

Efficiency of Combining Trastuzumab with Chemotherapy in case of advanced gastric carcinoma with low level amplification HER2 (c-erb-B2 protein)



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Gastric cancer is the second most common cause of cancer death in the world, although its incidence is declining over the last decades. Several factors of modern medicine have improved the management of gastric cancer. There has often been a poor prognosis because once symptoms occur, gastric cancer is often advanced. However, the multidisciplinary approach of gastric cancer therapy and adjuvant therapy are a promising management treatment.¹

Case Report

A 34-year-old known case of stomach cancer underwent distal esophageal resection. The pathological diagnosis was well differentiated intestinal type adenocarcinoma. The tumor involved the stomach and esophagus and there was serosal invasion of the entire thickness of muscular layer. The regional lymph nodes showed metastatic carcinoma. The immunohistochemical study of the tumor cell revealed no immunoreactivity with c-erb-B2 protein. The patient received complete full doses of radiation and capecitabine.

One year after the operation, the patient developed abdominal pain and the computed tomography (CT) of his abdomen showed enlargement to various sizes of para-aortic lymph nodes. The diagnosis of relapsed gastric cancer was noted. In order to determine the new chemotherapy plan, the repeated Hematoxylin eosin (H&E) and immunohistochemical (IHC) staining of his archive tissue of gastric cancer showed negative for HER2/neu (c-erb-B2 protein). When using fluorescence in situ hybridization (FISH) technique to identify this marker, it showed a weakly positive score for HER2/neu (1.30). The patient was informed about the potential option of using target therapy, Trastuzumab, in combination with chemotherapy. After the discussion about the benefits, he was then treated by, Trastuzumab in combination with paclitaxel. Without any significant side effects, the patient responded well; and his abdominal pain resolved. The follow up CT comparison of abdominal lymph nodes showed they subsided dramatically after only 2 cycles of treatment (Table 1) and some nodes had disappeared.

Table 1: CT abdomen shows comparative size of positive lymph nodes, before and after treatment.

Position of Positive Lymph node	Before Treatment Size (mm) (September 14, 2011)	After Treatment Size (mm) (December 6, 2011)
Celiac (Right)	40 x 31	25 x 13
Renal Hilum (Right)	25 x 27	12 x 13

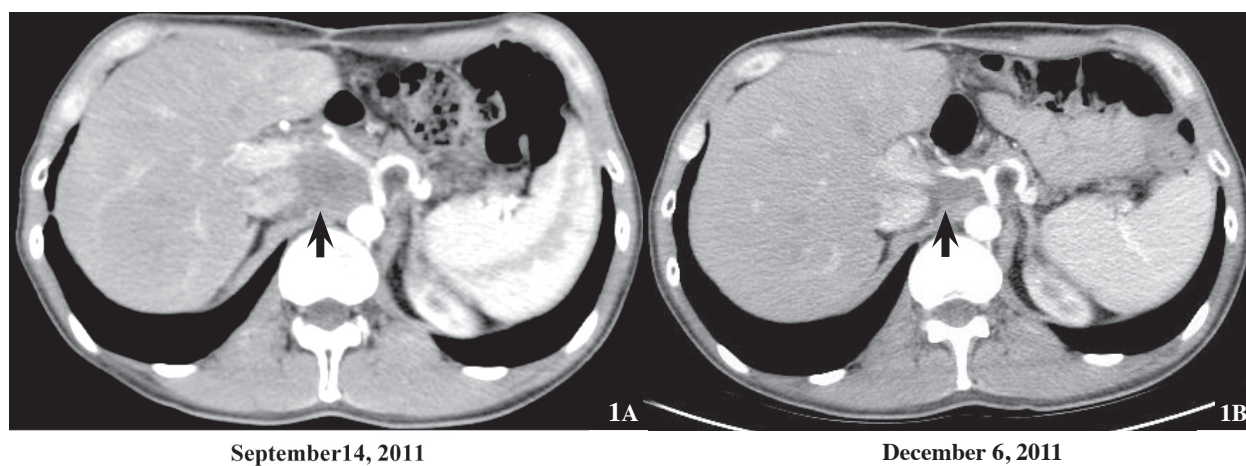


Figure 1A-B: CT Upper abdomen at level celiac region, before treatment (1A) and after 2 courses of treatment (1B).

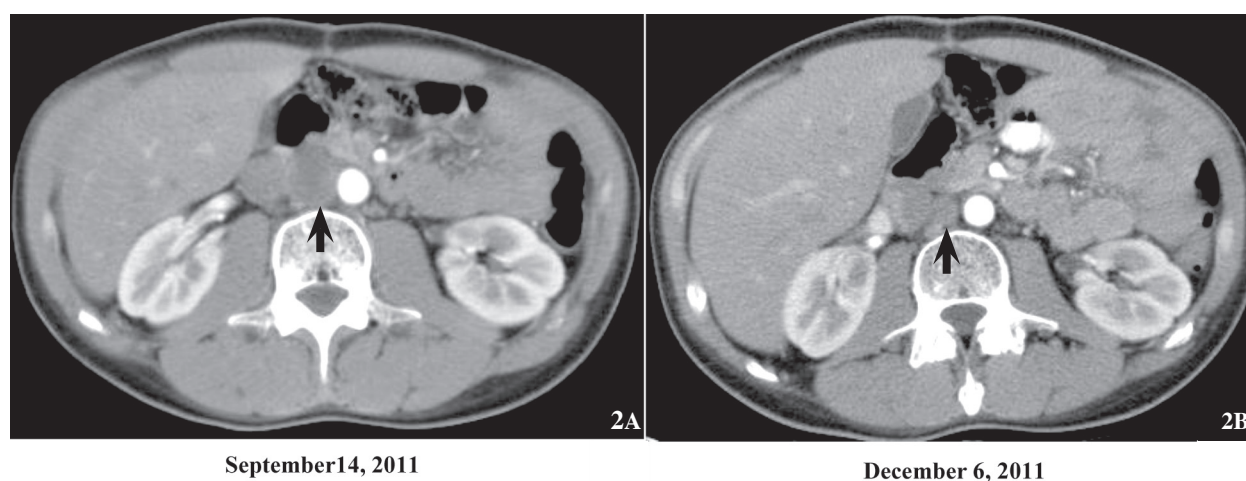


Figure 2A-B: CT Upper abdomen at level renal hilum, before treatment (2A) and after 2 courses of treatment (2B).

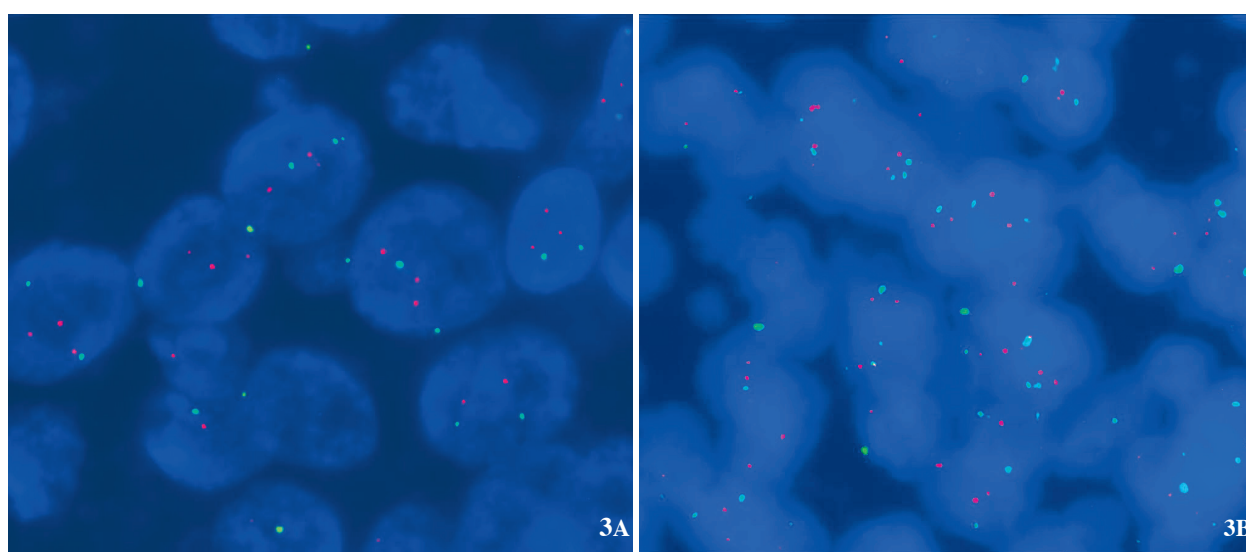


Figure 3A: Gastric specimen FISH technique (2/11/2011); Red dots represent HER2 Score 104, Green dots represent cen -17 score 80, HER 2/CEN -17, Ratio = 1.30

Figure 3B: Lymph node specimen FISH technique (15/11/2011); Red dots represent HER-2 Score 73, Green dots represent cen -17 score 73, HER 2/CEN -17, Ratio = 1.00

Discussion

In 1989, Slamon et al² found that there is an amplification of c-erb-B2 in the cellular membrane in cancer of the breast and ovary. C-erb-B2 protein (also called HER2 or Human Epidermal growth factor Receptor 2) is located at the long end of human chromosome 17. Overexpression of this receptor is associated with worse prognosis and higher recurrence of disease. Trastuzumab, a humanized version of a mouse monoclonal antibody that targets the receptor for therapy, was approved by the U.S. Food and Drug Administration in 1998 for treatment in combination with chemotherapy of women with HER2-overexpression metastatic breast cancer and became a popular treatment option for cancer of the breast in case of HER2/neu +ve.³ Menard and Scholl et al also demonstrated other tumor types to also have overexpression of HER2/neu including ovary, salivary gland, lung, esophageal and gastric carcinomas.^{4,5} Tanner et al also showed HER2/neu amplification is also common in intestinal types of gastric carcinoma and might be a useful therapy target in this disease; they also commented that immunohistochemistry (IHC) staining is less accurate than FISH (fluorescence in situ hybridization) technique in defining HER2 positively as well as ascertaining which patients were most likely to respond to treatment with Trastuzumab.⁶ In 2006 Menendez⁷ demonstrated that Trastuzumab when combined with chemotherapy induced a receptor-enhanced chemosensitivity (REC) effect in the absence of HER2-overexpression. In 2010, Yung-Jue Bang et al⁸ showed that Trastuzumab in combination with chemotherapy can be considered as a new standard option for patients with HER2-positive advanced gastric or gastro-esophageal junction cancer. In 2011, Negri et al⁹ commented on one case which showed discordant HER2 results between the primary tumor and corresponding lymph node metastasis; HER2 gene was found unamplified in the primary tumor, but there was strong amplification in the lymph nodes, thus suggesting

that “HER2 positivity can be heterogeneous within the same tumor and might develop upon progression.” This suggested that HER2 status should be assumed in the metastasis, thereby making them possible candidates for Trastuzumab.

As aforementioned, target therapy and chemotherapy in cases of advanced HER2 overexpression carcinoma of stomach have now become the standard of care in this scenario. Many investigators showed an interest in the group of patients with low HER2 expression who might also be benefited by combined target therapy and chemotherapy; this may be also be applied in cases of absence of HER2 expression. We presented a case of advanced gastric carcinoma with para-aortic metastases post gastrectomy and FISH showed the tumor to have low level HER2. We successfully treated the patient with combination of anti-HER2 and chemotherapy and rapid tumor regression was observed. This supports Menendez’s observation. We think therefore that FISH technique should be used to evaluate HER2 status at primary and secondary site(s) but we should consider to use trastuzumab and chemotherapy adjunctively, and effectively as a first treatment option in cases of both strong or low expression of HER2.

Conclusion

For gastric carcinoma, HER2 gene amplification by FISH technique may be different from the breast cancer. It can be heterogeneous within the same tumor, either at the primary site or at secondary lymph metastasis. HER2 may show up negative by IHC, but can be more accurately revealed using the FISH technique. Trastuzumab in combination with chemotherapy can be efficient, even if HER2 is only expressed at a low level. In this patient, after the optimal course of treatment, the maintenance of systemic therapy may be warranted and this may improve the overall survival.

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