Leptomeningeal Metastasis from Non-small Cell Lung Cancer

Survival and the Impact of Whole Brain Radiotherapy

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Introduction: Leptomeningeal metastasis (LM), or leptomeningeal carcinomatosis, is a devastating complication of non-small cell lung cancer (NSCLC), and the optimal therapeutic approach remains challenging. A retrospective review was carried out to assess the impact of whole brain radiotherapy (WBRT), intrathecal therapy (IT), and epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs) on outcomes.

Methods: Patients with newly diagnosed LM from NSCLC from January 2002 to December 2009 were identified through institutional databases and medical records reviewed. Survival was assessed by Kaplan-Meier and landmark analyses by administered treatment to minimize selection bias.

Results: We identified 125 patients (45 men, 80 women) with LM from NSCLC, median age 59 years (range, 28–87 years). Almost all (123 [98%]) patients have died and median overall survival was 3.0 months (95% confidence interval, 2.0–4.0). No differences in survival were seen between patients who were treated with WBRT (n = 46) and those who were not (n = 59, p = 0.84) in a landmark analysis. In the seven patients selected to receive IT chemotherapy, median survival was 18 months (range, 5–33 months) and appeared superior to those not selected for this treatment (p = 0.001) in a landmark analysis. The median survival of the nine patients with known EGFR mutations (all of whom received TKIs at some point) was 14 months (range, 1–28 months).

Conclusions: This retrospective study, the largest published series, demonstrates the poor survival of LM from NSCLC. In this study, survival was not improved by WBRT. The survival of patients selected for IT chemotherapy and those with EGFR mutations treated with TKIs highlights the importance of developing novel agents.

Key Words: Non-small cell, Leptomeningeal metastasis, Leptomeningeal carcinomatosis, Radiotherapy, Intrathecal chemotherapy.

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In recent years, therapeutic advances have led to improvements in survival from non-small cell lung cancer (NSCLC). Patients with tumors that harbor mutations in the epidermal growth factor receptor (EGFR) can achieve prolonged disease control and survival with tyrosine kinase inhibitors (TKIs) such as erlotinib and gefitinib.[1–5] These improvements in systemic control and survival may contribute to a relative increase in the prevalence of leptomeningeal metastasis (LM) from NSCLC, which remains a devastating complication associated with poor survival.[6,7] The optimal therapeutic approach for LM remains challenging. Patients are frequently treated with whole brain radiotherapy (WBRT), intrathecal therapy (IT) chemotherapy, or rarely both, but the relative benefits of these approaches remain poorly characterized. Available literature is based partly on studies reporting heterogeneous cohorts of patients comprising different solid tumors which vary in terms of chemosensitivity and overall prognosis,[8–11] in addition to relatively small studies specifically reporting on outcomes in LM from NSCLC.[12,13] Thus, overall results may not be applicable to one type of tumor or different subgroups of patients with NSCLC. To evaluate treatment patterns and outcomes in patients with LM from NSCLC, we carried out a retrospective review of practice at a single institution, with an emphasis on the impact of WBRT and IT chemotherapy on outcomes.

MATERIALS AND METHODS

Patients at Memorial Sloan-Kettering Cancer Center with newly diagnosed LM from NSCLC between January 2002 and December 2009 were identified through two institutional databases: a neurology patient database and a pathology database of all collected cerebrospinal fluid (CSF) cyto-

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logic specimens. As previously described,[7,14] patients were included in this study if they met one of the following diagnostic criteria: (1) cytological evidence of malignant cells on CSF or (2) neuroimaging (gadolinium enhanced T1-weighted magnetic resonance scan) consistent with LM, as defined by the presence of multifocal enhancing subarachnoid nodules. Medical records were reviewed to determine patient characteristics, patterns of care, and outcomes. Because some patients with LM have poor performance status, uncontrolled systemic disease, and resultant limited survival, we performed a landmark analysis to assess the survival impact of WBRT and IT chemotherapy. This methodology was used in an attempt to remove selection bias because patients are only included if they survive a predetermined time from LM diagnosis. In this analysis, patients were included after diagnosis of LM if they survived 30 days (WBRT) and 45 days (IT chemotherapy). In addition, those who did survive were included as WBRT treated only if they had received WBRT by 30 days after LM diagnosis. Similarly for IT chemotherapy, patients had to have received IT chemotherapy by 45 days after LM diagnosis and also have been followed for 45 days or more. These two time points were chosen as from our dataset it was clear that radiation was given within 30 days of diagnosis, whereas a course of IT chemotherapy was administered over 45 days. Hence, different time points were chosen to minimize the different selection bias associated with the different approaches. The Kaplan-Meier method was used to examine survival from date of LM diagnosis to date of death or date of last follow-up. Survival comparisons were made using the log-rank test statistic.

RESULTS

We identified 125 patients (45 men, 80 women) who met the inclusion criteria with LM from NSCLC, median age 59 years (range, 28–87 years) and median Karnofsky Performance Status 70 (range, 30–100). The median time from initial NSCLC diagnosis to LM was 15 months (range, 0–121 months). Parenchymal brain metastases (prior or current) were noted in 102 (82%) patients, of whom 54 (53%) had received prior WBRT. In total, 42 (34%) patients had symptoms or signs of raised intracranial pressure, of whom 16 (38%) underwent ventriculoperitoneal shunt. Almost all (123 [98%]) patients are known to have died and one was lost to follow-up. The median overall survival was 3.0 months (95% confidence interval, 2.0–4.0 months) and the overall survival is shown in Figure 1. Most patients (97 [78%]) had adenocarcinomas and the other histological subtypes were as follows; squamous—4, NSCLC with neuroendocrine features—3, bronchoalveolar—2, large cell—2, adenosquamous—1, and NSCLC not otherwise specified—16. Of the 97 patients with adenocarcinoma, 61 (63%) were women and 36 (37%) were men. This gender distribution was similar in the 28 patients with other histologies (68% women, 32% men), $p = 0.63$. The improved survival of patients with adenocarcinoma ($n = 97$) compared with patients with other histologies ($n = 28$) ($p = 0.04$) is shown in Figure 2.

The initial therapies administered for LM are shown in Table 1. WBRT was administered using a linear accelerator

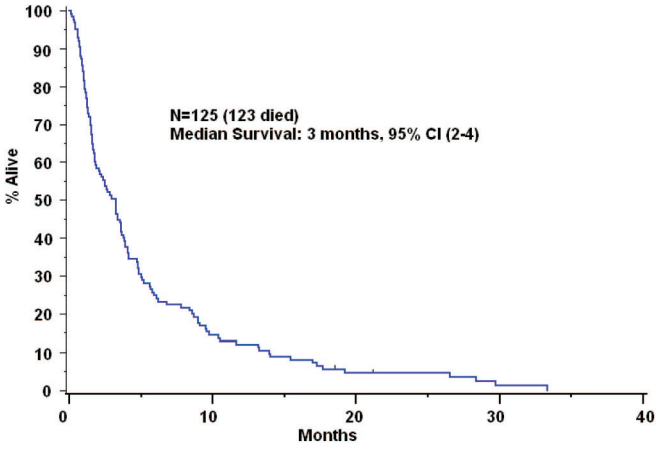

FIGURE 1. Overall survival from diagnosis of leptomeningeal metastasis.

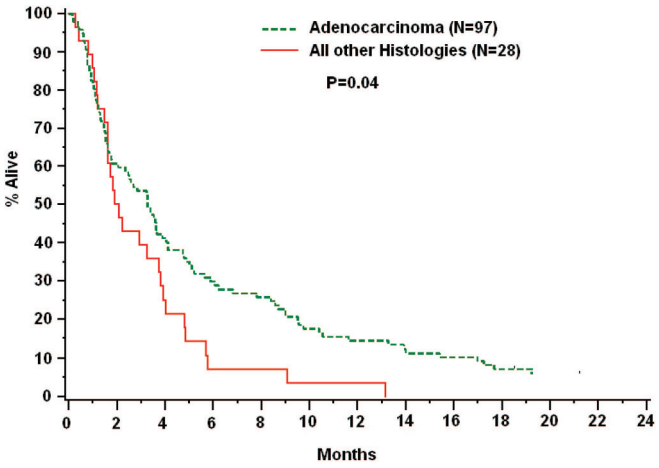

FIGURE 2. Overall survival by histological subtype.

TABLE 1. Initial Therapy for Leptomeningeal Metastasis

	n	%
Whole brain radiotherapy		
Yes	56	45
No	69	55
Intrathecal chemotherapy		
Yes	7	6
No	118	94
Systemic chemotherapy		
Yes	20	16
No	105	84
EGFR tyrosine kinase inhibitor		
Initiated	12	10
Continued	6	5
None	107	86
Palliative care alone	38	30

EGFR, epidermal growth factor receptor.

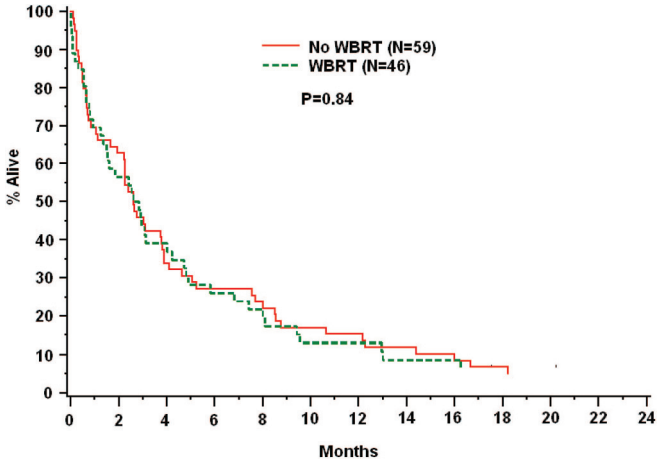

FIGURE 3. Overall survival by whole brain radiotherapy (WBRT). Proportion of patients surviving from date of leptomeningeal metastasis, by receipt of WBRT, landmarked at 30 days.

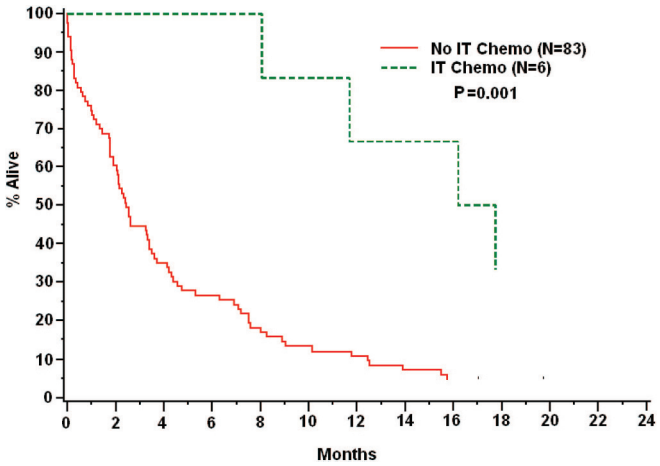

FIGURE 4. Overall survival by intrathecal (IT) chemotherapy. Proportion of patients surviving from date of leptomeningeal metastasis, by receipt of intrathecal chemotherapy, landmarked at 45 days.

and 6 MV photons, with doses ranging from 3000 to 3750 cGy, delivered in 10 to 15 fractions. After LM diagnosis, 56 (45%) patients were treated with WBRT, of whom 46 received WBRT by 30 days after LM diagnosis and survived ≥30 days after LM diagnosis. These patients were included in the landmark analysis and compared with the 59 patients who had not received WBRT by 30 days after LM diagnosis and who survived ≥30 days. As shown in Figure 3, no differences in survival were seen between patients who were treated with WBRT and those who were not ($p = 0.84$).

In total, seven (6%) patients, none of whose tumors were known to have a mutation in EGFR (six untested, one no mutation) received IT chemotherapy. The IT chemotherapy consisted of biweekly methotrexate ($n = 5$, median of 9 doses received) or liposomal cytarabine ($n = 2$, median of 6 doses). The median survival in the seven patients selected for IT chemotherapy was 18 months (range, 5–33 months). Of these, six received IT chemotherapy by 45 days after LM diagnosis and survived ≥45 days and were compared in the landmark analysis to the 83 patients who did not receive IT chemotherapy by 45 days after LM diagnosis and who survived ≥45 days. Although the overall numbers were small, it appeared that patients who were selected for IT chemotherapy survived longer than those who were not ($p = 0.001$) (Figure 4).

Tissue analyses from nine (7%) patients (five women, four men), all of whom had adenocarcinomas, were found to harbor mutations in EGFR. In 20 (16%) patients, there was no evidence of EGFR mutations and the status of the remaining 96 (77%) was unknown because this study was largely conducted before widespread testing for EGFR mutations. The nine patients with EGFR mutations developed LM at a median of 19 months (range, 2–47 months) from primary NSCLC diagnosis. In four (44%) of these patients, therapy with EGFR TKIs was ongoing in the month preceding LM diagnosis, two of these received WBRT and two had a change in systemic therapy as initial therapy for LM, but all four had subsequent EGFR TKI therapy. In addition, four (44%) other patients received EGFR TKIs subsequent to LM diagnosis. Hence, eight (89%) of nine patients with known EGFR mutations received EGFR TKIs at some time subsequent to the diagnosis of LM. The final patient had discontinued erlotinib 6 months before LM due to toxicity. The median survival of the nine patients with known EGFR mutations was 14 months (range, 1–28 months).

DISCUSSION

To the best of our knowledge, this retrospective study of 125 patients represents the largest published series on LM from NSCLC. This devastating clinical problem was associated with an extremely poor prognosis, with a median survival of only 3.0 months. Furthermore, using a landmark analysis, survival was poor whether or not patients were selected for WBRT, and therefore, we question the routine use of this approach in clinical practice. Although WBRT may play a role in symptom control, there is a lack of evidence supporting a survival benefit from available studies.[13,15] For example, in a retrospective study by Chuang et al.,[12] median overall survival was similarly short in patients who received WBRT (median, 5.6 weeks, $n = 16$) and those who did not (median, 2.9 weeks, $n = 18$), $p = 0.2$. The retrospective nature of our study prevents assessment of whether WBRT improved neurologic symptoms or quality of life, or whether it was associated with any toxicities.

In this report, 80 (64%) were women but no association was seen between gender and histological subtype, and the clinical importance of this finding is unclear. We also found a high incidence of raised intracranial pressure, which was diagnosed in 34% of our patients. Recognizing this complication is important because some patients with LM benefit from a ventriculoperitoneal shunt for palliation of symptoms, and shunt placement precludes the delivery of chemotherapy through an Ommaya reservoir. Thus, a lumbar puncture with CSF pressure measurement should be considered in patients

presenting with headache, nausea, and vomiting.[16] It must also be noted that raised intracranial pressure can occur in the absence of ventricular dilatation, and a ventriculoperitoneal shunt in this setting may also be helpful.[16]

The role of IT chemotherapy in solid tumors remains to be established. In our series, landmark analysis showed that patients selected to receive IT chemotherapy achieved prolonged survival (median, 18 months) compared with those who were not selected to receive this therapy ($p = 0.001$, Figure 4). Although definitive conclusions are limited by the small number of patients and the selection bias, this finding suggests that medical therapy with IT therapy or agents, which adequately penetrate the CSF, may play an important role in central nervous system disease control in some patients and be an important avenue of future research for the treatment of LM from NSCLC. This was seen even though agents traditionally used through the IT route such as methotrexate and cytarabine have limited activity in NSCLC. The impact of systemic chemotherapy on LM remains unclear, but anecdotal experience suggests that responses in LM may be attainable with agents active against NSCLC.

Many of the patients in this study represent a historic cohort, before the widespread testing for EGFR mutations and the use of EGFR TKIs. Nevertheless, in the small sample ($n = 9$) of patients with known sensitizing mutations in EGFR, a relatively long median survival of 14 months was seen. Because of the large number of patients with unknown EGFR mutation status (77%) and variable clinical practice relative to the introduction of EGFR TKIs, we were unable to elucidate the prognostic and predictive significance of sensitizing mutations in our population; however, the data suggest that this group of patients has superior survival to the overall cohort (median, 3.0 months). These findings are consistent with case reports and other series, which have demonstrated durable clinical benefit from TKIs such as erlotinib for patients with LM and sensitive EGFR mutations.[17–20] Furthermore, high-dose weekly erlotinib has been proposed as a possible therapeutic strategy for these patients, because this may increase CSF penetration.[21] These and other approaches may be appropriate for some patients and may offer improvement in outcomes for subgroups of patients with EGFR mutations. However, in the absence of EGFR mutations, alternative strategies are needed urgently. In that setting, the monoclonal antibody bevacizumab has shown some activity, but further validation of this approach and additional studies of active agents with adequate central nervous system penetration are needed.[22]

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