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The prognostic significance of surgically treated hydrocephalus in leptomeningeal metastases☆

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ABSTRACT

Objective: The median survival of leptomeningeal metastases is short despite therapy and is sometime associated with hydrocephalus. We investigated the prognostic significance of surgically treated hydrocephalus in leptomeningeal metastases.

Materials and methods: Between December 2005 and November 2012, 1343 patients had brain metastases from systemic solid tumors. Of these, 71 patients (5.3%) experienced leptomeningeal metastases from 45 lung cancers, 14 breast cancers, 4 gastric cancers and 8 other cancers. The mean age was 60 years (range 37–89). The clinical symptoms presented in the cerebral hemisphere and cerebellum in 58 patients, cranial nerve in 7 patients and spinal cord and nerves in 6 patients. Twenty-nine (40.8%) patients were Radiation Therapy Oncology Group recursive partitioning analysis (RTOG-RPA) class II and 42 (59.2%) were class III. Hydrocephalus was associated in 18 (25.4%) patients and 7 patients underwent ventriculoperioneal shunt. The primary cancer, clinical symptoms, RTOG-RPA class, surgically treated hydrocephalus and systemic chemotherapy were analyzed as the prognostic factors for overall survival.

Results: The overall incidence of leptomeningeal seeding was 5.0% of the brain metastases. The median duration of leptomeningeal metastases from first brain metastasis was 4.0 months and 24 (33.8%) patients showed leptomeningeal metastases as the first form of brain metastasis. The median overall survival (OS) was 2.1 months. Based on the univariate and multivariate analyses, RTOG-RPA class II patients, treatment of leptomeningeal metastases (such as radiotherapy or intrathecal chemotherapy) and systemic chemotherapy improved OS with statistical significance. Surgically untreated hydrocephalus (median OS, 1.7 months) showed poor OS compared with surgically treated hydrocephalus (median OS, 5.7 months) and no hydrocephalus (median OS, 2.3 months) without statistical significance.

Conclusions: The leptomeningeal metastases were often associated with hydrocephalus and the surgical treatment was helpful in limited patients. The prognosis was related with RTOG-RPA class and treatment of local and systemic treatment.

1. Introduction

Leptomeningeal seeding (LMS) from solid tumors is the result of seeding of the leptomeninges by cancer. LMS is also known as meningeal carcinomatosis, neoplastic meningitis and carcinomatous meningitis. It is diagnosed in around 1–5% of patients with solid tumors and offers a dismal prognosis [1,2]. The incidence has been increasing due to the introduction of diagnostic tools for earlier detection and the therapeutic development for longer survival [3]. The standard diagnosis of LMS is the identification of malignant cells in cerebrospinal fluid and magnetic resonance imaging (MRI) plays an important role, even in cytology-negative cases [4,5]. Adenocarcinoma from breast, lung, and melanoma is the frequent pathology of leptomeningeal metastasis in USA [6,7]. Small cell lung cancer and melanoma show the higher rates than other solid cancers [1,7,8].

The median survival after LMS is only a few weeks in untreated patients. LMS results in significant morbidity and short median survival despite currently available treatment. In this study, we investigated the prognostic factors related with overall survival (OS) following leptomeningeal metastases and especially focused the prognostic significance of surgically treated hydrocephalus.

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2. Materials and methods

2.1. Clinical characteristics of 71 patients with LMS

One thousand three hundred and forty-three patients had brain metastases from systemic solid tumors between December 2005 and November 2012. Of these, 71 patients (5.3%) had LMS. The Institutional Review Board of Chonnam National University Hwasun Hospital approved this study. The histological diagnosis of the 71 systemic solid tumors were non-small cell lung cancer in 37 patients, small cell lusng cancer in 8, breast cancer in 14, gastric cancers in 4, hepatocellular carcinoma in 2, rectal cancer in 1, submanibular gland cancer in 1, esophageal cancer in 1, gall bladder cancer in 1, thymus cancer in 1 and bladder cancer in 1. The mean age was 60 years (range 37–89). There were 38 males and 33 females. The synchronous brain metastasis was recognized either immediately or within 3 months of the initial diagnosis of primary cancer and metachronous metastasis was found at a later time. Synchronous metastases of LMS were evident in 24 patients (33.8%) and metachronous metastases were detected in 47 patients (66.2%). In the metachronous metastases, the median duration of LMS from the first brain metastasis was 4.0 ± 1.0 months. The number of brain metastases was divided into less than 5 ($n = 45$, 63.4%), 5–10 ($n = 10$, 14.1%) and more than 10 ($n = 16$, 22.5%) on the diagnosis of LMS.

The LMS was diagnosed based on the magnetic resonance imaging (MRI) of brain and spine with contrast enhancement and/or the cytology of CSF. The positive MRI findings showed the focal or diffuse contrast enhancement on meninges, ependyma, tentorium, basal cistern and sulci. Spinal taps were performed for CSF cytology testing. After cytospin preparations were made, the malignant cells in CSF defined the positive finding of LMS. Seventy-one patients showed positive findings on brain and/or spine MRI with contrast enhancement. The CSF cytology test was done in 23 patients. On the first examination, 19 patients (82.6%) out of 23 showed positive malignant cells and 4 patients (17.4%) showed negative cells. On repeat CSF exam, two patients with negative cells showed positive malignant cells.

The clinical symptoms were classified in three domains of neurologic function: cerebral hemispheres and cerebellum, cranial nerves and spinal cord and roots. Cerebral hemispheres and cerebellum symptoms included headache, nausea/vomiting, seizures, abnormal gait and mental changes. The symptoms of cranial nerves included diplopia, visual loss, facial weakness, dysphagia and hearing loss. Symptoms of the spinal cord and roots included back pain, radiculopathy, myelopathy, paresthesias and paraparesis. The main clinical symptoms were presented as signs of cerebral hemisphere and cerebellum in 58 patients (81.7%), cranial nerve in 7 patients (9.8%) and spinal cord and nerves in 6 patients (8.5%). The Radiation Therapy Oncology Group (RTOG) prognostic classes for brain metastases using a recursive partitioning analysis (RPA) based on a three-class system for the future stratification and reporting of brain metastases has been proposed. Class I comprises patients with Karnofsky performance status (KPS) $\geq$70, age <65 years and with controlled primary and no extracranial metastases. Class III patients have KPS <70. Class II patients are all others [9]. Twenty-nine (40.8%) patients showed RTOG-RPA class II and 42 patients (59.2%) class III. Hydrocephalus was associated in 18 (25.4%) patients. Seven patients underwent a ventriculoperitoneal shunt operation. We placed a pressure adjustable programmable valve (The CODMAN® HAKIM® Programmable Valve System) in three patients and a high pressure valve (The CODMAN® HAKIM® Precision Fixed Pressure Valve) in four patients.

2.2. Statistical methods

OS was calculated from the date of LMS until death or until the latest follow-up. We defined the median range as the follow-up length and determined the effects of single variables on OS via univariate and/or multivariate analyses. The primary cancer, clinical symptoms, RTOG-RPA classes, surgically treated hydrocephalus, treatment of LMS and systemic treatment were analyzed as the single variables. We calculated the survival probability using the Kaplan–Meier method, performing comparisons with the log-rank test. We examined variables in the proportional hazard analysis (Cox model) to identify the independent predictors of survival. All statistical analyses were performed at a significance level of $p < 0.05$, using the statistical package SPSS 19.0 (SPSS, Chicago, IL).

3. Results

3.1. Treatment of LMS and systemic cancer

The LMS patients had been treated using whole brain radiotherapy (WBRT, $n = 25$), spinal radiotherapy ($n = 2$), WBRT combined spinal radiotherapy ($n = 4$) and intrathecal chemotherapy ($n = 2$). The daily fraction of the external bean radiotherapy was 3.0 Gy, 5 days per week. The median total radiation dose was 30 Gy (range 30–39) for WBRT and 20 Gy (range 18–30) spinal radiotherapy. Intrathecal chemotherapy was administrated by an intraventricular Ommaya reservoir in two patients. Intraventricular methotrexate was administered at 2 mg per day for 5 consecutive days every other week during 1 month in one patient and 6 months in one. Systemic chemotherapy for primary cancer was carried out in 18 patients (25.4%). The pathology was non-small cell lung cancer in nine patients, breast cancer in six, small cell lung cancer in two and gastric cancer in one. Thirty-three (46.5%) out of total 71 patients did not receive any other treatment after LMS because of a poor clinical condition.

3.2. Prognostic factors related with OS

The median OS was 2.1 ± 0.3 months. Thirteen patients (18.7%) survived over 6 months and 4 patients (5.7%) over one year. Univariate analysis revealed an improved OS for the RTOG-RPA class ($p = 0.000$, Fig. 1A), treatment of LMS ($p = 0.003$, Fig. 1B) and systemic cancer treatment ($p = 0.000$, Fig. 1C). There were no significant differences based on primary cancer ($p = 0.812$), clinical symptoms ($p = 0.556$) and hydrocephalus ($p = 0.404$) (Table 1). RTOG-RPA class II (median OS, 4.6 months; 95% CI, 3.417–5.923) displayed improved OS compared with class III (median OS, 1.27 months; 95% CI, 0.849–1.691). LMS treatment including radiotherapy and chemotherapy had an improved OS (median OS, 3.13 months; 95% CI, 2.578–3.682) compared with the no treatment group (median OS, 1.4 months; 95% CI, 1.122–1.678). Systemic chemotherapy (median OS, 5.73 months; 95% CI, 3.859–7.601) had an improved OS compared with the no treatment group (median OS, 1.5 months; 95% CI, 1.314–1.686).

Multivariate analysis results are summarized in Table 2. RTOG-RPA class II was significantly associated with a longer OS ($p = 0.015$; hazard ratio = 0.451; 95% CI, 0.237–0.855) compared to patients who had III. No LMS treatment and no systemic treatment were significantly associated with a short OS ($p = 0.014$; hazard ratio = 2.024; 95% CI, 1.154–3.550, $p = 0.057$; hazard ratio = 2.043; 95% CI, 0.979–4.263) compared to patients who had treatments, respectively.

3.3. Hydrocephalus associated with LMS

Eighteen patients (25.4%) showed the symptomatic hydrocephalus associated with LMS. Of these, seven patients (9.9%) were treated using ventriculoperitoneal shunts. Five patients showed RTOG-RPA class II and 13 patients class III. Univariate analysis revealed no significant difference of survival based on hydrocephalus ($p = 0.404$). Patients without hydrocephalus had a similar