Abstract

Background: Although whole brain radiation therapy (WBRT) is commonly used as first-line treatment for leptomeningeal carcinomatosis, the prognosis is uncertain despite treatment. Moreover, the benefit of WBRT for leptomeningeal carcinomatosis has not been adequately evaluated. Therefore, this study aimed to clarify the utility of WBRT for leptomeningeal carcinomatosis.

Methods: Consecutive patients who received WBRT for leptomeningeal carcinomatosis or brain metastasis from solid tumors between January 2008 and July 2017 were retrospectively evaluated. The overall survival, symptom relief, and adverse events were compared between patients with leptomeningeal carcinomatosis and those with brain metastasis after WBRT.

Results: Of the 277 treated patients, 204 patients (22 with leptomeningeal carcinomatosis and 182 with brain metastasis) were included in the study. The median overall survival was 440 days (95% confidence interval [CI], 0-931 days) for patients with leptomeningeal carcinomatosis and 322 days (95% CI, 196-448 days) for those with brain metastasis (p=0.972 on the log-rank test). On evaluating the overall survival of patients with leptomeningeal carcinomatosis, the prognostic factors of performance status 0-1, no extracranial metastasis, and no symptoms at the time of WBRT showed a significant survival advantage on univariate analysis. Among patients with leptomeningeal carcinomatosis, those with headache and nausea often showed improvement while those with depressed levels of consciousness and seizures did not. On comparing all-grade adverse events, vomiting and seizures were more frequent in patients with leptomeningeal carcinomatosis than in those with brain metastasis.

Conclusions: WBRT was generally well tolerated and effective for treating patients with leptomeningeal carcinomatosis.

Key words: leptomeningeal carcinomatosis, palliative, radiotherapy, whole brain radiation therapy

Introduction

Leptomeningeal carcinomatosis is a rare complication of multiple cancers and may lead to death in 4-6 weeks if left untreated [1, 2]. Adenocarcinoma is the most frequent histology associated with leptomeningeal carcinomatosis, and breast and lung tumors are the most common primary tumors [1-4]. In leptomeningeal carcinomatosis, the most common symptoms of central nervous system dysfunction are headache and mental status changes, and the most common symptoms of cranial nerve dysfunction are diplopia followed by hearing loss, vision loss, and facial numbness [5]. Moreover, asymptomatic leptomeningeal carcinomatosis with brain metastases detected on magnetic resonance imaging (MRI) is sometimes neglected or treated using the same method used to treat multiple brain metastases. Furthermore, considering the prognosis and management, the difference between asymptomatic leptomeningeal carcinomatosis and multiple brain metastasis has not been clarified.

There is no consensus regarding the optimal treatment for patients with leptomeningeal carcinomatosis owing to the small number of published cases and randomized trials. In a randomized study to assess the benefit of intraventricular chemotherapy for leptomeningeal carcinomatosis, appropriate systemic therapy and radiation therapy was recommended for patients with an expected good prognosis while the addition of intrathecal chemotherapy did not lead to survival benefit or improve neurological responses [6]. Nevertheless, the optimal dose and fractionation schedule of radiation therapy for leptomeningeal carcinomatosis remain unknown. However, 30 Gy in 10 fractions is the schedule typically used as radiation therapy for leptomeningeal carcinomatosis, similar to whole brain radiation therapy (WBRT) for brain metastasis. Moreover, the utility of WBRT for leptomeningeal carcinomatosis has not been adequately evaluated. Therefore, this study aimed to clarify the utility of WBRT for leptomeningeal carcinomatosis by retrospectively reviewing the data of patients at a single institution.

Patients and Methods

Patients

This study was approved by the ethics committee of our institution and the need for informed consent was waived. Consecutive patients who received WBRT for leptomeningeal carcinomatosis or brain metastasis from solid tumors between January 2008 and July 2017 were enrolled in this study. Patients with leukemia or lymphoma were excluded. The indication for WBRT was determined according to the condition of the patient and the discretion of the treating physicians. We did not recommend WBRT for patients with a sharp decline in their consciousness levels or those in extremely poor general condition.

Diagnosis

The diagnosis of leptomeningeal carcinomatosis was based on the clinical characteristics of leptomeningeal carcinomatosis, confirmed via tumor-positive cerebrospinal fluid (CSF) cytology or characteristic findings on MRI. On the MRI scans of cases of leptomeningeal carcinomatosis, we defined diffuse enhancements as leptomeningeal enhancements detected in the whole brain, and focal enhancements as those limited to some areas of the brain (Fig. 1). Cases with multiple enhanced nodular lesions on the surface of the brain without leptomeningeal enhancement were diagnosed as brain metastasis. The MRI scans of all the patients with only brain metastasis were reviewed and reconfirmed for the absence of leptomeningeal carcinomatosis.

Survival analysis

Survival analysis was performed by using the Kaplan-Meier method, and differences between survival curves were tested using the log-rank test. Univariate and multivariate Cox proportional regression analyses were performed to identify prognostic factors of overall survival. Overall survival was calculated from the first day of radiation therapy to death due to any cause.

Symptom relief

The response to symptoms of patients with leptomeningeal carcinomatosis or brain metastasis was assessed within the first 2 months after the first day of irradiation. It was subjectively described by the patients themselves, and the information was entered on the medical charts. We defined improvement as symptom relief and being stable as no distinct change in the clinical status.

Adverse events

Adverse events were evaluated according to the Common Terminology Criteria for Adverse Events (CTCAE) version 4.0. Adverse events were assessed as symptoms arising or worsening after the first day of irradiation, and were graded based on the worst severity during this period. To compare the incidence of adverse events between patients with brain metastasis and those with leptomeningeal carcinomatosis, the chi-square tests or Fisher's exact tests were used.

Results

Patient characteristics and treatment details

Of the 277 included patients, 73 patients were excluded from the study because of the lack of detailed data or missing data owing to irregular follow-up visits. Then, data from 204 patients (22 with leptomeningeal carcinomatosis and 182 with only brain metastasis) were analyzed retrospectively. On evaluating the MRI findings in the 22 patients with leptomeningeal carcinomatosis, 5 patients showed only leptomeningeal enhancements without brain metastasis and the other 17 showed both leptomeningeal

enhancements and brain metastasis. The patient characteristics are summarized in Table 1. There was a significant difference in performance status. Steroids in addition to radiation therapy were administered to 16 patients with leptomeningeal carcinomatosis (73%) and 105 patients with brain metastasis (58%). In total, 2 patients with leptomeningeal carcinomatosis received intraventricular administration of methotrexate. One of these patients received treatment in combination with radiation therapy, and the other patient received treatment after radiation therapy. The fractionation schedules for WBRT are shown in Table 2. The most commonly prescribed dose of WBRT for both patients with leptomeningeal carcinomatosis and those with brain metastasis was 30 Gy in 10 fractions. Three patients with leptomeningeal carcinomatosis and 14 patients with brain metastasis did not complete the prescribed dose of 30 Gy in 10 fractions because of the worsening in their general condition. A booster dose of 5 to 16 Gy in 2 to 8 fractions was administered after WBRT to 6 patients with leptomeningeal carcinomatosis (27%), and 9 to 15 Gy in 3 to 6 fractions was administered to 42 patients with brain metastasis (23%).

Survival outcomes

Among all eligible patients, the median follow-up period was 146 days (range, 8–1514 days) for those with leptomeningeal carcinomatosis and 169 days (range, 5–3249) for those with brain metastasis. Follow-up until death was performed for 11 of the 22 patients (50%) with leptomeningeal carcinomatosis and 94 of the 182 patients (52%) with brain metastasis. The median follow-up period in censored cases was 276 days (range, 62–1367 days) for leptomeningeal carcinomatosis and 222 days (range, 61–3249 days) for brain metastasis. Kaplan-Meier survival curves of patients with leptomeningeal carcinomatosis and those with brain metastasis are shown in Fig. 2. The median overall survival was 440 days (95% CI, 0-931 days) for patients with leptomeningeal carcinomatosis and 322 days (95% CI, 196-448 days) for those with brain metastasis ($p=0.972$ on the log-rank test).

A comparison of the overall survival by prognostic factors in patients with leptomeningeal carcinomatosis is shown in Fig. 2. Considering the subgroups classified by prognostic factors, patients with

performance status 0-1 (p=0.028), no extracranial metastasis (p=0.019), and no symptoms at the time of WBRT (p=0.015) showed a significant survival advantage over those without the factors. These factors also showed significant survival advantages on univariate Cox proportional regression analysis, except for no symptoms at the time of WBRT that was excluded from the analysis because of no event of death (Table 3). On multivariate analysis, there were no significant prognostic factors. Among the 22 patients with leptomeningeal carcinomatosis, cytologic examination of CSF was performed for 7 patients. Overall survival was not significantly different between the 5 patients with positive CSF cytology and the other 17 patients, including 2 patients with negative cytology and 15 patients for whom cytologic examination was not performed (p=0.676).

Among 7 patients with lung adenocarcinoma, *EGFR* mutations were observed in 3 patients. The overall survival of the 3 patients with *EGFR* mutations were 52, 314, and 567 days, respectively, while that of the remaining 4 patients with wild-type *EGFR* were 8, 168, 440, and 1029 days, respectively. There was no significant difference in overall survival between the patients with *EGFR* mutations and those with wild-type *EGFR* (p=0.757 on the log-rank test).

Eight patients with leptomeningeal carcinomatosis lived for >6 months. Of these, 1 patient with breast cancer lived for >3 years. The other 7 patients included 6 with lung cancer and 1 with primary unknown cancer. Regarding the histology of lung cancer, 2 cases were small cell lung cancer and 4 were adenocarcinoma. Of the 4 patients with adenocarcinoma, 2 with *EGFR* mutations received epidermal growth factor receptor (EGFR)–tyrosine kinase inhibitors (TKIs), 1 with *ALK* translocation received anaplastic lymphoma kinase (ALK) inhibitors, and the remaining patient with wild-type *EGFR* mutations and who was *ALK* negative received programmed cell death-1 (PD-1) inhibitors. In contrast, 2 patients with leptomeningeal carcinomatosis lived for <1 month. One patient had lung adenocarcinoma expressing wild-type *EGFR* mutations and was *ALK* negative, with a performance status score of 4. The other patient had triple-negative breast cancer with a performance status score of 3. These 2 patients could not complete the prescribed dose of WBRT.

Symptom relief

Symptom relief was assessed in 17 patients with leptomeningeal carcinomatosis and 101 patients with brain metastasis who had symptoms related to leptomeningeal carcinomatosis or brain metastasis at the start of irradiation. Corticosteroids in addition to radiation therapy were administered to 15 patients among 17 patients with leptomeningeal carcinomatosis who had symptoms at the start of irradiation. Of the 15 patients who were administered corticosteroids, 13 (87%) showed improvement in at least one of the symptoms, and both the patients (100%) who were not administered corticosteroids showed improvement. The details of symptom relief in the patients with leptomeningeal carcinomatosis and those with brain metastasis are shown in Table 4. Among patients with leptomeningeal carcinomatosis, those with headache and nausea often showed improvement while those who had depressed levels of consciousness and seizures did not (Table 4).

Adverse events

Grade 3 or worse acute adverse events during WBRT developed in 2 patients: grade 3 dizziness in 1 patient with leptomeningeal carcinomatosis and grade 3 nausea in 1 patient with brain metastasis. On comparing all-grade adverse events, vomiting and seizures were observed more frequently in patients with leptomeningeal carcinomatosis than in those with brain metastasis (Table 5). The incidence and severity of cognitive disturbance were assessed in 15 patients with leptomeningeal carcinomatosis and in 147 patients with brain metastasis who survived for >2 months after the first day of WBRT. Grade 1 cognitive disturbance was observed in 2 patients with leptomeningeal carcinomatosis (13%) and in 15 with brain metastasis (10%), with no significant difference.

Discussion

The results of this study demonstrated that WBRT was effective for relief of symptoms due to leptomeningeal carcinomatosis. In a previous retrospective study that assessed survival, neurologic outcomes, and prognostic factors, the neurologic function status score, as a marker of the neurologic symptom response, stabilized or improved in 75.5% of the patients [7]. In a study comparing the efficacies of intrathecal methotrexate single therapy with a three-drug combination therapy (methotrexate, hydrocortisone and ara-C), patients who received concurrent cranial and/or spinal radiation therapy had a significantly higher neurologic response rate than those who did not (81.5% vs. 50.0%; p=0.014) [8]. This result is comparable to our study findings, although WBRT with concomitant intrathecal methotrexate was not commonly used in our study. In our study, symptoms such as headache and nausea improved in many patients, while depressed levels of consciousness and seizures rarely improved. As reported previously, fixed neurologic defects are difficult to treat [9].

The performance status is a common prognostic factor in retrospective studies to identify the prognostic factors for leptomeningeal carcinomatosis [7, 10-14]. A retrospective study evaluated the prognostic factors of leptomeningeal carcinomatosis after WBRT by comparing patients with brain metastasis and those with leptomeningeal carcinomatosis; better prognosis was observed in asymptomatic patients with leptomeningeal carcinomatosis, comparable to the results of our study [15]. However, leptomeningeal carcinomatosis was an independent favorable prognostic factor [15], which is in contrast to the result of our study. In that study, multiple parenchymal nodular enhancements without leptomeningeal enhancement were included in the cases of leptomeningeal carcinomatosis [15], and the difference in the results is thought to be mainly owing to the different definitions of leptomeningeal carcinomatosis. Moreover, for brain metastasis, on analyzing the Radiation Oncology Therapy Group (RTOG) experience including 1,200 patients, three recursive partitioning analysis (RPA) classes were suggested: RPA class 1: Karnofsky performance score (KPS) $\geqq$ 70, controlled primary, age < 65 years, no extracranial metastasis; class 3: KPS < 70; and class 2: all others. The median survival of patients in RPA class 1, class 2, and class 3 was 7.1 months, 4.2 months, and 2.3 months, respectively [16]. In our study, the significant prognostic

factors for overall survival in patients with leptomeningeal carcinomatosis were good performance status, no extracranial metastasis, and no symptoms at the time of WBRT. On multivariate Cox regression analysis, these differences failed to reach statistical significance mainly because the sample size in this study was small.

Among the patients with lung adenocarcinoma, *EGFR* mutations resulted in no significant survival benefit over wild-type *EGFR* in the current study mainly owing to the small sample size. However, some retrospective studies reported prolonged survival of patients with leptomeningeal carcinomatosis with *EGFR*-mutant non-small-cell lung cancer (NSCLC) treated with first-generation EGFR-TKIs [17, 18]. In a retrospective study assessing the impact of WBRT for leptomeningeal carcinomatosis, patients with *EGFR* mutations had superior survival than the overall cohort [19]. In addition, some prospective studies demonstrated the effect of TKIs for the control of brain metastases [20, 21]. In a phase 2 trial of gefitinib alone for patients with brain metastasis from *EGFR*-mutant lung adenocarcinoma, the response rate was 87.8% and the median progression-free survival time was 14.5 months (95% CI, 18.5-30.3 months) [20]. Osimertinib is a third-generation EGFR-TKI selective for both EGFR-TKI sensitizing and *EGFR* T790M resistance mutations. Reungwetwattana et al. reported a reduced risk of CNS progression with osimertinib versus standard EGFR-TKIs (gefitinib or erlotinib) in a subgroup analysis of the FLAURA study comparing osimertinib with standard EGFR-TKIs as first-line therapy for patients with advanced non-small-cell lung cancer [22]. Some patients with leptomeningeal carcinomatosis might survive long, particularly those who are likely to respond well to treatment.

In our study, the patient with the performance status score of 4 and the patient with the performance status score of 3 who experienced depressed levels of consciousness and multiple cranial nerve disorders lived less than 1 month. Thus, WBRT is expected to have little benefit for patients expected to have poor survival and those with symptoms derived from fixed neurologic defects. Therefore, patient selection is important for treating leptomeningeal carcinomatosis because overtreatment should be avoided for patients with limited survival prognosis.

Although the results of this study demonstrate the efficacy of WBRT for leptomeningeal carcinomatosis, the study had some limitations. First, the follow-up duration was not sufficient to evaluate the long-term late toxicities and survival time, and the inclusion of the many patients lost to follow-up might have resulted in better survival rates. Second, the number of patients in this study was too small to reach a definitive conclusion. Third, the data could not be used to estimate the outcomes of patients with depressed levels of consciousness or those in extremely poor general condition. We did not recommend WBRT for such patients because they would not benefit from WBRT. Finally, the retrospective nature of this study may have introduced bias in the evaluation of the severity of adverse events and the assessment of symptoms related to leptomeningeal carcinomatosis or brain metastasis. In the current study, the response was assessed on the basis of the subjective description provided by the patients. However, prospective studies in future should use the method of response evaluation proposed by the Response Assessment in the Neuro-Oncology working group for patients with leptomeningeal carcinomatosis [23].

In conclusion, the prognosis was favorable in patients with a good performance status, no extracranial metastasis, and no symptoms at the time of WBRT for leptomeningeal carcinomatosis. WBRT was effective for improving the symptoms of patients with leptomeningeal carcinomatosis. The incidence and severity of adverse events after WBRT for leptomeningeal carcinomatosis were within acceptable levels in this study.

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Conflict of interest

The authors declare that they have no conflict of interest.

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Figure captions

Fig. 1 (a) Diffuse enhancement: leptomeningeal enhancements detected in the whole brain on gadolinium-enhanced T1-weighted images

(b) Focal enhancement: leptomeningeal enhancements detected in limited areas of the brain on gadolinium-enhanced T1-weighted images

Fig. 2 Overall survival of (a) patients with leptomeningeal carcinomatosis and brain metastasis, (b) patients with leptomeningeal carcinomatosis according to the performance status (PS), (c) patients with leptomeningeal carcinomatosis according to the presence of extracranial metastasis, (d) patients with leptomeningeal carcinomatosis according to the symptoms at the time of start of whole brain radiation therapy, (e) patients with leptomeningeal carcinomatosis according to the primary lesion status, (f) patients with leptomeningeal carcinomatosis according to the lesion causing dissemination