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Upfront association of carboplatin plus pemetrexed in patients with brain metastases of lung adenocarcinoma

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Approximately 10% of patients with non-small cell lung cancer (NSCLC) have brain metastases at the time of diagnosis. When surgical resection is not possible, whole brain radiotherapy is the standard of care, with a cerebral response rate of approximately 30%. We report our experience with an upfront association of carboplatin and pemetrexed (areas under the curve, 5 and 500 mg/m^2, respectively), every 3 weeks, in 30 patients presenting with newly diagnosed brain metastases and NSCLC. Cerebral MRIs were performed every 6–9 weeks. The radiologic response rates were assessed according to Response Evaluation Criteria in Solid Tumors. Overall survival was also determined. Twenty-six patients were evaluable for response, and the objective cerebral response rate (complete and partial response) in the intent-to-treat population was 40% (12 of 30 patients). Event-free survival was 31 weeks, and median overall survival was 39 weeks. The upfront association of carboplatin plus pemetrexed allows simultaneous treatment of cerebral and systemic disease in patients with NSCLC with newly diagnosed brain metastases and appears to be particularly interesting in terms of radiologic response and overall survival. Further clinical studies are warranted.

Keywords: brain metastasis, carboplatin, chemotherapy, lung cancer, pemetrexed.

Up to 30% of patients with lung cancer develop metastases during the evolution of their disease,[1–3] and 10% of patients have metastases at the time of diagnosis.[4] Patients presenting with 1–3 metastases situated in a noneloquent area are eligible for surgical resection or radiosurgery because of the positive effect of these treatments on survival, local control, and quality of life.[5–8] When surgical resection or radiosurgery are not possible, whole brain radiotherapy is currently the standard of care.

Current data suggest that platinum-based chemotherapy induces a 30% radiologic response rate,[9–11] a rate similar to that obtained with whole brain radiotherapy.[12–14]

Pemetrexed is a new therapeutic agent that inhibits folate metabolism and is currently approved as a first-line treatment for nonsquamous non-small cell lung cancer (NSCLC), in association with platinum-based chemotherapy.[15–20] Of interest, a recent trial has shown that a pemetrexed-based regimen can be effective against brain metastases.[21]

We report our experience with the association of carboplatin plus pemetrexed in a series of patients presenting with cerebral metastases secondary to nonsquamous NSCLC. All patients were administered chemotherapy only as a first-line therapy.

Materials and Methods

Patients

In this observational study, 30 consecutive patients with pathologically confirmed nonsquamous NSCLC and

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newly diagnosed brain metastases, treated in a single institution (Avicenne Hospital) with chemotherapy from April 2009 through July 2011, were studied. In these patients, surgery or radiosurgery of the brain metastases was not deemed to be appropriate, either because of the number (i.e., 3 or more) or the location of the metastatic lesions. These patient were not treated with whole brain radiotherapy upfront, either because the cerebral mass effect did not allow radiotherapy or because the patients were paucisymptomatic, with no or minimum neurological symptoms that were easily controlled by corticosteroids. Patients had not received prior radiotherapy or chemotherapy.

In patients who did not have a brain biopsy, diagnosis of brain metastases was based on cerebral MRI and histologically documented lung carcinoma.

The patients were treated with carboplatin at a dose of area under curve (AUC) 5 and pemetrexed at a dose of 500 mg/m^2, administered on a single day and repeated every 3 weeks until disease progression, unacceptable toxicity, or noncompliance. All patients received folic acid and B12 vitamin supplementation before chemotherapy.

All patients had documented radiological progression before changing the chemotherapeutic regimen.

Response Assessment and Toxicity Evaluation

The medical history, physical examination results, Eastern Cooperative Oncology Group performance status, and recursive partitioning analysis (RPA) were retrieved from the medical records. Objective tumor response was assessed using brain MRI and thoracic CT, according to the revised Response Evaluation Criteria in Solid Tumors, taking into account the largest lesions.[22] A complete response was defined as the disappearance of all lesions. A partial response was defined as at least a 30% decrease in the sum of the longest baseline diameter and persistence of 1 or more nontargeted lesions. Progressive disease was defined as at least a 20% increase in the sum of the longest diameter, taking as reference the smallest sum of the longest diameter recorded after treatment or the appearance of 1 one or more new lesions, or the unequivocal progression of existing nontarget lesions. Stable disease was defined as the absence of significant shrinkage or enlargement qualifying a complete response, partial response, or progressive disease, taking as reference the smallest sum of the longest diameter recorded after treatment. Small lesions with diameter less than 10 mm are considered as nonmeasurable lesions. Cerebral and systemic responses were assessed every 6–9 weeks prospectively by the multidisciplinary staff and retrospectively by 1 author (O.B.). Response evaluation was the best response, calculated after 2 or more cycles. Toxicity was assessed according to Common Terminology Criteria for Adverse Events, version 3.0.[23]

The study was approved by the institutional review board and the local ethical committee.

Statistics

Event-free survival was defined as the time from the date of brain imaging before starting chemotherapy to the documented day of radiologic progression (cerebral or extracerebral progressions) or death. Living patients without progression were treated as censored. Overall survival was defined as the time from the date of brain imaging before starting chemotherapy to death from any cause in the intent-to-treat population. Event-free survival and overall survival were estimated using the Kaplan-Meier method.

Results

Patient Characteristics

From April 2009 through July 2011, 30 patients with pathologically confirmed nonsquamous NSCLC and newly diagnosed brain metastases were analyzed (over the same period, approximately 500 patients with nonsquamous NSCLC were referred to our hospital). Upfront radiotherapy was not considered to be appropriate because of no or minimal neurological symptoms in 28 patients or because of poor performance status and mass effect on the third or the fourth ventricle in 2 patients. The characteristics of these 30 patients are

Table 1. Patient demographic and baseline characteristics

Characteristic	No. of patients (n = 30)	%
Age, years, median ± SD	58 ± 10	
Sex, M/F	21/9	70/30
Histologic subtype		
Adenocarcinoma	27	90
Large cell carcinoma	3	10
Performance status (ECOG)		
0	7	23
1	20	67
2	3	10
3	0	0
RPA		
1	8	27
2	20	67
3	2	6
Metastases other than brain	18	60
Brain metastases/patient		
1	9	30
1–3	9	30
>3	12	40
Time between initial diagnosis and brain metastasis, (days), median ± SD	18 ± 42	
Brain metastasis revealed lung cancer	22	73
Corticosteroid (prednisone equivalent)		
<30 mg	11	37
30–60 mg	13	43
>60 mg	6	20

Abbreviations: ECOG, Eastern Cooperative Oncology group; RPA, recursive partitioning analysis; SD, standard deviation.

shown in Table 1. All patients were smokers, and none were Asian. Four patients were not assessable for radiologic response because chemotherapy was interrupted prematurely because of adverse events: severe fatigue (grade 3) in a 75-year-old patient, severe respiratory distress syndrome (grade 4) in a 55-year-old patient, severe pancytopenia (grade 4) in an 85-year-old patient, and pulmonary embolism (grade 4) in a 61-year-old patient.

Overall Cerebral Response Rate

Of the 26 patients evaluable for response, 24 had measurable lesions (more than 1 cm). Ten of these 24 patients achieved a partial response (−50%, 55%, 40%, 35%, 50%, 40%, 30%, 40%, 30%, and 30%) (Fig. 1). Both patients with nonmeasurable lesions (less than 1 cm) had a complete response. The overall cerebral response rate was therefore 40% in the intent-to-treat population. In the 12 responder patients, the median time to best tumor response was 9.8 weeks after onset of chemotherapy. Although the radiologic responses outside the central nervous system (CNS) appeared to be less impressive (partial response in only 17%) than the cerebral responses, the primary sites of progression involved the brain in 16 of 21 patients (progressions limited to the brain in 7 patients). Of the 2 patients with a bad Karnofsky index, one had a cerebral partial response lasting 26 weeks, and the other showed a progressive disease. In the 12 patients who had a cerebral response, the mean steroid dose was reduced from 41 ± 39 mg to 24 ± 30 mg (equivalent prednisolone) at the time of best cerebral response.

Event-Free Survival and Overall Survival

The median duration of follow-up was 46 weeks (range, 8–171 weeks). Median event-free survival was 31 weeks (Fig. 2A). In the intent-to-treat population (30 patients), median overall survival was 39 weeks (Fig. 2B). Eight patients (26%) were RPA class I, 20 (67%) were RPA class II, and only 2 (7%) were RPA class III. In these groups of patients, overall survival was 7.5 and 9.9 months for RPA class I and class II, respectively.

Discussion

Whole brain radiotherapy is the standard of care for cerebral metastases when surgery or radiosurgery is not possible. The place of chemotherapy in this context remains unclear. Pemetrexed in combination with cisplatin is recognized as a first-line treatment in advanced NSCLC,[20,24,25] and preliminary data exist

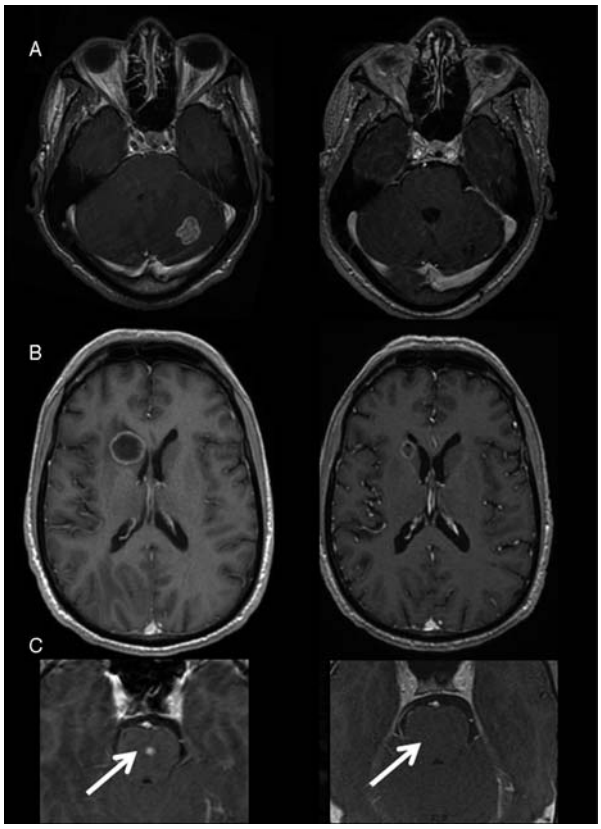

Fig. 1. Cerebral MRI (T1-weighted axial images after gadolinium) showing a radiologic response in 3 patients (A, B, and C). Left: before treatment; right: after 2 or 3 cycles of chemotherapy alone.

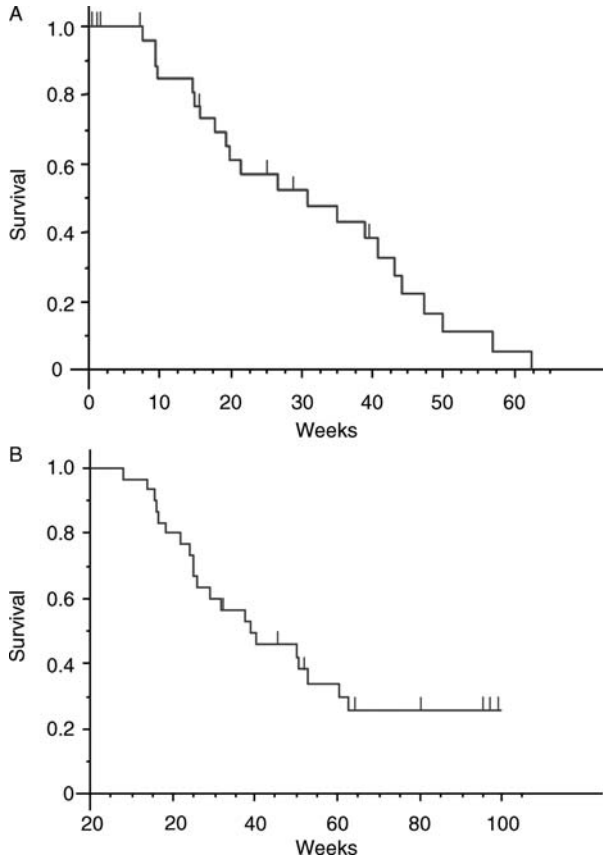

Fig. 2. Event-free survival (A) and overall survival (B). Tick marks indicate censored data.

on its efficacy as an upfront treatment for brain metastases.[21] We report a high cerebral response rate (40%) in a series of patients, with a good correlation between extracerebral and cerebral response. The radiologic responses appeared to be less impressive in the lung than in the brain, possibly because the extracerebral lesions were larger and were sometimes associated with lymphangitis carcinomatosis, bone metastases, or pleural lesions. Moreover, the primary sites of progression involved the brain in most patients, highlighting the different kinetics of radiologic response depending on the tumor site.

There are some limitations to our study. First, our population of patients was heterogeneous in terms of initial performance status. Second, this partially prospective study might have induced bias in patients' selection. Third, our limited number of patients precludes any formal comparison between response rates with other series. However, the efficacy observed in our series is in line with 2 studies that reported similar cerebral response rates in patients with brain metastases treated with a similar regimen either as an upfront regimen[21] or at recurrence after whole brain radiotherapy.[26] Of interest, this good response rate translated into an overall survival that compares favorably with the figures reported in the RPA classification[27] (7.5 and 9.9 months for RPA class I and class II, respectively). Again, these figures should be taken with caution, because our population was limited to patients with NSCLC with upfront metastases, contrary to the broader population (probably carrying a worse prognosis) from which the RPA classification was defined.

Classically, chemotherapy is not considered a standard of care for brain metastases because of the limited diffusion of most chemotherapeutic agents through the blood-brain barrier.[28] However, contrast enhancement after gadolinium injection demonstrates that this barrier is not functional. Moreover, similar systemic and cerebral response rates (approximately 30%) have been reported with platinum-based chemotherapy,[9,11,29–32] demonstrating that this chemotherapy does reach brain metastases. Our cerebral response rate of 40% with carboplatin and pemetrexed confirms that the blood-brain barrier did not impede the effectiveness of intravenous chemotherapy. It is not possible to assess the respective efficacies of carboplatin and pemetrexed. Pemetrexed is a multitargeted antifolate cytotoxic chemotherapeutic agent that inhibits at least 3 target enzymes in the folate pathway (thymidilate synthase, dihydrofolate reductase, and glycinamide ribonucleotide formyl transferase). Thymidilate synthase is the main molecular target of pemetrexed. Overexpression of thymidilate synthase activity seems to be correlated with reduced activity.[33] Correlation with thymidilate synthase activity in the tumor samples from our patients is ongoing.

Our results underline the potential role of upfront chemotherapy in the management of brain metastases, allowing the treatment of both cerebral and extracranial disease at the same time. Such a strategy advantageously delays radiotherapy until the time of cerebral progression and reduces cerebral toxicity, because radiotherapy may induce cognitive dysfunction. Withholding whole brain radiotherapy did not appear to affect overall survival in 2 randomized trials using platinum-based chemotherapy.[9,10] According to the literature, whole brain radiotherapy does not induce a higher radiologic response rate or cerebral progression-free survival[12–14] than that observed in our study. In a recent study, a combination of pemetrexed and cisplatin followed by whole brain radiotherapy (in 63% of cases) gave a cerebral and systemic response rate in 42% and 35% of patients, respectively, and a cerebral progression-free survival of 5.7 months,[21] a figure similar to that found in our series.

A randomized clinical trial comparing whole brain radiotherapy with an association of platinum-based chemotherapy and pemetrexed is warranted.

Conflict of interest statement. None declared.

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