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Case Report Open Access

# Is there an Increased Risk of Central Nervous System Metastasis in Cases with Gastric Cancer Showing Her2 Expression and Treated by Trastuzumab?

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## Introduction

The oncogene encoding Her2 receptor which has an important biologic significance in human cancers has been described 30 years ago by Schecter et al. [1]. Her2 amplification in gastric cancer has been shown in MKN-7 gastric cancer cell line firstly by Fukushige et al. in 1986 [2]. Later studies showed variable expression of ERBB2 in gastric cancer and Her2 expression rate has been found between 8% and 54% [3,4]. Significant survival advantage has been reported with the introduction of trastuzumab in cases with gastric cancer expressing ERBB2 [5]. Other anti-ERBB2 agents are used in ongoing studies and longer survival times are expected. By analogy with ERBB2 breast cancer it can be speculated that central nervous system metastases may increase in these cases with increased survival times. Here we reported brain metastases in a case with metastatic gastric cancer treated by trastuzumab containing regimen.

## Case Report

62 year-old-man admitted to the hospital on June 2011 with the history of gastrointestinal bleeding and two units of blood transfusion. On physical exam there was pallor and hepatomegaly. His past medical history was negative except ten pocket years of smoking

Laboratory: Abnormal findings were Hb 6 g/dl, Hct 20%, ferritin 10.5 ng/ml.

Upper endoscopy showed 5 cm ulcerated mass at cardia and endoscopic biopsy was reported as well differentiated adeno cancer. Her2 Neu was found to be (+++) and FISH analysis showed high amplification for Her2 Neu. Serum tumor markers were found to be high; CA19.9: 653 IU and CEA: 166 IU.

PET/CT showed 7×2.5 cm mass at gatric cardia (SUV max 25.64) and multiple hepatic metastases (SUV max 22.75). There was no evidence of cerebral metastasis at CT scans (Figures 1a and 1b). He received trastuzumab plus cisplatin and fluoropyrimidine containing regimen for 8 cycles and at the end of this treatment PET/CT and tumor markers were found to be negative. Maintenance trastuzumab could not be given due to the social security reasons. After 5 months of the last dose of treatment; tumor markers were found to be increased and repeated PET/CT showed relapsed disease at gastric cardia and liver again. Cisplatin, capecitabine and trastuzumab combination was started on February 2013 and 5 cycles were given and partial response was achieved. However at the end of June (at the end of 22nd month of metastatic gastric cancer) left hemipharesis developed. Brain CT showed right parieto-occipital and fronto-parietal lesions with large peri-tumoral edema (Figure 2). Anti-edema treatment with dexamethasone and cranial irradiation were started immediately. After 10 days of cranial irradiation, his condition deteriorated rapidly. Acute renal failure and jaundice developed. Repeated abdominal image showed disseminated liver metastases. He died within two weeks after cranial irradiation. Any other anti-Her2 treatment including lapatinib could not be given due to rapid progression of the disease.

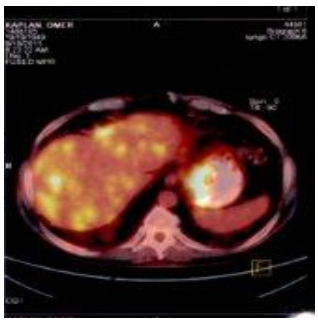

**Figure 1a:** PET/CT image shows gastric mass and multiple hepatic metastases.

## Discussion

Although there is no standard treatment for metastatic gastric cancer, platinum-fluoropyrimidine containing regimens with or without antracycline or docetaxel are the most commonly used doublets or triplets [6-8]. However with the combination of these drugs median survival is less than one year [9,10]. On the other hand, biology of gastric cancer has been found to be more important after the introduction of trastuzumab in the treatment of advanced gastric cancer. Median survival has been found to be increased in cases with ERBB2 expression and treated by trastuzumab containing regimens. ERBB2 expression rate is highest in proximal cancers and lowest in distal cancers and the most successful treatment results have been reported in high expressors [5,11,12]. The most famous study about this matter is Phase III-ToGA trial and significant overall survival advantage (10 vs 13 months) has

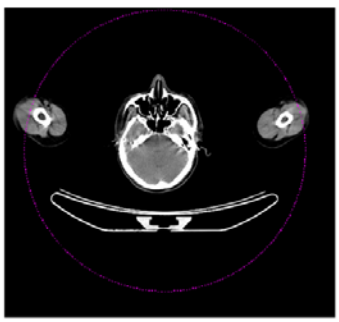

**Figure 1b:** No evidence of central nervous system involvement at the beginning.

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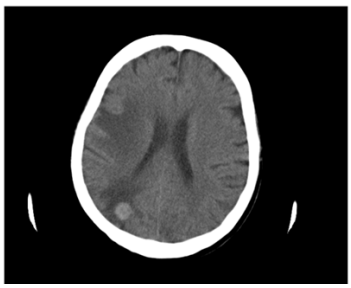

**Figure 2:** Central nervous system metastasis and edema.

been documented in cases receiving trastuzumab in addition to the conventional chemotherapy [5]. This study and other similar studies suggest that ERBB2 is an important therapeutic target in these cases. It can be said that 15-25% of the cases with gastroesophageal cancers show ERBB2 expression similar to the breast cancers and about one in five cases with breast cancer is candidate for anti-ERBB2 treatment modalities [13]. Our case had proximal cancer and he lived about 2 years and brain metastasis developed. What is the cause of central nervous system metastasis in our case?

1-Can it be due to the tumor biology? We do not know the exact answer but it has not been reported increased risk of central nervous system metastases in these cases in large scale multi-centric studies.

2-Can we make another comment by analogy from breast cancer? In breast cancer, there is no confirmation of correlation between trastuzumab and brain metastases and it has been suggested that systemic control of the disease with trastuzumab along with its inability to penetrate the blood-brain barrier may cause to the higher incidence of brain metastases [14]. In our case, relatively longer survival for a metastatic gastric cancer may be a cause of brain metastasis.

3-What are the therapeutic choices in these cases? In our case, we started anti-edema dexamethasone and cranial irradiation immediately due to his progressive neurologic signs and symptoms. At this point what are the available and the possible choices in this case and similar cases? Lapatinib plus capecitabine may be an important choice in our case due to the high penetrance of small molecule lapatinib to the central nervous system and higher activity of capecitabine in central nervous system disease especially after cranial irradiation [15,16]. On the other hand it has been shown that lapatinib reverses irinotecan resistance in vitro and it is reasonable to combine lapatinib and irinotecan which is an active drug in second line treatment of gastric cancer [17]. Another choice may be the combination of capecitabine, lapatinib and oxaliplatin which this regimen will be tested in LOGiC trial [13]. Trastuzumab and lapatinib combination which has been found to be effective in metastatic breast cancer may be another option [18]. Intrathecal trastuzumab may be another choice in this case.

In conclusion the occurrence of central nervous system metastasis may be seen in cases with gastric cancer showing ERBB2 expression and treated by trastuzumab containing regimens. Novel combinations and or approaches are needed in these cases.

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