

Gastric cancer with brain metastasis and the role of human epidermal growth factor 2 status

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Abstract. Central nervous system (CNS) metastases from cancers of the gastrointestinal tract (GIT) are rare, and occur in 0.16-0.69% of patients with gastric or gastro-esophageal (GE) junction cancer. Overexpression of the human epidermal growth factor 2 (HER-2) is associated with poor prognosis in the absence of HER-2-targeted therapy, and with an increased incidence of CNS metastases in patients with breast cancer. The role of HER-2 overexpression in CNS metastases is not well known in gastric adenocarcinoma. The purpose of the present retrospective study was to assess the incidence of CNS metastases and to evaluate the associations between the CNS and HER-2 status in a series of consecutive patients with gastric or GE junction cancer. Between 2007 and 2013, 300 patients with gastric cancer (GC) or gastroesophageal junction, were admitted to Piacenza General Hospital, Italy. These cases were retrospectively analyzed to evaluate CNS metastases. The metastases were diagnosed with imaging techniques performed on symptomatic patients. Gastric histological samples of patients with CNS metastases were reviewed and tested for HER-2. A total of 7 of the 300 patients (2.33%) with GC were observed to have CNS metastases and 6 (85.71%) had HER-2 positive disease. These patients exhibited a poor prognosis with a median overall survival rate of 4.1 months (range, 2.1-6.6 months). These results suggested there may be CNS recurrence susceptibility in patients with HER-2 positive GC. To the best of our knowledge, this is the first report that associates CNS metastases and HER-2 status in gastric or GE junction cancer.

Introduction

Worldwide, gastric cancer (GC) remains a leading cause of cancer death, second only to lung cancer (1). Recurrence of GC often appears in the form of peritoneal dissemination, liver, lymph nodes and bone recurrence metastases are often seen (1). Central nervous system (CNS) metastasis from advanced gastric or gastro-esophageal (GE) junction cancer is extremely rare, occurring in 0.16-0.69% of patients (2-5). CNS metastasis is often multiple and associated with metastasis to other organs and a resection is uncommon. Response to treatment is poor: the prognosis is often dismal, as the median survival time ranges from 1.3 to 2.4 months (2-6). Among patients with gastric or GE junction cancer and brain metastasis, the mean interval from gastrectomy to the occurrence of brain metastasis is reported to be 9 months (range 1-23 months) in the United States study (3), and 9.6 months (range 0.1-43.7 months) in the Japanese study (2). Several reports (2-4) and two reviews (5,6) have described CNS metastases from GC; however, in these studies, the correlation between human epidermal growth factor 2 (HER-2 status) and CNS metastases is lacking; and reports on CNS involvement from HER-2 positive GC are fragmentary and very poor (7).

Overexpression/amplification of HER-2 in breast cancer, resulting in HER-2-positive subtypes, is associated with more aggressive behaviour when compared with HER-2-negative breast cancer and is also associated with increased risk of local growth and distant metastasis; furthermore, HER-2-positive breast cancer also appears to be associated with an increased risk of developing CNS metastases (8-12). The higher incidence of CNS metastasis from HER-2 positive breast cancer was also reported to be associated with Trastuzumab-based therapy (13). The humanized anti-HER-2 monoclonal antibody Trastuzumab is an effective treatment for patients with HER-2 positive breast cancer (14,15) and more recently, Trastuzumab in combination with chemotherapy improved progression-free survival and overall survival (OS) in patients with HER-2 positive advanced gastric or GE junction cancer (16).

To our knowledge to date, there are no studies that evaluate the correlation between HER-2 expression in gastric and GE junction cancer with CNS metastases. The purposes of this retrospective study are to assess the incidence of CNS

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metastases in a series of consecutive patients with gastric or GE junction cancer and to correlate the CNS involvement with HER-2 status.

Materials and methods

Study design. The objectives of this retrospective study are to evaluate the incidence of CNS metastases in a series of patients with gastric or GE junction cancer and to evaluate the relationship between HER-2 status with this incidence.

After obtaining internal ethical committee approval for the study, the records of 300 consecutive patients with gastric or GE junction cancer diagnosed between January 1, 2007 and December 31, 2013 admitted to the Piacenza General Hospital, Italy, were reviewed. Date of gastroscopy, histologic diagnosis, stage at diagnosis, treatment of primary and metastatic cancer and follow-up were collected in an electronic data base. The site of metastasis was categorized as loco-regional/lymph nodes or distant, visceral and CNS. Diagnosis of CNS recurrence was based on either computed tomography and/or magnetic resonance imaging scans of the brain. CNS imaging studies were performed in patients who developed neurological signs showing clinical suspicion of CNS recurrence, such as headache, gait disturbance, hemiparesis, aphasia, visual troubles and/or muscular weakness. Histological samples of gastric or GE junction tumours in patients with CNS metastases were reviewed and tested for HER-2. HER-2 positive disease was defined according to the ToGA trial criteria (16).

The clinical course, treatment, and OS of patients with gastric or GE junction cancer and CNS metastases were also analyzed and reported.

Statistical analysis. The clinical course of patients with CNS metastases was calculated from the initial diagnostic gastroscopy that confirmed the cancer. OS of these patients was calculated from the date of diagnosis of GC and death. To evaluate the prognosis of CNS involvement, survival was furthermore calculated from date of the diagnosis of CNS metastases by imaging studies to date of death. The median OS was calculated by the Kaplan-Meier method using STATA Release 11 software.

Results

Between 2007 and 2013, 300 patients were diagnosed with gastric or GE junction cancer at the Piacenza General Hospital. Diagnosis was done by esophagogastroduodenoscopy (EGDS) and biopsies. Seven out of 300 patients (2.33%) were found to have CNS metastases on imaging studies performed in symptomatic patients. The characteristics of the subjects are shown in Table I.

There were four women and three men, the median age was 55 years (range 46-77 years).

Primary sites of gastric tumour were cardia (5 patients), corpus (1 patient) and antrum (1 patient); histological types were intestinal in 4 and diffuse in 3 cases.

All seven patients with CNS involvement had advanced disease at diagnosis, with metastases in other organs: liver, peritoneum and lymphonodes (4 patients), lung (3 patients), lymphonodes and bone (1 case). Four patients received

Table I. Characteristics of patients with gastric or gastro-esophageal junction cancer and CNS metastases.

Characteristic	Number of patients (n=7)
Sex	
Female	4
Male	3
Median age, years (range)	55 (46-77)
Site of primary gastric cancer	
Cardia	5
Corpus	1
Antrum	1
Histological type	
Intestinal	4
Diffuse	3
Stage at diagnosis	
I	0
II	0
III	0
IV	7
Metastasis sites prior to CNS	
Liver	4
Peritoneum	4
Lymphonodes	4
Lung	3
Bone	1
Prior to chemotherapy	4
Prior to chemotherapy and Trastuzumab	2
Neurological symptoms of CNS involvement	
Headache, muscular weakness, gait disturbance	4
Hemiparesis, aphasia	2
Visual troubles	1

CNS, central nervous system.

chemotherapy and two chemotherapy plus Trastuzumab before CNS involvement.

All patients had neurological symptoms of CNS involvement: headache, gait disturbance and muscular weakness were the initial manifestations in four patients, hemiparesis and aphasia in two cases and visual troubles in the remaining patient. Six patients showed multiple intracranial lesions and one had leptomeningeal carcinomatosis. Six out of seven patients with CNS metastases (85.71%) showed HER-2 positivity on immunohistochemistry (Table II). Treatment of CNS metastases was based on whole-brain radiation therapy (WBRT) in six cases: four patients received systemic chemotherapy; two patients received Trastuzumab plus chemotherapy, and one of those cases also intratecal chemotherapy plus Trastuzumab, (patients with leptomeningeal carcinomatosis); one patient was treated with best palliative care.

Table II. HER-2 status, management and survival of 7 patients with gastric or gastro-esophageal junction cancer and CNS metastasis.

Case no.	Sex	HER-2 status of gastro-esophageal cancer	Time from diagnosis of gastro-esophageal cancer to CNS metastasis (months)	Treatment	Time from diagnosis of gastro-esophageal cancer to mortality (months)	Time from diagnosis of CNS metastasis to mortality (months)
1	F	POS	7.2	CT+WBRT	10.3	3.1
2	F	POS	3.2	CT+WBRT+TRA	7.7	4.5
3	F	POS	0.5	CT+WBRT	4.6	4.1
4	F	POS	10.3	CT+WBRT+TRA	16.8	6.5
5 ^a	M	POS	6.2	CT+WBRT+IT-TRA	9.4	3.2
6	M	POS	4.3	Supportive care	6.4	2.1
7	M	NEG	12.6	CT+WBRT	19.2	6.6
Median (range)		-	6.2 (0.5-12.6)	-	9.4 (4.6-19.2)	4.1 (2.1-6.6)

^aPatient with leptomeningeal carcinomatosis. POS, positive; NEG, negative; WBRT, whole brain radiation therapy; CT, chemotherapy; TRA, Trastuzumab; IT, Intratecal; CNS, central nervous system; HER-2, human epidermal growth factor 2; F, female; M, male.

The median time from the diagnosis of gastric or GE junction cancer to the diagnosis of CNS metastases in the seven patients was 6.2 months (range 0.5-12.6 months), median OS time from the diagnosis of GC in the 7 patients was 9.4 months (range: 4.6-19.2 months) (Fig. 1), while the median OS time from the diagnosis of CNS metastases was 4.1 months (range 2.1-6.6 months) (Fig. 2).

Discussion

HER-2 has increasingly become an important biomarker of gastric and GE junction cancers. Current estimations suggest approximately 16% of gastric and GE junction tumours over-express HER-2, although the precise figure remains uncertain with reported frequencies of HER-2-positive GC ranging from 6.0 to 30.0%. A meta-analysis showed that HER-2 overexpression was associated with poor prognosis in GC patients. HER-2 positive rates may be associated with sex, tumor site, TNM staging system, distant metastasis, lymph node metastasis, Lauren's classification, and differentiation grade in GC patients. The HER-2 expression rate in Asians may be higher than that in Europeans (17,18).

CNS metastases are manifestations of advanced/systemic cancer. Lung cancer, melanoma, kidney cancer and breast cancer (especially HER-2 positive and triple negative) show the highest incidence of brain metastases (8,9,13). Other primary neoplasms such as prostate and gastrointestinal cancer rarely metastasize to the CNS (13). The increased incidence of brain metastases in HER-2 amplified breast cancer has been reported to be multifactorial: direct biological effect, poor CSF penetration of Trastuzumab, to render the brain a 'sanctuary site' for HER-2 neoplastic metastatic cells (13). However it must be emphasized that a retrospective analysis of 9,524 women with early breast cancer enrolled in 10 adjuvant trials, identified HER-2 as a risk factor for the development of CNS metastases independently of Trastuzumab exposure (19). These data argue for a biological predisposition to metastasize to the brain of

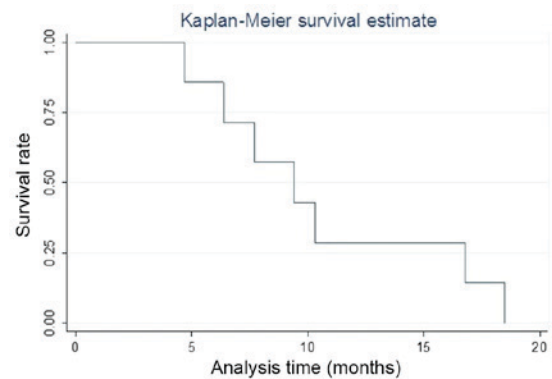


Figure 1. Overall survival (in months) from the diagnosis of gastric or gastro-esophageal junction cancer in 7 patients with central nervous system metastasis from gastric cancer.

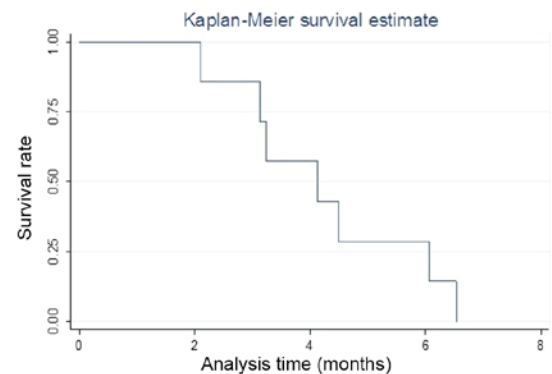


Figure 2. Overall survival (in months) from the diagnosis of central nervous system metastasis of the 7 patients with diagnosis of gastric or gastro-esophageal junction cancer

HER-2 positive breast cancer cells. The clinical predilection of HER-2 cancer cells to colonize the brain probably relies

on paracrine mechanism and recently it was suggested that heterodimerization of HER-2 and tropomyosin-related kinase B (TrkB) receptors gives HER-2 cancer cells a survival advantage in the brain (20). Brain metastases from gastric or GE junction cancer are very rare; <1% as reported in previous retrospective studies. York *et al* (3) reported that only 24 out of 3,320 (0.7%) GC patients were identified with brain metastasis over a 40-year period (1957-1997) at the MD Anderson Cancer Center. Likewise, Kasakura *et al* (2) identified brain metastasis in only 11 out of 2,322 (0.47%) patients between 1980 and 1998. It must be emphasized that in these previous reports, HER-2 status of patients with gastric or GE junction cancer and brain metastasis was unknown. Our group firstly reported a case of a patient with HER-2-over-expressing GC who developed leptomeningeal carcinomatosis (LC) and in this case we demonstrated the HER-2 positive status of malignant cells in the cerebrospinal fluid by fluorescence *in situ* hybridization (21). This patient was treated with intrathecal Trastuzumab plus Methotrexate, dexamethasone and radiotherapy; however she died 3 months after the diagnosis of LC. (This patient was not included in the present study). In a recent systematic review of 2,538 patients with brain metastases from the gastrointestinal tract, 148 patients (5.83%) had gastric or GE junction cancer (6); the HER-2 status of these patients was not reported. In the present study, we report that in a series of 300 patients with gastric or GE junction cancer, 7 cases developed brain metastases (2.33%), of which 6 cases had multiple brain solid lesions and one had leptomeningeal carcinomatosis. We are aware that our series is a small sample; in fact, only seven cases were included. However, it must be emphasized that brain metastases from gastric or gastric-esophageal cancer are very rare. In line with research reported in previous reviews (5,6) the majority of our patients, 5 of 7 patients (71%) who developed CNS metastases had primary tumours in the gastric cardia and concurrent systemic metastases were present in all 7 patients, and most commonly involved the liver, peritoneum, lymphonodes (56.8%), lung (42.6%) and bone (14.2%). It must be emphasized that in our series HER-2 status of GC and CNS metastases is known: 6 of 7 patients (85.71%) showed HER-2-over-expression of the primary GC.

The first four cases of HER-2-positive GC were diagnosed and treated prior to the availability of Trastuzumab in HER-2-positive GC, so these data can argue for a biological predisposition of HER-2 GC cells, to metastasize to the brain independently of Trastuzumab therapy such as HER-2-positive breast cancer cells. The median duration from the diagnosis of GC to the diagnosis of CNS metastases in our patients was 6.2 months (range: 0.5-12.4 months), which is lower as regards to the reported data (2,3). In fact, among GC patients with brain metastasis, the mean interval from gastrectomy to the occurrence of brain metastasis is reported to be 9 months (range 1-23 months) in the United States study (3), and 9.6 months (range 0.1-43.7 months) in the Japanese study (2). Response to treatment is poor: The prognosis is often dismal, as the median survival time ranged from 1.3-2.4 months (5,6) and treatment is palliative. According to these data, the median OS time from the diagnosis of CNS metastases in the 7 patients was 4.1 months (range 2.1-6.5 months).

Cinar *et al* (7) reported 3 patients with HER-2-positive GE junction cancer presenting with widespread metastatic disease

prior to development of symptoms from the primary tumours; 2 of these 3 patients presented with brain metastases. These two patients died approximately 10 and 24 months after diagnosis, a very long time when compared with our patients. Kim *et al* (22) reported a case with internal auditory canal metastasis due to leptomeningeal carcinomatosis from HER-2 positive GC. The interval from the date of diagnosis of GC and leptomeningeal carcinomatosis was seven months, and the patient survival time following the CNS involvement was only two months. Yang *et al* (23) described a case of a HER-2-positive GC patient who 8 months after surgery for the primary tumour developed a solitary brain metastasis treated with stereotactic radiotherapy. This patient is alive and healthy 8 months after radiotherapy. These Authors (7,22,23) raise the hypothesis that HER-2-positivity may be associated with a possible propensity for CNS metastases. In conclusion, we have reviewed retrospectively the records of 300 patients with gastric or GE junction cancer. Seven of these patients showed CNS metastases (2.33%) and six of the seven patients with CNS metastases showed HER-2-over-expression of their cancer. While acknowledging the limitations of a retrospective study, our 6 cases, as with the five patients previously described (7,21-23), raise the hypothesis that HER-2-over-expressed GC may have similar behaviour of HER-2-positive breast cancer showing a predilection for brain metastases, which are rare in GE junction cancer.

While accepting the limitations of the small number of patients with brain metastasis from gastric and GE junction cancer analyzed in this report, our data suggest the possibility of a CNS recurrence susceptibility in patients with HER-2-positive GC. To the best of our knowledge, this is the first report that correlates CNS metastases and HER-2 status in gastric or GE junction cancer.

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