efficacy

One patient was non-assessable for response. Regarding the primary end point, by intent to treat analysis, a total of 18 patients, 41.9% (95% CI 27–57.9), achieved a cerebral ORR with one complete response. The global ORR was 34.9% (95% CI 21–50.9) with a 72.1% disease control rate [DCR; ORR plus stable disease)]. The cerebral-specific ORR is given in Table 2.

Regarding the secondary end points, the median time to cerebral progression was 5.7 months (95% CI 4.0–7.6 months), the median PFS was 4.0 months (95% CI 2.7–6.2 months) and the median OS was 7.4 months (95% CI 5.8–9.6 months) (Figure 2).

Table 2. Best objective global and cerebral response rates

	Assessment of response by site[a]		
	Cerebral (%)	Extracerebral (%)	Global (%)
Complete response	1 (2.3)	0	0
Partial response	17 (39.5)	15 (34.9)	15 (34.9)
Stable disease	18 (41.9)	19 (44.2)	16 (37.2)
Progression	6 (13.9)	8 (18.6)	11 (25.6)

[a]One patient (2.3%) was non-assessable for response.

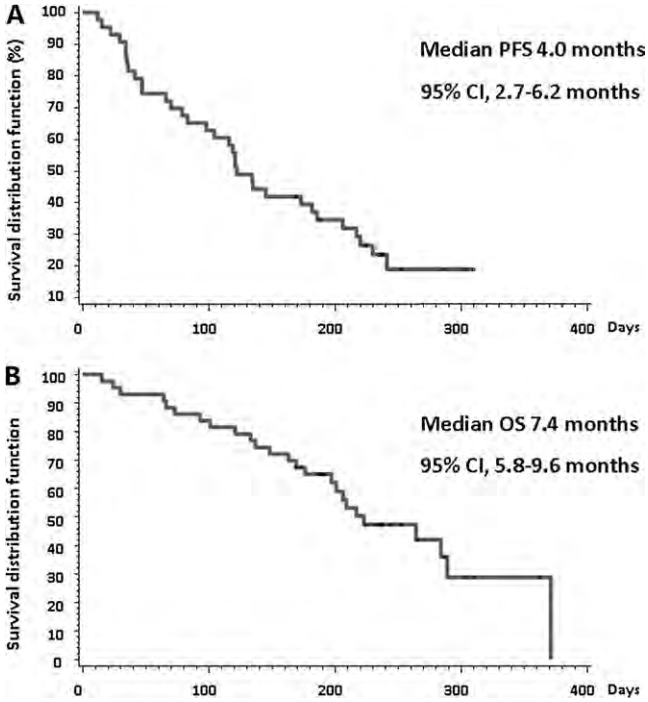

Figure 2. Median PFS (panel A) and OS (panel B). PFS, progression-free survival; OS, overall survival; CI, confidence interval.

safety

Overall, 58% and 30.2% of the patients presented with any grade 3–4 AE or a serious AE, respectively. No patient died as a result of the treatment. Hematological and non-hematological toxic effects are reported in Tables 3 and 4, respectively. No specific side-effect regarding BM was observed.

discussion

This phase II trial is the first study based on the combination of cisplatin plus pemetrexed specifically dedicated to the management of stage IV NSCLC patients with nonirradiated inoperable BM. This trial showed a high activity of this regimen in this population with a 41.9% cerebral RR and a 83.7% cerebral DCR, along with a good safety profile as attested by the absence of grade >3 non-hematological AE.

While WBRT remains the standard of care in many countries, a cisplatin-based chemotherapy might therefore replace frontline WBRT as supported by the present results. In

Table 3. Hematological grade ≥3 AEs

Grade ≥3 AE	Grade 3		Grade 4	
	n	%	*n*	%
Leukopenia	1	2.3	–	–
Neutropenia	7	16.3	3	7.0
Febrile neutropenia	–	–	1	2.3
Anemia	5	11.6	1	2.3
Thrombopenia	–	–	1	2.3
Aplasia	–	–	1	2.3

AE, adverse event.

Table 4. Non-hematological grade ≥2 AEs

AE	Grade 2		Grade 3		Grade 4	
	n	%	*n*	%	*n*	%
Nausea/vomiting	7	16.3	–	–	–	–
Renal insufficiency	5	11.5	1	2.3	–	–
Asthenia	4	9.3	–	–	–	–
Pneumonia	–	–	2	4.7	–	–
Neuropathy	2	4.7	–	–	–	–
Skin (rash)	2	4.7	–	–	–	–
Abdominal pain	2	4.7	–	–	–	–
Hypoacousia	–	–	1	2.3	–	–
Fluid retention	1	2.3	–	–	–	–
Oral mycosis	1	2.3	–	–	–	–
Hypotension	1	2.3	–	–	–	–
Urinary infection	1	2.3	–	–	–	–

AE, adverse event.

fact, the efficacy of a cisplatin–vinorelbine chemotherapy has been suggested by a previous study of our group where patients were randomly allocated to early and delayed WBRT. The ORR (21% versus 20%), intracranial ORR (27% versus 33%), and median survival (24 versus 21 weeks) were not significantly different between the two arms. In addition, a survey conducted in Italy in 2006 where 70% of the patients received frontline chemotherapy with a 37% ORR, a PFS of 6 months and an OS of 11 months confirms the increasing place of this strategy [6]. The potentially better activity of the new cisplatin-based regimens allows us to use the WBRT later in case of BM progression than minimizing the risk of a decrease in cognitive functions related to radiations [11, 12]. This strategy should be validated through clinical trials as some patients may escape the planned WBRT as for some of the patients reported in this trial.

Since 2008, cisplatin plus pemetrexed has become a new option in the treatment of NSQ NSCLC giving the results above described [7]. However, patients with progressive BM were excluded from this previous trial. Although three patients of the present study were not carrying a NSQ NSCLC, the activity of the first-line cisplatin plus pemetrexed regimen for the NSCLC patients with BM is demonstrated by the results reported here, as it was previously suggested with single-agent pemetrexed as second-line treatment for the same patients' population [13, 14]. Their median survival remains however shorter when compared with standard NSCLC patients' population but comparable with the median survival previously reported in the setting (5.2, 4.0 and 2.5 for Radiation Therapy Oncology Group RPA class I, II and III patients, respectively) [15].

The safety profile of the cisplatin plus pemetrexed combination reported here is appreciable in this frail patients' population and favorably compares with the 59.5% grade ≥3 hematological (neutropenia), 10.5% grade ≥3 non-hematological (neurotoxicity) toxic effects and 8.9% toxic deaths reported for the cisplatin plus vinorelbine combination [5]. Another potential advantage of the cisplatin–pemetrexed combination is suggested by the preliminary results of phases I and II studies combining the drugs plus radiotherapy [16, 17]. These studies suggested a good safety profile maybe allowing a concomitant treatment with chemotherapy plus radiotherapy or radiosurgery. However, a neurocognitive assessment of the patients receiving chemotherapy plus radiotherapy would be mandatory that has not been carried out in the present trial. Therefore, taking into account all these data, a randomized trial assessing cisplatin plus pemetrexed and systematic WBRT versus the same chemotherapy and WBRT at progression only, with a neurocognitive assessment by the Montreal Cognitive Assessment test [18], would be of interest.

Finally, the activity of cisplatin plus pemetrexed might also be improved by the addition of bevacizumab as the safety of the anti-vascular endothelial growth factor antibody has been demonstrated for patients with BM and preliminary encouraging results have been reported with this combination. However, our efforts should especially be dedicated to learn on the biology of NSCLC BM in order to guide development and improved selection for new drugs [19].

In conclusion, the combination of cisplatin and pemetrexed demonstrated a great activity as well as a good safety profile in managing the NSCLC patients with inoperable BM in this phase II trial. This regimen therefore needs further studies in this setting.

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disclosure

The authors declare no conflict of interest.

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appendix 1

All the investigators below included patients in this trial: Hervé Le Caer, Centre Hospitalier, Service de Pneumologie, Draguignan, France; Gislaine Fraboule, Centre Hospitalier René Dubos, Service d'Oncologie–Hématologie Clinique, Pontoise, France; Daniel Castera, Centre Catalan d'Oncologie, Perpignan, France; Crystèle Locher, Hôpital Saint Faron, Service de Pneumologie, Meaux, France; Lionel Falchero, Service de Pneumologie, Centre Hospitalier, Villefranche sur Saone, France; Jean-Michel Chavaillon, Centre Hospitalier General de la Fontonne, Service de Médecine 4, Antibes, France; Jean-Bernard Auliac, Centre Hospitalier, Service de Pneumologie-Neurologie, Mantes La Jolie, France; Christos Chouaid, Hôpital St Antoine, Service de Pneumologie, Paris, France; Laurence Geriniere, Service de Pneumologie, Centre Hospitalier de Lyon-Sud, Pierre-Benite, France.