

Response of Asymptomatic Brain Metastases From Small-Cell Lung Cancer to Systemic First-Line Chemotherapy

Tatjana Seute, Pieter Leffers, Jan T. Wilmink, Guul P.M. ten Velde, and Albert Twijnstra

ABSTRACT

Purpose

The purpose of this study was to investigate the radiologic response of asymptomatic brain metastases (BM) from small-cell lung cancer (SCLC) to first-line systemic chemotherapy.

Patients and Methods

From 1990 to 2003, 181 consecutive patients with SCLC were enrolled onto this study. Patients were examined by a neurologist on a regular basis. Magnetic resonance imaging (MRI) of the brain was performed routinely before (at diagnosis of SCLC) and after first-line systemic chemotherapy. Patients were treated with combination chemotherapy consisting of cyclophosphamide, doxorubicin, and etoposide. Clinically manifest BM were treated with whole-brain radiotherapy (WBRT). The response rate (RR) of BM was assessed by changes in the size or the number of enhanced lesions on MRI using standard criteria.

Results

Synchronous asymptomatic BM were found in 24 SCLC patients (13%). In six (27%) of the 22 assessable patients, the asymptomatic BM responded to systemic chemotherapy. A systemic response was found in 16 patients (73%). All patients became symptomatic during follow-up. The symptom-free survival did not differ between cranial responders and cranial nonresponders.

Conclusion

The RR of asymptomatic BM from SCLC to systemic chemotherapy is 27% and evidently lower than the systemic RR. Future studies should focus on the possible beneficial effect of WBRT for patients with asymptomatic synchronous BM.

J Clin Oncol 24:2079-2083. © 2006 by American Society of Clinical Oncology

INTRODUCTION

Brain metastases (BM) are a frequent and devastating complication in patients with a malignancy. At autopsy, BM are found in approximately 25% of patients who die of cancer. Although any systemic cancer can metastasize to the brain, lung cancer, breast cancer, and melanoma are the most common primary tumors.¹ At the time of diagnosis, at least 18% of the patients with small-cell lung cancer (SCLC) have symptomatic or asymptomatic BM.²

The aims of treatment of symptomatic BM from SCLC are to reduce symptoms and to prevent complications, such as neurologic deficits and cognitive impairment. The standard treatment is whole-brain radiotherapy (WBRT), with reported response rates (RRs) ranging from 56% to 92%.^{3,4}

For a long time, the brain was considered a pharmacologic sanctuary in which metastases could grow under the protection of the blood-brain barrier (BBB). However, in recent decades, it has become clear that the BBB is disrupted in metastatic

tumor tissue.⁵⁻⁸ Since then, the effectiveness of first-line and second-line systemic chemotherapy for the treatment of BM from SCLC has been the topic of several studies.⁹⁻¹⁴

Several authors claimed that synchronous BM show a good RR to systemic chemotherapy that is similar to the RR for the primary tumor.¹⁵⁻¹⁷ Pooled data from seven studies show a 79% RR of synchronous symptomatic BM from SCLC to first-line systemic chemotherapy (Table 1).¹⁸⁻²⁴

On the basis of these studies, it has been suggested that BM from SCLC should initially be treated with systemic chemotherapy.⁴ The debate about whether WBRT should be part of the initial treatment is still ongoing.²⁵

To add relevant information for this debate, we studied the radiologic response of asymptomatic BM from SCLC to first-line systemic chemotherapy. The data were derived from an ongoing register in which neurologic complications of SCLC are documented.² All patients in our study underwent routine imaging of the brain at diagnosis of SCLC,

From the Departments of Neurology, Radiology, and Pulmonology, University Hospital Maastricht; and the Department of Epidemiology, University of Maastricht, Maastricht, the Netherlands.

Submitted June 28, 2005; accepted February 22, 2006.

Presented in part at the 57th Annual Meeting of the American Academy of Neurology, Miami, FL, April 9-16, 2005.

Authors' disclosures of potential conflicts of interest and author contributions are found at the end of this article.

Address reprint requests to Tatjana Seute, MD, Department of Neurology, University Hospital Maastricht, PO Box 5800, 6202 AZ Maastricht, the Netherlands; e-mail: tatseute@yahoo.co.uk or tatjanaseute@hetnet.nl.

© 2006 by American Society of Clinical Oncology

0732-183X/06/2413-2079/\$20.00

DOI: 10.1200/JCO.2005.03.2946

Table 1. Response of BM From SCLC to First-Line Chemotherapy in Earlier Studies

Reference	Regimen	No. of Patients	No. of Assessable Patients	No. of CRs	No. of PRs	Overall Clinical Response (%)
Kantarjian et al, ¹⁸ 1984	CTX, DX, VCR, VP-16 + PCZ, NM, MTX	2	2	2	0	100
Kristjansen and Hansen, ¹⁹ 1988	CCNU, CTX, VCR, VP-16 or CDDP, VM26, VCR	10	7	4	3	100
Lee et al, ²⁰ 1989	VP-16, CTX, DX, VCR	14	11	1	8	82
Humblet et al, ²¹ 1989	CBDCa, DX, VP-16 or CBDCa epiDX, VP-16	10	6	4	2	100
Twelves et al, ²² 1990	CTX, VP-16, VCR	19	14	1	8	47
Kristjansen et al, ²³ 1993	CDDP, VP-16, VCR + CTX, CCNU, VP-16, VCR + DX, VCR + VIN, CDDP, HM	21	13	4	7	85
Tumarello et al, ²⁴ 1998	CTX, DX, VCR, VP-16	9	9	3	2	56
Total	—	85	62	19	30	79

Abbreviations: BM, brain metastases; SCLC, small-cell lung cancer; CR, complete response; PR, partial response; CTX, cyclophosphamide; DX, doxorubicin; VCR, vincristine; VP-16, etoposide; PCZ, procarbazine; NM, mechlorethamine; MTX, methotrexate; CCNU, lomustine; CDDP, cisplatin; VM26, teniposide; CBDCa, carboplatin; epiDX, epirubicin; VIN, vindesine; HM, hexamethylmelamine.

enabling us to detect patients with symptomatic and asymptomatic BM. In the asymptomatic patient group, the effect of first-line chemotherapy could be measured without interference of cranial irradiation.

PATIENTS AND METHODS

Patients

From January 1990 to May 2003, 181 consecutive patients with microscopically or histologically proven SCLC were enrolled onto this study. Patients were diagnosed and treated at the University Hospital Maastricht (Maastricht, the Netherlands). Potential follow-up time for all patients was at least 1 year. Patients were initially staged by a pulmonologist. Physical examination, routine blood and chemistry profile, chest x-ray, computed tomography (CT) scan of the chest, and fiberoptic bronchoscopy were routinely performed. All patients underwent treatment and diagnostic evaluation according to the standard protocol used in our hospital.

Neurologic Follow-Up

The same experienced neurologist (A.T.) examined all patients at diagnosis, every 3 months during the first year, and every 6 months thereafter. Magnetic resonance imaging (MRI) of the brain was performed before (at diagnosis of SCLC) and after initial chemotherapy. An additional brain MRI scan was performed when patients had survived for 12 months after the diagnosis of SCLC. If new neurologic symptoms or signs arose, the frequency of neurologic consultations and diagnostics was increased.

Treatment Plan

All patients were initially treated with combination chemotherapy, consisting of cyclophosphamide 1,000 mg/m² and doxorubicin 45 mg/m² on day 1 and etoposide 100 mg/m² on days 1, 3, and 5, repeated every 3 weeks, with a maximum of five cycles. Patients received dexamethasone 8 mg at the start of each cycle as an antiemetic.

Clinically manifest BM were treated with WBRT with fractions of 3 Gy administered five times a week up to a total dose of 30 Gy. In the case of cerebral edema, patients received corticosteroid medication.

Response Evaluation

Response of the asymptomatic BM to chemotherapy was assessed by changes in the size or the number of enhanced lesions on MRI scans (0.5T system), before and after chemotherapy. MRI scans were made before and after intravenous injection of the MRI contrast medium gadolinium diethylenetriaminepentaacetic acid in a dose of 0.1 mmol/kg. The MRI technique stayed the same over the study period. The MRI scans were reviewed by an experienced neuroradiologist (J.T.W.). The neuroradiologist had not seen the patients in person and was not aware of the patients' systemic response. Response was assessed using the standard criteria according to the WHO

handbook for reporting results of cancer treatment.²⁶ Complete remission was defined as the complete disappearance of all tumor lesions on MRI. Partial remission was defined as an at least 50% decrease of total tumor size of the lesions that had been measured, without the appearance of any new lesions or progression of any lesions. Stable disease was defined as a less than 50% decrease or less than 25% increase in size of lesions and no new lesions. Progressive disease was defined as a more than 25% increase in the size of lesions or the appearance of new lesions.

The response of the primary tumor and systemic metastases was measured by CT of the thorax and CT of the abdomen. The same criteria were used as described earlier.

Statistics

The Wilson score method was used to estimate 95% CIs for RRs. The McNemar test was used to test for differences in RRs of BM and systemic metastases. Survival curves were estimated by the Kaplan-Meier method.²⁷ Differences between survival curves were tested with the log-rank test. $P < .05$ was considered statistically significant.

RESULTS

Among the 181 patients, there were 38 patients (21%) with synchronous BM. In 24 of these patients (13%), the BM were asymptomatic. The characteristics of all patients with synchronous BM are listed in Table 2.

Two of the asymptomatic patients were not treated; one patient was not treated because of his poor physical condition, and one patient died during the first course of chemotherapy. The other 22 patients completed five cycles of first-line chemotherapy and were, therefore, assessable for response. Twenty-one patients received an MRI scan of the brain after chemotherapy. Because of claustrophobia, one patient underwent a CT scan instead. None of the patients received cranial irradiation before or during first-line chemotherapy.

The response of the asymptomatic BM and the systemic response (primary tumor and extracranial metastases) after initial chemotherapy are listed in Table 3. In six of the 22 asymptomatic patients, the BM responded to chemotherapy, whereas a systemic response was found in 16 of these patients. The brain response (27%; 95% CI, 13% to 48%) was significantly less ($P = .006$) than the systemic response (73%; 95% CI, 52% to 87%). In 10 patients, systemic response and cranial response were equal. Five of the six patients with responding BM were a subset of the 16 systemic responders.

Table 2. Patient Characteristics at Diagnosis of Small-Cell Lung Cancer

Characteristic	Symptomatic BM (n = 14)		Asymptomatic BM (n = 24)	
	No. of Patients	%	No. of Patients	%
Age, years				
Median	68		66	
Range	49-81		46-81	
Male	13	93	18	75
BM only	3	21	5	21
BM in posterior fossa	7	50	19	80
Other metastatic sites				
Bone	7	50	10	42
Liver	1	7	8	33
Mediastinum	4	29	4	17
Other	7	50	10	42

Abbreviation: BM, brain metastases.

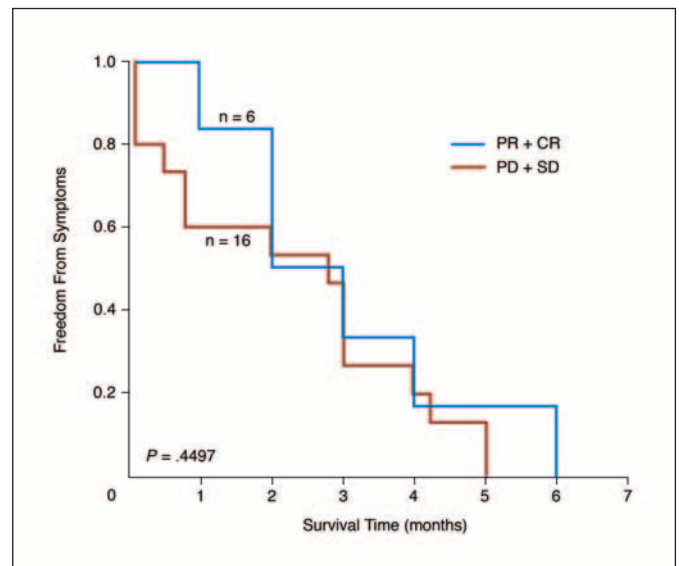


Fig 1. Kaplan-Meier survival curve showing symptom-free survival of small-cell lung cancer patients with asymptomatic brain metastases measured from the last day of the fifth chemotherapy cycle ($P = .4497$). PR, partial response; CR, complete response; PD, progressive disease; SD, stable disease.

Three patients became symptomatic during the last cycle of first-line chemotherapy. All other 19 patients became symptomatic after completing chemotherapy, with a median duration of 2.3 months (range, 0.5 to 5 months) measured from the last day of the fifth chemotherapy cycle. The two patients with a cranial complete response had a symptom-free period of 3 and 4 months. Figure 1 shows that the symptom-free survival in patients with asymptomatic BM did not clearly differ between cranial responders and cranial nonresponders to chemotherapy.

Patients with asymptomatic BM ($n = 22$) had a median survival time of 8.3 months (range, 1.3 to 43.4 months). Patients with symptomatic BM who received WBRT ($n = 9$) had a median survival time of 10.5 months (range, 1.7 to 34.5 months). Five symptomatic patients did not receive WBRT because of their poor clinical condition; they had a median survival time of 6.9 months (range, 1.0 to 12.7 months). The percentage of patients who were assumed to have died as an immediate result of BM was similar for asymptomatic and symptomatic patients (41% and 36%, respectively).

DISCUSSION

In the present study, we investigated the radiologic response of synchronous asymptomatic BM from SCLC to first-line combination

chemotherapy. Previous studies (Table 1) found a high RR of synchronous BM from SCLC to chemotherapy (RR, 79%). These and other studies have led to the current view that first-line chemotherapy is a sufficient initial treatment in SCLC patients with synchronous BM and that WBRT may be deferred until symptoms arise.^{3,4} However, these studies had several shortcomings. First, in most studies, patients with a variety of treatment regimens were mixed, and some studies even included cranial irradiation before evaluation of response.²² Because it is known that BM respond to radiation, the RR from chemotherapy will probably have been overestimated. Second, the reports did not state who determined the RR and whether the assessor was aware of the clinical state of the patients and their systemic response. Therefore, expectation bias may have led to overestimation of the association between systemic and cranial response. Finally and most importantly, no direct comparison was made with systemic response in the same patients.

In our study, 22 of the 24 asymptomatic patients were assessable, and all received the same treatment. None of these patients underwent cranial irradiation before or during chemotherapy. RR of BM was evaluated by MRI scanning, which is more sensitive than CT for the detection of BM.²⁸ Radiologic response was evaluated blindly. The number of patients included in the present analysis is larger than the number of patients in previous studies (Table 1). However, the number is still relatively small, and therefore, caution should be used when interpreting the data.

In our study, the radiologic RR of asymptomatic BM was only 27%, whereas the systemic RR was 73% (Table 3). The cranial RR in asymptomatic patients was substantially lower than the cranial RR found in earlier studies with symptomatic BM patients (Table 1). We further found that almost all cranial responders responded systemically but that systemic response did not guarantee a cranial response at all (Table 3). These findings contradict the postulated idea that the cranial response to chemotherapy is equal to the response of systemic metastases and the primary tumor.^{16,17}

Table 3. Response to First-Line Chemotherapy in Small-Cell Lung Cancer Patients

Response	Systemic Response (No. of patients)				Total (brain response)
	CR	PR	SD	PD	
Brain response					
CR	2				2 } 27%
PR	3		1		
SD	1	3		1	5
PD	1	6	2	2	11
Total (systemic response)	7	9	3	3	22
	73%				

Abbreviations: CR, complete response; PR, partial response; PD, progressive disease; SD, stable disease.

The most striking difference between our study and earlier publications is that our BM patients were asymptomatic. One might argue that the BBB is less disrupted in patients with asymptomatic BM and, therefore, smaller amounts of chemotherapeutic agents can reach the tumor sites.²⁹ However, this argument is contradicted by the fact that symptomatic as well as asymptomatic BM enhance on MRI after intravenous injection of gadolinium.

It is known that corticosteroid treatment can partly restore the BBB.³⁰ The symptomatic BM patients in the earlier studies probably received high doses of corticosteroids to diminish cerebral edema. Hence, the low dose of corticosteroids administered as an antiemetic treatment alone cannot be held responsible for the lower cranial RR in our patient group.

In our patient group, symptom-free survival did not differ between responders and nonresponders (Fig 1). Therefore, even in the patients with a radiologic response, it seems that systemic chemother-

apy is not able to postpone the occurrence of symptoms of BM. Because the number of patients in this analysis (Fig 1) is small, this conclusion only tentatively supports the notion that chemotherapy is not effective against BM.

The clinical relevance of the findings of our study is the fact that, after the completion of chemotherapy, there remains a substantial number of patients who still have asymptomatic BM. Therefore, initial chemotherapy is not sufficiently effective for treatment of BM, and the question of whether symptoms in these patients can be postponed by WBRT becomes a relevant topic for future research.

In conclusion, the RR of asymptomatic BM from SCLC to systemic chemotherapy is 27% (95% CI, 13% to 48%), and the response of asymptomatic BM to systemic chemotherapy is much lower than the systemic response. Future studies should focus on the possible beneficial effect of WBRT for patients with asymptomatic synchronous BM.

REFERENCES

- Posner J: Neurologic Complications of Cancer. Philadelphia, PA, F.A. Davis Company, 1995
- Seute T, Leffers P, ten Velde GP, et al: Neurologic disorders in 432 consecutive patients with small cell lung carcinoma. *Cancer* 100:801-806, 2004
- Postmus PE: Brain metastases from small cell lung cancer: Chemotherapy, radiotherapy, or both? *Semin Radiat Oncol* 5:69-73, 1995
- Grossi F, Scolaro T, Tixi L, et al: The role of systemic chemotherapy in the treatment of brain metastases from small-cell lung cancer. *Crit Rev Oncol Hematol* 37:61-67, 2001
- Siegers HP: Chemotherapy for brain metastases: Recent developments and clinical considerations. *Cancer Treat Rev* 17:63-76, 1990
- Stewart DJ, Lu K, Benjamin RS, et al: Concentration of vinblastine in human intracerebral tumor and other tissues. *J Neurooncol* 1:139-144, 1983
- Stewart DJ, Richard MT, Hugenholtz H, et al: Penetration of teniposide (VM-26) into human intracerebral tumors: Preliminary observations on the effect of tumor type, rate of drug infusion and prior treatment with amphotericin B or oral glycerol. *J Neurooncol* 2:315-324, 1984
- Stewart DJ: A critique of the role of the blood-brain barrier in the chemotherapy of human brain tumors. *J Neurooncol* 20:121-139, 1994
- Franciosi V, Cocconi G, Michiara M, et al: Front-line chemotherapy with cisplatin and etoposide for patients with brain metastases from breast carcinoma, nonsmall cell lung carcinoma, or malignant melanoma: A prospective study. *Cancer* 85:1599-1605, 1999
- Boogerd W, Dalesio O, Bais EM, et al: Response of brain metastases from breast cancer to systemic chemotherapy. *Cancer* 69:972-980, 1992
- Postmus PE, Smit EF, Berendsen HH, et al: Treatment of brain metastases of small cell lung cancer with teniposide. *Semin Oncol* 19:89-94, 1992
- Groen HJ, van der Leest AH, de Vries EG, et al: Continuous carboplatin infusion during 6 weeks' radiotherapy in locally inoperable non-small-cell lung cancer: A phase I and pharmacokinetic study. *Br J Cancer* 72:992-997, 1995
- Korfel A, Oehm C, von Pawel J, et al: Response to topotecan of symptomatic brain metastases of small-cell lung cancer also after whole-brain irradiation: A multicentre phase II study. *Eur J Cancer* 38:1724-1729, 2002
- Postmus PE, Haaxma-Reiche H, Smit EF, et al: Treatment of brain metastases of small-cell lung cancer: Comparing teniposide and teniposide with whole-brain radiotherapy—A phase III study of the European Organization for the Research and Treatment of Cancer Lung Cancer Cooperative Group. *J Clin Oncol* 18:3400-3408, 2000
- Kristensen CA, Kristjansen PE, Hansen HH: Systemic chemotherapy of brain metastases from small-cell lung cancer: A review. *J Clin Oncol* 10:1498-1502, 1992
- van den Bent MJ: The role of chemotherapy in brain metastases. *Eur J Cancer* 39:2114-2120, 2003
- Postmus PE, Smit EF: Chemotherapy for brain metastases of lung cancer: A review. *Ann Oncol* 10:753-759, 1999
- Kantarjian H, Farha PA, Spitzer G, et al: Systemic combination chemotherapy as primary treatment of brain metastasis from lung cancer. *South Med J* 77:426-430, 1984
- Kristjansen PE, Hansen HH: Brain metastases from small cell lung cancer treated with combination chemotherapy. *Eur J Cancer Clin Oncol* 24:545-549, 1988
- Lee JS, Murphy WK, Glisson BS, et al: Primary chemotherapy of brain metastasis in small-cell lung cancer. *J Clin Oncol* 7:916-922, 1989
- Humblet Y, Weynants P, Bosly A, et al: Carboplatin in association with etoposide and either Adriamycin or epirubicin for untreated small cell lung cancer: A dose escalation study of carboplatin—UCL Clinical Oncology Group. *Med Oncol Tumor Pharmacother* 6:207-212, 1989
- Twelves CJ, Souhami RL, Harper PG, et al: The response of cerebral metastases in small cell lung cancer to systemic chemotherapy. *Br J Cancer* 61:147-150, 1990
- Kristjansen PE, Soelberg Sorensen P, Skov Hansen M, et al: Prospective evaluation of the effect on initial brain metastases from small cell lung cancer of platinum-etoposide based induction chemotherapy followed by an alternating multidrug regimen. *Ann Oncol* 4:579-583, 1993
- Tummarello D, Lippe P, Bracci R, et al: First line chemotherapy in patients with brain metastases from non-small and small cell lung cancer. *Oncol Rep* 5:897-900, 1998
- Schuette W: Treatment of brain metastases from lung cancer: Chemotherapy. *Lung Cancer* 45:S253-S257, 2004 (suppl 2)
- WHO: WHO Handbook for Reporting Results of Cancer Treatment. Geneva, Switzerland, WHO, 1979
- Kleinbaum DG: Kaplan-Meier survival curves and the log-rank test in survival analysis: A self learning text (ed 2). New York, NY, Springer Verlag, 1997, pp 45-76
- Schellinger PD, Meinck HM, Thron A: Diagnostic accuracy of MRI compared to CCT in patients with brain metastases. *J Neurooncol* 44:275-281, 1999
- Blasberg RG, Groothuis DR: Chemotherapy of brain tumors: Physiological and pharmacokinetic considerations. *Semin Oncol* 13:70-82, 1986
- Neuwelt EA, Barnett PA, Bigner DD, et al: Effects of adrenal cortical steroids and osmotic blood-brain barrier opening on methotrexate delivery to gliomas in the rodent: The factor of the blood-brain barrier. *Proc Natl Acad Sci U S A* 79:4420-4423, 1982

Authors' Disclosures of Potential Conflicts of Interest

The authors indicated no potential conflicts of interest.

Author Contributions

Conception and design: Tatjana Seute, Pieter Leffers, Albert Twijnstra
Provision of study materials or patients: Jan T. Wilmink, Guul P.M. ten Velde, Albert Twijnstra
Collection and assembly of data: Tatjana Seute, Guul P.M. ten Velde, Albert Twijnstra
Data analysis and interpretation: Tatjana Seute, Pieter Leffers, Jan T. Wilmink
Manuscript writing: Tatjana Seute, Pieter Leffers, Albert Twijnstra
Final approval of manuscript: Pieter Leffers, Guul P.M. ten Velde, Albert Twijnstra