

Trastuzumab Re-Introduction with FOLFIRI for Treatment of HER2 Overexpression-Advanced Gastric Adenocarcinoma Following Failure of Other Trastuzumab-Based Chemotherapy Regimens

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Abstract

A 67-year-old man diagnosed with HER2 overexpression advanced gastric adenocarcinoma and metastasis to liver and lungs was admitted for tertiary care. He received a third line chemotherapy that consists of trastuzumab combined with FOLFIRI regimen (irinotecan plus 5-FU/LV) following a disease relapse after an initial successful response to a combination of 5FU + oxaliplatin and trastuzumab. The patient showed a favorable and prolonged response to it. In addition the chemotherapy was well tolerated and devoid of remarkable side effects. The response to trastuzumab + FOLFIRI was assessed clinically and through CT scan imaging and upper gastrointestinal endoscopy. This case report shows that firstly the combination of FOLFIRI and trastuzumab could be tested as another regimen in metastatic gastric cancer, and, secondly, that in this disease, like in metastatic breast cancer, the continuation of trastuzumab after an initial progression under this antibody could be tested in order to improve the efficacy of the treatment Trastuzumab re-introduction with FOLFIRI for treatment of HER2 overexpression-advanced gastric adenocarcinoma following failure of other trastuzumab-based chemotherapy regimens.

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Keywords

Stomach Neoplasm, Trastuzumab, Treatment Reintroduction

1. Introduction

Gastric carcinoma is the fourth most common cancer in the world with almost 1 million cases in 2008, and the second most frequent cause of cancer-related death with about 740,000 deaths per year worldwide [1].

In the metastatic setting, chemotherapy remains the standard of care, several regimens having shown a benefit in overall survival (OS) in first line treatment. The main drugs used in this situation are fluoropyrimidines (5-Fluorouracil (5FU) and capecitabine), epirubicin, platinum salts (cisplatin or oxaliplatin), docetaxel and irinotecan [2]-[5].

Recently, the TOGA study showed that the addition of trastuzumab to fluoropyrimidine and cisplatin improved tumor response rate (RR), progression free survival (PFS) and OS in patients with a HER2-positive (scored 3+ on immunohistochemistry or 2+ and FISH positive) metastatic gastric cancer [6].

Furthermore, few recent publications have reported that trastuzumab in combination with FOLFIRI may have some efficacy in second, or more, line of chemotherapy in trastuzumab naïve patients [7] [8].

We hereby report a patient with HER2 overexpression advanced gastric adenocarcinoma with a favorable response to trastuzumab-based first chemotherapy who has been re-challenged with FOLFIRI and Trastuzumab combination in third line treatment following disease progression under a second line chemotherapy.

2. Case Report

On a routine pre-operative evaluation for a cardiac surgery, the chest X-ray of a 67-year-old man demonstrated the presence of several metastatic nodules in both lung fields. A computed tomography (CT) scan further confirmed the presence of metastases in lungs as well as in the liver (Figure 1 and Figure 2). Upper GI endoscopy and histopathology of gastric biopsies confirmed the diagnosis of moderately differentiated adenocarcinoma of gastric cardia with an over-expression of human epidermal growth factor receptor 2 (HER2) as identified by immunohistochemistry (score 3+). Serum tumor markers (CEA and CA 19-9) were not elevated. Surprisingly the medical history was unremarkable for symptoms related to gastrointestinal tract except for a long standing heartburn for which he was receiving proton pump inhibitors (PPIs).

The first line chemotherapy was initiated with combination of FOLFOX (oxaliplatin 85 mg/m², Leucovorin 400 mg/m², 5FU bolus 400 mg/m² and 5FU infusion 1200 mg/m² in days 1 - 2) and a monoclonal antibody, trastuzumab (6 mg/kg first cycle then 4 mg/kg) every two weeks. CT-scan evaluation of the lesions after 4 cycles was encouraging with impressive shrinkage of liver metastases.

Following further two more cycles of FOLFOX and trastuzumab, we were obligated to stop oxaliplatin due to its obvious neurotoxicity but to continue with LV5FU2 and trastuzumab. The initial response was also favorable and after one year of treatment, the liver and lung metastasis had almost disappeared (Figure 1). The remnant of cardia scar was the only finding on a subsequent upper GI-scopy and the biopsy specimens were devoid of any malignant cells. The cardia thickening was also completely disappeared on the CT-scan.

Unfortunately the disease relapsed after a completion of 24 cycles of chemotherapy, and for this reason a clinical trial of paclitaxel and ramucirumab was initiated as an alternative chemotherapy and after 4 months of therapy we observed tumor progression of the lung and liver metastases.

Due to successful response with the trastuzumab in first line chemotherapy, and encouraging results from the data reported in the literature [7] [8], a treatment with FOLFIRI and trastuzumab every two weeks was proposed at the weekly multidisciplinary meeting (Irinotecan 180 mg/m², Leucovorin 400 mg/m², 5FU bolus 400 mg/m², 5FU infusion 1200 mg/m² in days 1 - 2, and trastuzumab 6 mg/kg for first cycle then 4 mg/kg every 2 weeks for subsequent cycles.

After 3 cycles the disease became stable (−10% according to RECIST criteria), but the patient experienced thrombopenia grade 2 (CTCAE v4.0), thus to avoid this problem, some modification in cycle duration was performed so the treatment with FOLFIRI and trastuzumab (in a dose of 6 mg/kg) every 3 weeks instead was continued.

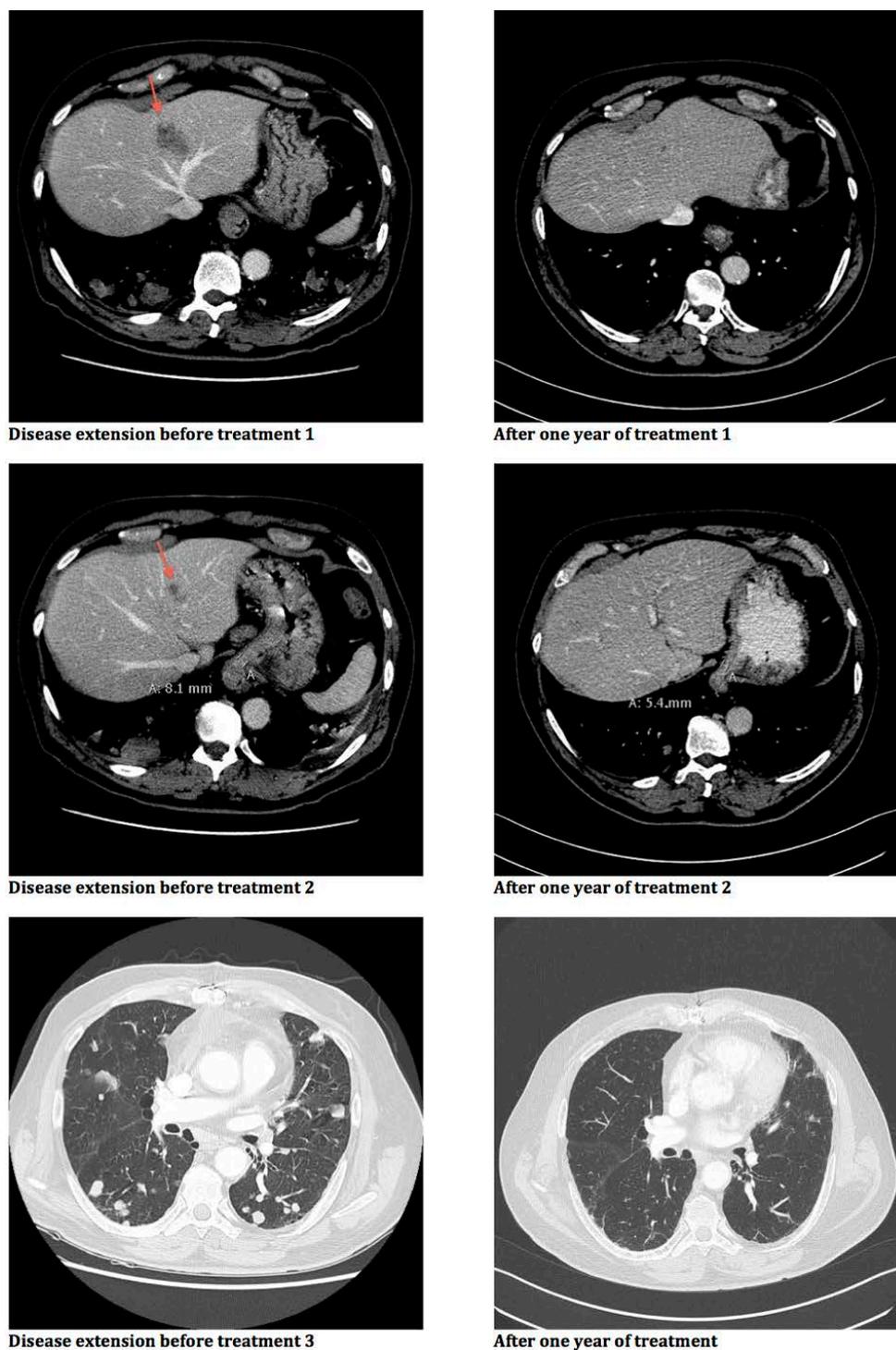
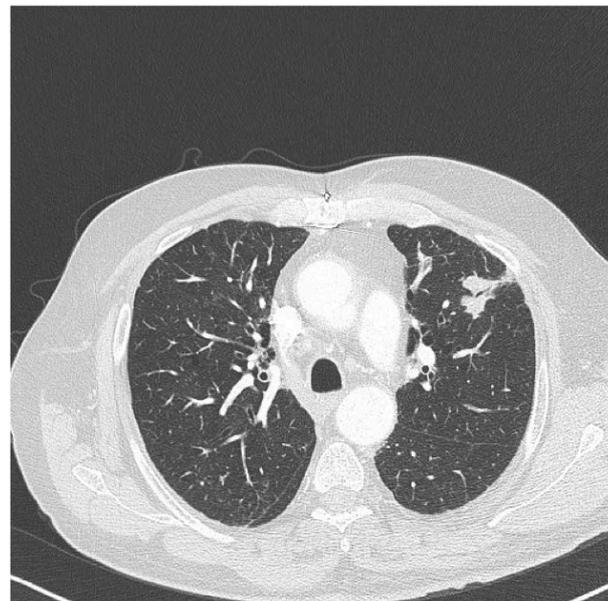


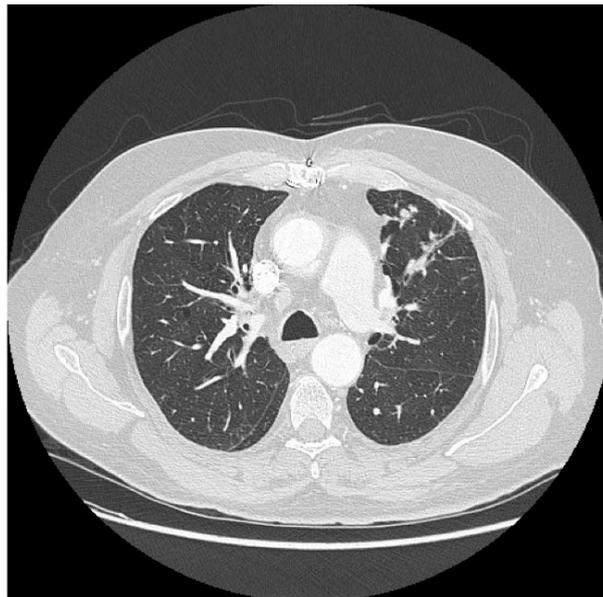
Figure 1. Disease extension at baseline and after one year of first-line treatment.

After 4 new cycles of this regimen, the CT-scan showed a partial response (**Figure 2**), but the disease became stable with a notable declining in both the size and number of metastases following 12 cycles of chemotherapy. Except for grade 1 thrombocytopenia and mild fatigue, no other remarkable side effects (including cardiac toxicity) were noted and treatment was well tolerated.

Finally, the disease progressed on June 2014, after 21 months of treatment.



Before initiation of 3rd line treatment



After 7 cycles of 3rd line treatment

Figure 2. Disease extension before 3rd-line treatment and after 7 cycles of this treatment.

3. Discussion

This case illustrates two strategies that could lead to further research. Firstly, the association of FOLFIRI with Trastuzumab, and secondly the rechallenge of trastuzumab after an initial tumor progression.

As discussed above, trastuzumab is a monoclonal antibody which has been developed with cisplatin and capecitabine (CC) in patients with advanced gastric cancer in first line of chemotherapy [6]. In a randomized phase III study, FOLFIRI has been shown as effective as ECC in first line treatment but was associated with a better safety profile and time to treatment failure [5]. Despite the fact that FOLFIRI is a known active regimen in gastric cancer, very few pre-clinical data on the association concerning the association of irinotecan and trastuzumab in gastric cancer cells have been reported. Yamade *et al.* recently published that the SN-38, the active metabolite of Irinotecan, was more effective on Her2+++ gastric cancer cell lines if the trastuzumab was administered

after the SN-38 [9].

Clinical data are also relatively poor. In a small, randomized, trial of 34 patients, Sun *et al.* reported that the association of FOLFIRI and Trastuzumab was associated with a RR of 58.8% and a disease control rate of 88% [7].

Weissinger *et al.* reported the case of a heavily pretreated patient, but trastuzumab-naïve, who received the trastuzumab in association with FOLFIRI in third line chemotherapy. There again, the result was spectacular, with a new prolonged complete remission of the disease [8].

These rare data, associated with those of our case-report, are encouraging, and suggest that the association of FOLFIRI and trastuzumab warrant to be tested in a larger population study to better evaluate its tolerance and its efficacy.

Another interesting point in our patient history is that we have observed an objective response in third line in a patient pre-treated with trastuzumab. To our knowledge, it is the first reported case on the efficacy of the reintroduction of trastuzumab after an initial progression in a patient with a gastric cancer. This strategy of using the trastuzumab beyond progression is standard in breast cancers [10]-[12], but we do not have any data on the outcome of this strategy in gastric cancers. In this case, our patient had a very good and prolonged partial response to chemotherapy and trastuzumab in first line treatment, and after a six months break without trastuzumab, the reintroduction of this antibody resulted in another very good and prolonged response. Such results have been recently reported with cetuximab in patients with metastatic colorectal cancer [13], showing that the re-introduction of monoclonal antibodies after initial progression could be an interesting point to be developed in clinical research. Because the FOLFIRI regimen is a well-tolerated and active regimen in advanced gastric cancer, the efficacy and tolerance of its association with trastuzumab in second line after progression under trastuzumab could be of interest, as proposed by Sakai *et al.* in a single arm phase II trial [14].

4. Conclusions

In conclusion, we report here the first case of a successful trastuzumab reintroduction in a patient with gastric cancer, and the interest of its association with FOLFIRI.

This association still needs to be evaluated in prospective randomized trials to better assess its safety profile and its efficacy, but the reported data are very encouraging.

As observed in breast cancers, the reintroduction or continuation of trastuzumab beyond progression may be an interesting concept. This strategy has now to be explored in prospective trials in order to be allowed to integrate this strategy in HER2 positive gastric cancer patients.

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