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The Clinical Outcomes of Leptomeningeal Metastasis and Intrathecal MTX in Patients with Gastric Cancer: A Retrospective Analysis

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Abstract

Aim: The aim of this study was to report the clinical features of patients with LM originating from gastric cancer and the outcomes of intrathecal (IT) chemotherapy with methotrexate (MTX) in these patients.

Method: This study analyzed retrospectively the medical records of 10 patients with gastric cancer, who were diagnosed with LM and received IT chemotherapy with MTX at Kosin University Gospel Hospital between January 2007 and December 2017.

Results: Of 10 patients, half was male and the median age at LM diagnosis was 49 years (rang, 33-72). All patients but one had a poor performance status. Seven patients had poorly differentiated or signet ring cell adenocarcinomas, and six had Borrmann type III or IV gastric cancer. The median time from diagnosis of gastric cancer to the development of LM was 22.6 months (range, 4.93-103.7). LM was detected by brain magnetic resonance imaging in 6 patients, and was established in cerebrospinal fluid (CSF) analysis in all 10 patients. IT MTX for LM was administrated in all 10 patients, and the median 6 cycles of IT MTX was performed (range, 1-35). Three patients achieved negative conversion of malignant cytology in CSF. Systemic chemotherapy was performed in 5 patients. The median survival time from LM diagnosis was 2.1 months (95% confidence interval [CI], 1.5-2.7). Two patients survived about 12 months after LM diagnosis.

Conclusion: Although the prognosis of LM in gastric cancer patients was poor, the administration of IT MTX might have clinical benefit in some selected patients.

Keywords: Leptomeningeal carcinomatosis, Gastric cancer, Methotrexate, Intrathecal chemotherapy

Introduction

Leptomeningeal metastasis (LM), also known as leptomeningeal carcinomatosis or carcinomatous meningitis when malignant cells originated from a solid tumor, refers to the multifocal seeding of leptomeninges by cancer [1]. LM is detected clinically in approximately 5–8% of patients with solid tumor, and mostly presented at the late stage of disease [2][3]. The incidence of LM is increased due to prolonged survival time of patients with advanced solid tumors and improvement in

neuroimaging modalities for detection of LM [1][2].

Unfortunately, there is no standard treatment for LM. Treatment options are radiotherapy of the affected area, intrathecal (IT) chemotherapy, and systemic chemotherapy for primary tumors [1]. IT chemotherapy is a currently main treatment, because IT administration of drugs bypasses the blood-brain barrier (BBB) and results in higher drug concentration. Methotrexate (MTX), cytarabine, and, less often, thiothepa are available drugs

for IT chemotherapy, and MTX is the most commonly used and studies agent [2].

Gastric cancer is currently the fifth most common malignancy and the third leading cause of cancer-related mortality worldwide, and the most common cancer in Korea [4][5]. However, the clinical features and treatment outcomes of LM originating from gastric cancer have not been clarified. The aim of this retrospective study was to report the clinical feature of patients with gastric cancer who were diagnosed with LM and the treatment outcomes of IT MTX for LM in these patients.

Materials and Methods

Patients

This study analyzed the clinical data from the medical records retrospectively. At Kosin University Gospel Hospital between January 2007 to December 2017, a total of 10 patients with histologically confirmed gastric cancer were diagnosed with LM and received IT chemotherapy with MTX for treatment of LM. LM was confirmed in patients who presented with symptoms of signs suggesting LM, by either (1) radiologic evidence of LM on contrast-enhanced magnetic resonance imaging (MRI) of the brain, or (2) abnormal findings of cerebrospinal fluid (CSF) analysis suggesting LM (malignant cytology, or increased proteins levels and/or increased cell counts without malignant cytology). IT MTX was given 15 mg by lumbar puncture or Ommaya reservoir twice a week until the neurologic symptoms were improved, and then weekly according to patient's conditions.

Statistical analysis

The clinical data from the medical records was collected retrospectively. Overall survival (OS) was defined as the time from the date of diagnosis of LM to the date of death from any cause. The Kaplan-Meier method was used to estimate OS. Statistical analyses were performed using SPSS 18.0 software (SPSS, Inc. Chicago, IL, USA).

Results

Patient characteristics

A total of 10 patients were included in this study. The patient characteristics are summarized in table 1. Half of patients (50%) were male, and the median age of patients at LM diagnosis was 49 years (range, 33-72). All patients but one had a poor the Eastern Cooperative Oncology Group (ECOG) performance status (PS) (>2). Four patients had recurred disease after curative gastrectomy, and six had

metastatic disease at initial diagnosis of gastric cancer. Of 9 patients (histological differentiation were unknown in 1 patient), 7 patients had poorly differentiated or signet ring cell adenocarcinomas. Borrmann type III or IV were observed in 6 patients (one patient had EGC at initial diagnosis, and two had no available data of Bormann type). At the time of LM diagnosis, metastatic sites except for LM were distant lymph nodes (*n* = 6), bone (*n* = 3), peritoneum (*n* = 2), ovary (*n* = 2) and liver (*n* = 1); and brain metastasis were presented in 1 patient. All patients but one had prior history of palliative chemotherapy for gastric cancer.

Table 1: Basal clinical characteristics of patients (*n* = 10).

Patient characteristics	Number of patients (n)
Age (years), median (range)	49 (33–72)
Gender	
Male/female	5/5
ECOG PS at LM diagnosis	
≤ 2 / > 2	1/9
Disease status	
Recurrent/initially metastatic	4/7
Gastrectomy	
Yes/no	4/6
Differentiation	
Moderate/poor/signet ring cell/unknown	2/2/5/1
Location	
Upper/body/lower/whole/unknown	1/1/6/1/1
Borrmann type	
EGC/I/II/III/IV/unknown	1/0/1/4/2/2
Metastatic sites	
Lymph nodes/bone/peritoneum/ovary/liver/brain	6/3/2/2/1/1
Number of metastatic sites (except for LM)	
0/1/2/3	1/1/5/3
Number of prior palliative chemotherapy regimen	
0/1/2/3/4	1/1/5/2/1

ECOG: Eastern Cooperative Oncology Group; PS: Performance Status; LM: Leptomeningeal Metastasis

Diagnosis of LM

The commonly presented symptom suggesting LM was headache (80%), seizure (40%), and altered mental status (30%). The median time from diagnosis of the primary tumor to the development of LM was 22.6 months

(range, 4.93-103.7 months) (Table 2). LM was presented in 1 patient as a recurrence after curative gastrectomy without other metastatic sites. MRI studies of brain and CSF analysis were performed for all 10 patients. LM was detected by brain MRI in 6 patients, and was established in CSF studies in all 10 patients. MRI studies of spine were performed in 3 patients, but there was no evidence of leptomeningeal involvement of cancer in spine MRI.

Table 2: Pattern of LM (n = 10).

Symptoms of LM	Number of patients (n)
Headache	8
Seizure	4
Altered mental status	3
Diplopia	2
Dizziness	2
Nausea & vomiting	2
Gait disturbance	1
Time from diagnosis of primary cancer to diagnosis of LM (months), median (range)	22.6 (4.93–103.7)
≤ 12 months	4
> 12 months	6
Positive findings of LM in brain MRI	6
Positive findings of LM in CSF studies	10

LM: Leptomeningeal Metastasis; MRI: Magnetic Resonance Imaging; CSF: Cerebrospinal Fluid

Table 3 shows CSF analysis results. Malignant cells in CSF cytology were observed in 9 patients, and cell counts in CSF were elevated in 7 patients. The protein levels and the opening pressure were elevated in 6 patients (> 50 mg/dL) and 4 patients (> 20 cm H₂O), respectively (1 patient had no data on protein level in CSF and opening pressure at lumbar puncture). The glucose level, which was measured in 8 patients, was decreased (< 50 mg/dL) in 4 patients (50%).

Treatment for LM and survival

IT chemotherapy with MTX was administrated in all 10 patients. The median 6 cycles of IT MTX was performed (range, 1-35), and 3 patients achieved negative conversions of malignant cytology in CSF. After administration of IT MTX for LM, the clinical neurologic symptoms were improved in 6 patients; headache in 5 patients, and dizziness in 1 patient. Additional systemic chemotherapy was given to 5 patients after LM diagnosis. One patient received radiotherapy to simultaneous brain

metastasis, but nobody received radiotherapy to involved field of leptomeninges.

Table 3: CSF analysis findings in patients with LM.

Parameters	Number of patients/total patients [n/n (%)]
Positive malignant cytology	9/10 (100)
Pleocytosis (cells > 5/mm3)	7/10 (70)
Elevated protein (protein >50mg/dL)	6/9 (66.7)
Increased ICP (opening pressure > 20 cmH2O)	4/9 (44.4)
Decreased glucose (glucose < 50 mg/dL)	4/8 (50.0)

CSF: Cerebrospinal Fluid; LM: Leptomeningeal Metastasis; ICP: Intracranial Pressure

The clinical outcomes in patients are showed in Table 4. All 10 patients had died at the time of this analysis. The median OS was 2.1 months in 10 patients (95% confidence interval [CI], 1.5–2.7). Two patients survived around 12 months after LM diagnosis (13.1 months in case 1 and 11.3 months 8 in Table 4). One patient (case 1 in Table 4) presented LM as a recurrence after surgery without other metastasis, and had relatively good ECOG PS. She received a total 35 times of IT MTX. In the other case (case 8 in Table 4), although she showed poor PS at the time of LM diagnosis, the neurologic symptoms and sighs were dramatically improved after administration of IT MTX. She received a total of 30 times of IT MTX and systemic chemotherapy for disease

Discussion

LM is a rare but devastating complication in solid tumors and is becoming increasingly common as patients with advanced cancer liver longer [3]. Although nearly every advanced solid tumor has been reported to metastasize to leptomeninges, LM is frequently detected in lung cancer, breast cancer, and melanoma [3][6]. However, in studies on LM from Asian countries, cases arising from melanoma were rare, and gastric cancer was one of the most principal etiologies of LM [7][8][9]. However, LM is not a common complication of gastric cancer, the prevalence of LM was reported 0.17-0.43% [10][11][12].

In the previous studies of LM from gastric cancer, most patients had pathologically poorly differentiated or signet ring cell adenocarcinomas, and endoscopically Borrmann

Table 4: Treatments for LM and outcomes.

Case	Age (years)/ Sex	ECOG PS	Number of IT MTX	Negative conversion of malignant CSF cytology	Systemic chemotherapy after LM diagnosis	Survival after LM diagnosis (months)
1	49/F	2	35	Yes	No	13.1
2	62/M	3	1	Not evaluable	No	1.8
3	60/F	4	3	No	No	1.0
4	45/F	3	2	No	No	0.4
5	72/M	4	3	No	No	0.8
6	46/F	4	9	No	Yes	4.9
7	49/M	3	8	No	Yes	2.1
8	33/F	4	30	Yes	Yes	11.3
9	51/M	3	6	No	Yes	5.2
10	43/M	3	7	Yes	Yes	2.2

LM: Leptomeningeal Metastasis; ECOG: Eastern Cooperative Oncology Group; PS: Performance Status; IT: Intrathecal; MTX: Methotrexate; CSF: Cerebrospinal Fluid

type III or IV gastric cancers [10][12]. The result of this study was consistent with previous studies. These clinical features, poorly differentiated or signet ring cell histology and Borrmann type III or IV, are associated with relatively poor outcomes in gastric cancer [13][14].

LM usually occurs at a late stage of the disease of advanced solid tumor. At the time of LM diagnosis, most patients present multifocal neurologic signs and symptoms associated with LM and have a high systemic tumor burden. Therefore, once LM is diagnosed, the prognosis is poor, with the median survival is approximately 3-5 months [15][16][17]. In the studies of LM in gastric cancer, the median time from diagnosis of gastric cancer to development of LM was reported 6-15 months, and the median OS after LM diagnosis was 1-3 months [11][12][18][19]. In this study, most of patients (80%) had multiple metastasis sites (≥ 2) at the time of LM diagnosis, and had been heavily treated with several palliative chemotherapeutic regimens (≥ 2) before LM diagnosis. The median time from diagnosis of primary tumor to development of LM with 22.6 months was longer than results of previous retrospective studies. However, the median OS with 2.1 months after LM diagnosis was poor, like the results of other studies [11][12][18][19].

IT chemotherapy is the mainstay treatment for LM, although its effectiveness may be limited. Theoretically direct administration of drugs into CSF gives the best exposure to the chemotherapy, because the impermeability of the BBB limits the availability of drugs delivered systemically, and reduces systemic toxicity of

drugs [2]. MTX is a folate antimetabolite that interferes with DNA synthesis by inhibiting dihydrofolate reductase, with a CSF half-life 1.5-8.0 hours. MTX successfully cleared malignant cells from CSF in 20-61% of cases [20][21][22]. Oh et al. reported that approximately half patients with gastric LM who received IT chemotherapy achieved cytologic negative conversion, and this was associated prolonged survival [10]. In my study, among 3 patients who achieved negative conversion of malignant cytology after IT MTX, two patients survived around 12 months.

Systemic chemotherapy is limited for treatment of LM, because most drugs do not penetrate an intact BBB. However, the BBB may be disrupted by malignant cells, due to which, drugs could penetrate into the CNS [23]. In a randomized study to compare IT chemotherapy to systemic chemotherapy for LM in patients with breast cancer, the IT chemotherapy did not show survival benefit; the median survivals were 18.8 weeks in IT chemotherapy arm and 30.0 weeks in systemic chemotherapy, but there was no statistical significance [24]. Several retrospective studies showed that systemic chemotherapy for LM had a positive impact on survival in patients with solid tumor [8][9][25]. Most patients have extensive systemic tumor burden at time of LM diagnosis, and systemic chemotherapy could be effective for treatment of systemic disease.

Several studies reported that PS was one of the most important prognostic factors in patients with LM [7][8][16][25]. Patients with good PS could be offered aggressive treatments for LM that include not only

symptomatic management but also active chemotherapy. In my study, among 10 patients, only one case (case 1 in Table 4) had shown relatively good ECOG PS 2 at the time of LM and survived the longest with 13.1 months. However, in other patient who showed relatively longer survival with 11.3 months, despite poor initial ECOG PS, IT chemotherapy improved dramatically neurologic symptoms and PS, and then the patient received systemic chemotherapy. Therefore, appropriate choices and combinations of treatment modalities according to the patient's condition and disease state are needed to improve outcomes in patients with LM [1][2].

Conclusions

LM was not common in gastric cancer, and the prognosis after diagnosis of LM was poor. IT chemotherapy might have survival benefit in some selected patients, with especially good PS. And negative conversion of malignant cells in CSF may be associated good outcome. However, due to a very small sample size and a retrospective design of this study, these must be interpreted with caution. Further studies are needed to clarify the clinical characteristics of LM, and to improve outcomes of disease.

Declarations

- The Institutional Review Board of my hospitals approved this study. (KUGH 2018-05-043)
- There are no potential conflicts of interest.
- This study received no funding.

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