Prevalence of Brain Metastases Immediately before Prophylactic Cranial Irradiation in Limited Disease Small Cell Lung Cancer Patients with Complete Remission to Chemoradiotherapy: A Single Institution Experience

Farkhat Manapov, MD, Gunther Klautke, MD,* and Rainer Fietkau, MD*†*

This single-center study investigated the prevalence of brain metastases immediately before prophylactic cranial irradiation in 40 consecutive limited disease small cell lung cancer complete responders to chemoradiotherapy and revealed that 13/40 (32.5%; 95% confidence interval: 18–47%) patients suffer relapse with brain metastases and show a significantly worse prognosis than those without detected brain metastases.

Key Words: Prophylactic cranial irradiation, Small cell lung cancer.

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The central nervous system is a favorable site of failure for patients with small cell lung cancer (SCLC).[1,2] Asymptomatic brain metastases (BM) have been detected in 24% of all SCLC patients evaluated by contrast-enhanced cranial magnetic resonance imaging (MRI) at initial diagnosis.[3] Currently, concurrent chemoradiotherapy (CRT) followed by four courses of consolidation chemotherapy (CT) is the standard treatment for limited disease (LD) SCLC and all LD SCLC patients exhibiting a complete remission (CR) should be indicated to prophylactic cranial irradiation (PCI).[4] A meta-analysis has shown that PCI significantly reduces the incidence of BM and improves disease-free survival and overall survival in complete responders, regardless of whether they receive CT with or without thoracic irradiation.[5] Previous studies assessing the rationales for timing of PCI have also shown that early PCI is more effective than late PCI in preventing overt BM of SCLC.[5–7] However, MRI-based information about the prevalence of BM immediately before PCI in complete responders to CRT is lacking. Theoretically, this population could contain patients with occult brain BM.[8] To address this question, we performed a second contrast-enhanced cranial MRI in 40 consecutive LD SCLC complete responders to CRT immediately before PCI. A descriptive analysis of our findings regarding the prevalence of pre-PCI detected BM and their effect on prognosis are included in this report.

*Medical Faculty, Department of Radiotherapy, University of Rostock, and †Medical Faculty, Department of Radiotherapy, University of Erlangen, Germany.

Address for correspondence: Prof. Dr. med. Habil. Rainer Fietkau, Strahlenklinik, Medizinische Fakultät, Universität Erlangen-Nürnberg, Universitätstr. 27, D-91054 Erlangen, Germany. E-mail: rainer.fietkau@uk-erlangen.de

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PATIENTS AND METHODS

Patient Eligibility

Between 1997 and 2006, 105 patients with histologically confirmed LD SCLC received concurrent or sequential CRT at our hospital. All patients consented to participate in the study. Initial staging included bronchoscopy with biopsy, computer tomography scans of the chest and abdomen, bone scintigraphy, and first contrast-enhanced cranial MRI. Re-evaluation after completion of CRT included bronchoscopy with biopsy, computer tomography scans of the chest and abdomen, and bone scintigraphy. Patients with a tumor-free biopsy were defined as complete responders in cases where staging did not demonstrate any signs of tumor. Forty complete responders were identified. All of these patients received a second contrast-enhanced cranial MRI immediately before PCI and formed a population of interest (Figure 1).

CRT of LD SCLC

Sequential CRT (six cycles of CT followed by thoracic irradiation) was the standard treatment for LD SCLC up to 2000. Since 2000, it has been replaced by concurrent CRT (thoracic irradiation simultaneous with the first and second cycles of CT followed by four cycles of consolidation CT). Thirty of the overall group of 105 patients received a combination of cisplatin and irinotecan according to Rostock's phase I study protocol.[9] About 70/105 patients received other combinations such as carboplatin, etoposide and vincristine; carboplatin and etoposide; carboplatin and vincristine or nonplatinum-based combinations. Twenty-one (70%) of the 30 patients treated with cisplatin and irinotecan achieved CR compared with 19/75 (25.3%) of those treated with other combinations ($p < 0.001$).

Thoracic irradiation was delivered with megavoltage equipment (8–10 MV) using a multiple field technique. Three-dimensional treatment planning was performed. All

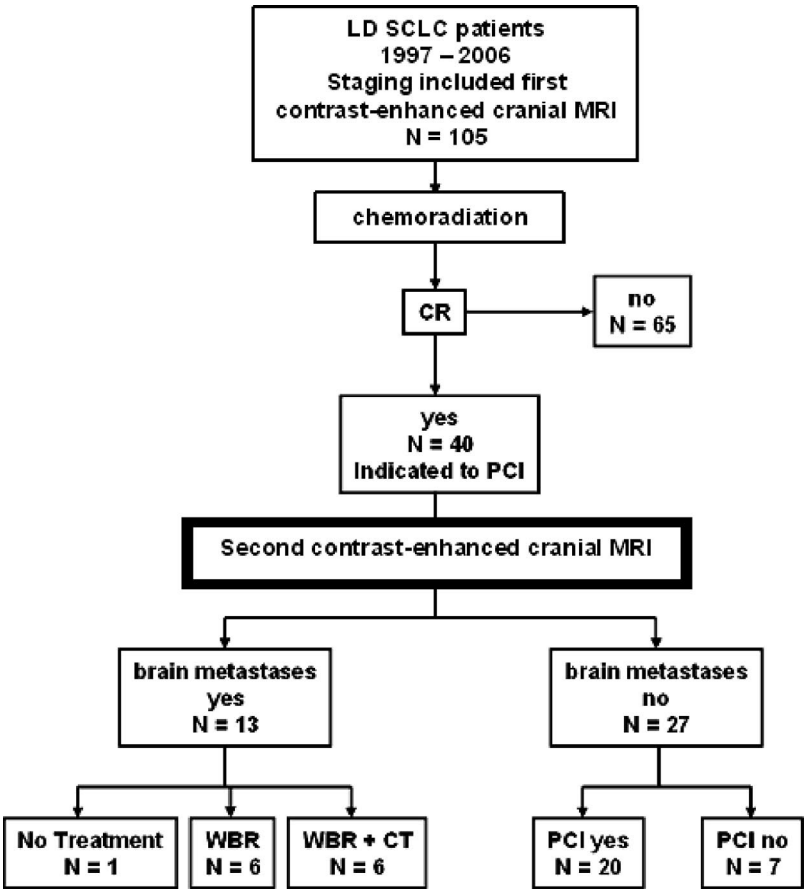

FIGURE 1. Patient selection according to the outcome of CRT and the findings of the second cranial MRI performed immediately before a planned PCI.

patients were irradiated 5 days a week (daily fractions of 1.8 Gy to a total dose of 54 Gy).

Contrast-Enhanced Cranial MRI

Investigation was performed at initial staging and within a week of diagnosis of CR to CRT with a 1.5 Tesla system according to a standard protocol (T1 spin echo transversal + coronar [saggital optional], TR <700 milliseconds, slice thickness 5 mm; MR contrast medium: gadolinium DTPA at a dose of 0.1 mmol/kg).

Treatment of pre-PCI Detected BM

BM were detected in 13 patients immediately before PCI. Treatment consisted of either whole-brain radiation alone (WBR) with 3.0 Gy fractions to a total dose of 30 Gy ($n = 6$) or WBR with 2.0 Gy fractions to a total dose of 40 Gy ($n = 6$) as a part of second-line CRT with topotecan. No treatment was administered in one case because the patient refused treatment. Topotecan was administered according to Rostock's phase II study protocol.[10] There were no criteria determining which one of the two treatment regimens was to be used.

PCI

PCI (1.8 Gy fractions to a total dose of 36.0 Gy) was performed in 20 (74%) of the 27 in whom no BM after completion of CRT were detected. The other seven patients (26%) declined PCI treatment.

Statistics

This descriptive analysis describes the prevalence of BM in LD SCLC complete responders to CRT, as determined by a second post-CRT contrast-enhanced cranial MRI, and the outcome of complete responders with and without pre-PCI detected BM. One must be aware that treatment decision-making was guided by the results of this second cranial MRI. The cut-off date for evaluation was November 1 2006. The median follow-up period was 16 months (range: 2–49 months). Using SPSS 14.0 software, Kaplan-Meier survival was calculated relative to the date of LD-SCLC diagnosis and the date of second cranial MRI to the death of the patient or to the last follow-up, respectively. All p values are derived from two-sided statistical tests; $p < 0.05$ was considered to be significant.

RESULTS

Prevalence of BM Immediately before PCI in LD SCLC Complete Responders to CRT

The 40 (38%) out of 105 LD SCLC patients who achieved CR to CRT received a second contrast-enhanced cranial MRI immediately before PCI (Table 1). The mean

TABLE 1. Patient Characteristics

Characteristic	No. of Patients
LD SCLC patients	105
LD SCLC patients with CR to CRT	40
Female	17
Median age, yr	63
Range	44–83
Male	23
Median age, yr	61
Range	39–79
LD SCLC complete responders treated with	
Concurrent CRT	21
Sequential CRT	19
Time from diagnosis of LD SCLC to second cranial MRI immediately before PCI, mo	7
Range	4–10
LD SCLC complete responders with immediately before PCI detected BM	13
After concurrent CRT	6
After sequential CRT	7
Symptomatic in brain	2
Asymptomatic in brain	11
LD SCLC complete responders without immediately before PCI detected BM	27
After concurrent CRT	15
After sequential CRT	12
LD SCLC complete responders with immediately before PCI detected BM	
Treated with	
WBR	6
WBR + CT with Topotecan	6
Untreated	1
LD SCLC complete responders without immediately before PCI detected BM	
Subjected to PCI	20
Not subjected to PCI	7

CR, complete remission; CRT, chemoradiation; CT, chemotherapy; LD, limited disease; MRI, magnetic resonance imaging; PCI, prophylactic cranial irradiation; SCLC, small cell lung cancer; WBR, whole brain irradiation.

time between LD SCLC diagnosis and the second cranial MRI was 7 months (range: 4–10 months). All 40 complete responders were neurologically asymptomatic after completion of CRT.

The second cranial MRI revealed BM in 13/40 patients (32.5%; 95% confidence interval: 18–47%), two (5%) of whom have developed neurologic symptoms within a week of diagnosis of CR to CRT. The mean time between completion of systemic treatment and second cranial MRI was not different in the BM-positive (28 days) and BM-negative patients (26 days). Additionally, the prevalence of BM was not different in patients treated with (6/21; 28.6%) or without (7/19; 36.8%; $p = 0.577$) irinotecan-containing combinations.

Prognoses of LD SCLC Complete Responders with and without pre-PCI Detected BM

In the 40 complete responders, median survival (MS) from the time of LD SCLC diagnosis was 20 months (95% CI, 11.6–28.3), and MS from second cranial MRI to the last follow-up or death was 13 (95% CI, 7.6–18.3). The 1- and 2-year survival rates after LD SCLC diagnosis were 81.4 ± 6.3% and 42.1 ± 9.2%, respectively; those after second cranial MRI were 54.0 ± 8.8% and 22.9 ± 9.2%, respectively.

In the 13 complete responders with pre-PCI detected BM MS from the time of LD SCLC diagnosis was 14 months (95% CI, range: 10.6–17.3), and that from the time of second cranial MRI was 6.5 months (95% CI, 1.6–11.3). One-year survival after LD SCLC diagnosis was 58.7 ± 14.2% versus 17.3 ± 11.1% after second cranial MRI. Eleven (84.6%) of the 13 patients developed neurologic symptoms that persisted until death or until the end of follow-up, indicating a progression in the brain. Six of the 13 (46.2%) were treated with WBR alone, and another six (46.2%) received WBR as a part of second-line CRT with topotecan (continuous infusion at a dose of 0.4 mg/m^2/d). The 13th patient (7.6%), who declined treatment, died 1 month after the second cranial MRI. Median and 1-year survival after second cranial MRI in the group treated with WBR alone was four months (95% CI, range: 0–8) and 16.7 ± 15.2%, respectively, compared with 10 months (95% CI, range: 0–25.6) and 22.2 ± 19.2% in the group treated with second-line CRT ($p = 0.02$). Extracranial progression, including local recurrence and/or distant metastases, was subsequently diagnosed in 7/13 (53.8%) patients (Table 2).

In the 27 complete responders without pre-PCI detected BM, MS after LD SCLC diagnosis was 26 months (95% CI, range: 20.9–31.0), and that after second cranial MRI was 22 months (95% CI, range: 13.1–30.8). The 1- and 2-year survival rates were 92 ± 5.4% and 61.1 ± 11.3% and 74.2 ± 9.2% and 34.6 ± 13% after diagnosis and after second cranial MRI, respectively. These values were significantly better than those in the 13 complete responders with pre-PCI detected BM ($p = 0.0001$). PCI was performed in 20 (74%) of the BM-negative patients, 4 (20%), of whom developed BM 6, 15, 15, and 21 months after treatment (the brain was the only a site of failure in one case). Seven complete responders (26%) without pre-PCI detected BM did not receive PCI; one (14%) of these patients developed BM 10 months later. Extracranial progression was subsequently diagnosed in 12 (44.4%) of the 27 BM-negative patients (Table 2).

DISCUSSION

Most national guidelines recommend contrast-enhanced cranial MRI in the initial staging of SCLC,[3,11] but not immediately before PCI. In the present study, occult BM were detected by pre-PCI second contrast-enhanced cranial MRI in 32.5% (95% confidence interval: 18–47%) of LD SCLC complete responders to concurrent or sequential CRT. Moreover, complete responders with pre-PCI detected BM had a significantly worse prognosis than those without detected BM.

TABLE 2. Survival, Intracranial Relapse, and Extracranial Progress by LD SCLC Complete Responders to CRT

	LD SCLC Complete Responders without Immediately before PCI Detected BM (n = 27)	LD SCLC Complete Responders with Immediately before PCI Detected BM (n = 13)
MS from diagnosis of LD SCLC (mo)	26 (95 CI, 20.9–31.0)	14 (95 CI, 10.6–17.3)
1-yr survival from diagnosis of LD SCLC (%)	92 ± 5.4	58.7 ± 14.2
2-yr survival from diagnosis of LD SCLC (%)	61.1 ± 11.3	Not achieved
MS from date of second cranial MRI before PCI (mo)	22 (95 CI, 13.1–30.8)	6.5 (95 CI, 1.6–11.3)
1-yr survival from date of second cranial MRI before PCI (%)	74.2 ± 9.3	17.3 ± 11.1
2-yr-survival from date of second cranial MRI before PCI (%)	34.6 ± 13	Not achieved
Intracranial relapse	5/27 (18.5%)	11/13 (84.6%)
Extracranial progress	12/27 (44.4%)	7/13 (53.8%)
Second-line CT or CRT	7/27 (25.9%)	6/13 (46.1%)
dead at the end of follow-up period	12/27 (44.4%)	11/13 (84.6%)

CR, complete remission; CRT, chemoradiation; CT, chemotherapy; LD, limited disease; MRI, magnetic resonance imaging; MS, median survival; PCI, prophylactic cranial irradiation; SCLC, small cell lung cancer; WBR, whole brain irradiation.

The present results are in agreement with previous studies demonstrating an important role of timing of PCI for BM-free survival, showing a steep dose-response curve after early PCI, but not after late PCI and suggesting that the loss of the steep dose-response curve occurs due to the development of overt BM from subclinical disease.[6,7] Indeed, in our study, PCI was applied late in the treatment protocol that can influence the prevalence of BM, as was already shown by Auperin et al.[5] Based on the previous and present results, we advise performing a second contrast-enhanced cranial MRI if PCI will delayed more than four months after the start of CRT because overt BM may develop from subclinical disease during this time. In addition, the second cranial MRI can help to distinguish complete responders who already have occult BM from those who should receive prophylactic PCI.

The present study also provides evidence that CT a key part of multimodality treatment concept was not enough to prevent occult BM in complete responders; however, the prolonged (up to 10 months) and nonstandardized (with presumably different effectiveness) induction phase can be considered as a most plausible explanation for this phenomenon. Nevertheless, the present data are in accordance with previous report that demonstrated unexpectedly high rate of BM as the first site of failure in LD SCLC patients treated with concurrent CRT and with the finding of evidently lower response rate of asymptomatic BM from SCLC to CT compared with the systemic response rate.[12,13] Therefore, it is also reasonable to discuss the possibility to incorporate PCI into the treatment of LD SCLC before the completion of CRT. This consideration is supported by previous investigations indicating that PCI is less effective when performed later.[5–7] However, the possibility that performing PCI simultaneous with CT might increase the neurotoxicity rate must also be considered, that is, Ball and Matthews[14] found a 26% incidence of neurotoxicity in studies where the PCI and CT were given concomitantly, versus 12% where they were not. If so, this may compromise the application of systemic treatment.

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