Case 2 – Lack of response to trastuzumab in a patient with metastatic gastric cancer progressing after extended response to MET inhibitor therapy

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Abstract

In patients with advanced gastric cancer with high expression of HER2 protein, the addition of trastuzumab to chemotherapy significantly improves overall survival compared with chemotherapy alone in the first line setting. However, there are no data on anti-HER2 therapies beyond disease progression after first-line therapy. In many types of cancers, including gastric cancer, dysregulation of the receptor tyrosine kinase MET may lead to a more aggressive cancer phenotype and may be a negative prognostic indicator. Therapeutic targeting of MET/hepatocyte growth factor (HGF) signalling has used monoclonal antibodies and small-molecule tyrosine kinase inhibitors (TKIs) against the MET receptor and its ligand, with several drugs in late-phase clinical trials, including onartuzumab. Onartuzumab is a humanized monovalent monoclonal antibody directed against the hepatocyte growth factor receptor (c-Met). In advanced gastric cancer, the addition of onartuzumab to a standard chemotherapy regimen with oxaliplatin and fluoropyrimidine did not improve efficacy in gastric cancer patients in the overall study population or in those selected for positive MET status by immunohistochemistry. In this clinical case we observed a good clinical response to FOLFOX plus onartuzumab in a young patient with MET-positive gastric cancer. However, therapy with cisplatin, 5-fluorouracil and trastuzumab used after progression did not provide a benefit. This case report therefore highlights the importance of always fully identifying potential therapeutic targets in our patients in order to offer more personalized therapies. A correct molecular analysis is very important in deciding the therapeutic sequences in the metastatic setting.

Key words: gastric cancer, onartuzumab, trastuzumab

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Introduction

Gastric cancer is the fifth most common cancer in the world, with 14 new cases per 100,000 population [1]. The incidence is greater in male and in Asian population and the onset can be correlated with *Helicobacter pylori* infection, diet and genetic factors. Gastric cancer is an heterogeneous disease with different epidemiology and etiology. It is classified on the basis of anatomical location (stomach proximal/gastroesophageal junction, stomach distal) or histological type (intestinal or diffuse) [2]. Gastric cancer is a disease also characterized by molecular alterations correlated to signalling pathways related to cell proliferation, apoptosis and angiogenesis otherwise relevant in the mechanisms of disease onset and progression. Specifically, HER2 is found to be amplified in 17% of cases, with greater expression in tumors of the proximal stomach and oesophagogastric junction and with intestinal histol-

ogy [3]. Chemotherapy is the first choice treatment for advanced disease; however the median survival does not exceed 12 months [4]. HER2 is the first validated molecular target in gastric cancer and trastuzumab is the only molecular targeted therapy currently approved for patients with HER2-positive advanced gastric carcinoma [5]. Among the other targeted therapies evaluated in advanced gastric cancer is onartuzumab, a humanized monovalent monoclonal antibody directed against the hepatocyte growth factor receptor (c-Met) with potential antineoplastic activity. Onartuzumab binds to the extracellular domain of c-Met, preventing the binding of its ligand, the hepatocyte growth factor (HGF); this results in the c-Met signalling pathway inhibition, which may lead to cell death in c-Met-expressing tumor cells. Onartuzumab was evaluated in combination with mFOLFOX6 as treatment for immunohistochemistry-confirmed HER2-negative (HER2–), MET-positive (MET+) advanced gastric cancer patients in a randomized phase III trial [6]. This trial showed that the addition of onartuzumab to mFOLFOX6 was ineffective in MET immunohistochemistry 2+/3+ patients.

We report the clinical case of a patient with advanced HER2+, MET+ gastric cancer who had an extended response to mFOLFOX6 and onartuzumab in a phase III trial. However, the patient did not respond when treated with anti-HER2 therapy with trastuzumab at progression, highlighting the importance of standardising evaluation of the molecular target in gastric cancer and the need for continuous inhibition of the target to maintain the best tumor response.

Case report

A 38-year-old man without any relevant comorbidities presented with a history of dysphagia and weight loss over the previous two months. Gastroscopy revealed a diagnosis of gastric cancer of the proximal stomach; the histological report was compatible with gastric intestinal type (Lauren classification) adenocarcinoma (Figure 1).

A total body computed tomography (CT) scan confirmed gastric thickening and showed liver metastasis. HER2 evaluation by immunohistochemistry was performed and showed a score of 2+.

The patient was evaluated for the "MetGastric phase III trial of onartuzumab plus mFOLFOX6 in patients with metastatic HER2-negative (HER2–) and MET-positive (MET+) adenocarcinoma of the stomach or gastroesophageal junction (GEC)", which was open to enrollment at our institution. We performed a histological centralised review, as per study protocol, and the tumor appeared to be HER2– and MET+, so the patient was eligible for the trial [6].

He was then enrolled in the MetGastric phase III trial and started treatment on 27th June 2013.

For further tumor evaluation, we performed a fluorescence *in situ* hybridization (FISH) test in our local laboratory and the result was HER2 amplified.

Chemotherapy was well tolerated until the sixth cycle when the patient developed an allergic reaction to oxaliplatin, which was treated with symptomatic therapy (intravenous steroid). The patient continued therapy with anti-allergic premedication before chemotherapy administration. He received 12 cycles until December 2013,

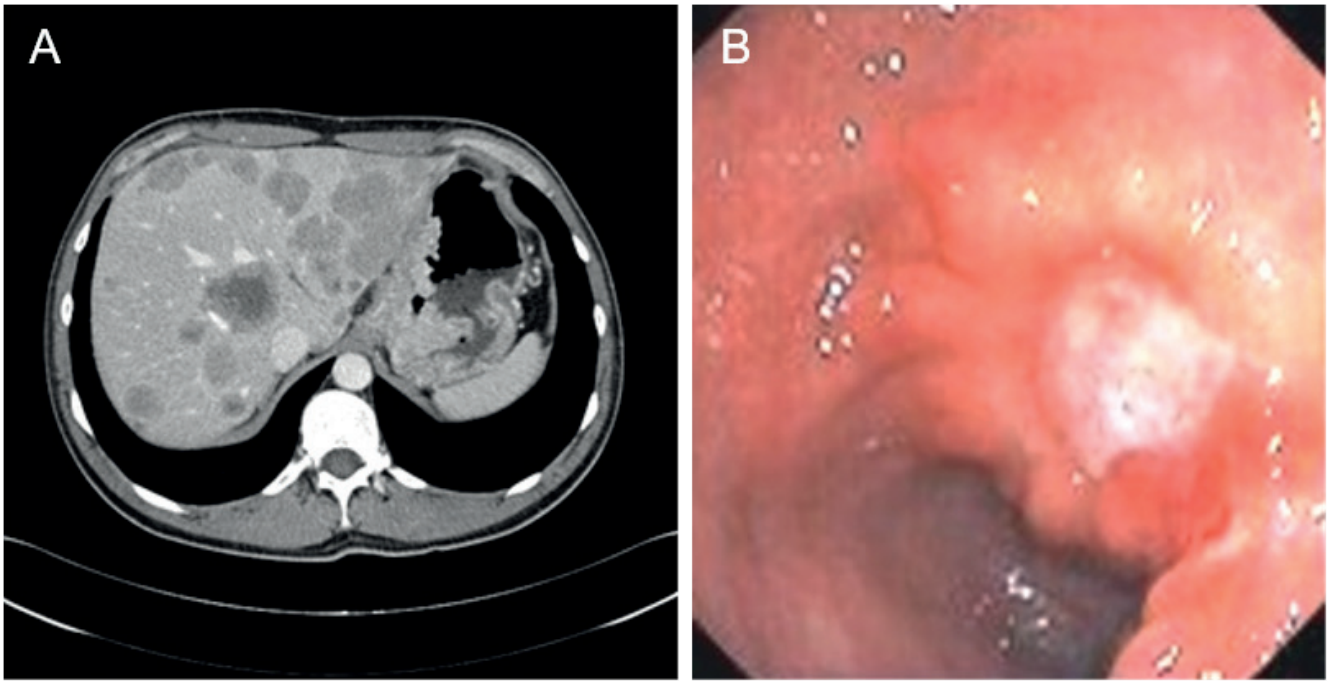

Fig. 1. (A) Computed tomography scan showing multiple liver metastases, and (B) gastroscopy showing gastric cancer.

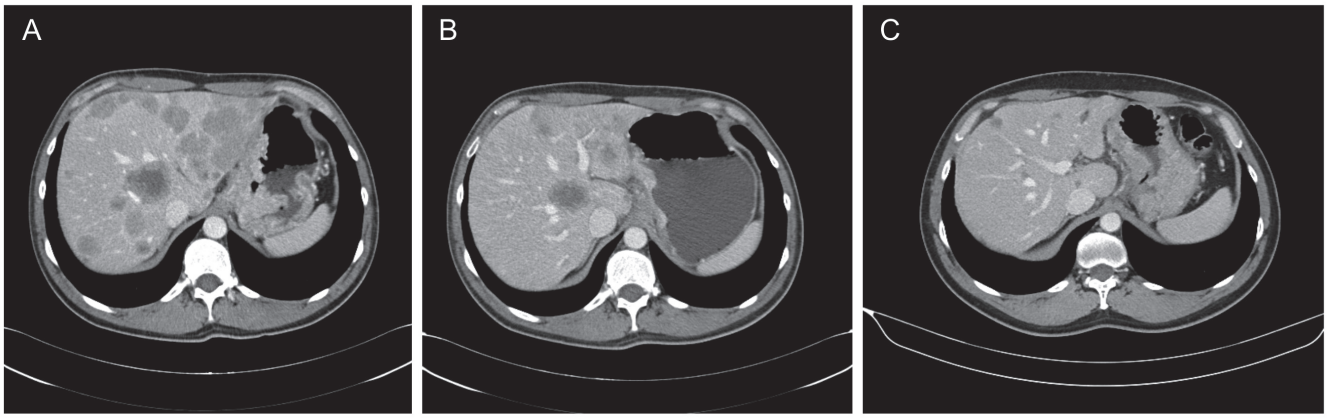

Fig. 2. Computed tomography scans (A) at May 2013 (baseline), (B) at August 2013 (after six cycles) and (C) at December 2013 (after twelve cycles).

when a CT scan showed stable disease of the gastric lesion and a partial response of liver metastasis, reached after 6 cycles (Figure 2).

After 12 cycles, the patient started maintenance therapy with onartuzumab/placebo only, as per protocol; after three cycles he developed gastric bleeding which required hospitalisation and that was treated with conservative therapy. In consideration of this serious adverse event, as per protocol, the treatment was permanently discontinued because the recovery from this adverse event was longer than a month. The treatment assigned to the patient was revealed to be onartuzumab.

In February 2014 a CT scan showed progressive disease to the liver metastasis. We decided to start FOLFIRI (irinotecan, 5-fluorouracil and leucovorin calcium) as second-line treatment [7], continued for four cycles. In May 2014 a CT scan showed progression of the liver metastasis.

We discussed the clinical case at our weekly gastrointestinal multidisciplinary board and, in view of the discrepancy in HER2 status between the original evaluation of the centralized laboratory (HER2–) and the subsequent finding of our internal laboratory (HER2/neu 2+ with amplified FISH), also taking into account the good performance status of the patient [Eastern Cooperative Oncology Group (ECOG) 0], we decided to start a third line of chemotherapy with cisplatin, 5-fluorouracil and trastuzumab in an "off-label" use, since trastuzumab is approved in HER2+ disease for first-line treatment in association with platinum-based chemotherapy [5].

A CT scan was done after the third cycle and showed progressive disease of the gastric primary lesion and liver metastasis with new lesions in the abdominal lymph node and peritoneum.

The patient started a fourth line classic chemotherapy with weekly paclitaxel [8]; after the second administration, he experienced a rapid deterioration of general condition and died of progressive disease.

Conclusion

Deregulation of the HGF/MET pathway in patients with gastric cancer is associated with poor survival and poor prognostic features, such as nodal and visceral metastasis, disease stage and tumor invasiveness. Overexpression of HGF or MET has also been linked to metastatic spread to the liver and peritoneum in patients with gastro-oesophageal carcinoma.

As noted, the addition of onartuzumab to mFOLFOX6 did not improve efficacy overall or in MET 2+/3+ patients with advanced gastric cancer [6]. In patients with advanced gastric or gastro-oesophageal junction cancer, addition of trastuzumab to chemotherapy significantly improved overall survival compared with chemotherapy alone in patients with high expression of HER2 protein (immunohistochemistry 2+ and FISH-positive or immunohistochemistry 3+) [5].

In our case, therapy with FOLFOX/onartuzumab obtained an extended partial response of the disease, while the therapy with cisplatin, 5-fluorouracil and trastuzumab used after the first progression did not provide benefit. The poor response to cisplatin, 5-fluorouracil and trastuzumab is not surprising for several reasons: the status of HER2 in this case was unclear, the data on the efficacy of anti-HER2 drugs beyond the first line are poor, and results regarding the use of trastuzumab plus chemotherapy in the third-line setting are lacking. Nevertheless, our patient obtained a longer survival duration than average [9].

The median survival of patients with metastatic gastric cancer is 9-12 months, but this patient was able to receive the best available drugs, and reached a survival of

17 months, which is very good for a metastatic setting.
There are no data on the failure of anti-MET therapy in gastric cancer, but a hypothesis is the incorrect selection of patients potentially responsive to therapy by immunohistochemistry, and future studies should aim to establish standard and validated assay methodology for patient selection to take advantage of the benefits of MET inhibition, and to assess the correlation between gene amplification, protein expression, and treatment efficacy. Furthermore, assessing the consistency of measurement of MET overexpression across studies is particularly difficult, as different investigators have used varying percentage of cell staining alone as a measure, whereas others have used both percentage of cells and intensity of staining and various composites of these to yield a composite (H) score [10]. Future studies on this topic are warranted.
This case report therefore highlights the importance of always fully identifying therapeutic targets to allow us to offer our patients more personalized therapies, as well as highlighting the importance of performing an accurate histological analysis. It is important in patients with gastric cancer, particularly if they are young and otherwise fit, to offer the maximum number of possible therapeutic lines in order to increase overall survival and allow a better quality of life.

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Conflicts of Interest

The Authors declare there are no conflicts of interest in relation to this article.

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Commentary

The case described by Mori et al. refers to a young patient with gastric adenocarcinoma (intestinal type) metastatic to the liver, treated in first line within a clinical trial with FOLFOX + onartuzumab (a humanized monoclonal antibody directed against c-Met). After progression, the patient was treated with an "off-label" second line chemotherapy with cisplatin, 5-fluorouracil and trastuzumab, the latter added to chemotherapy because of a positive FISH test despite a negative immunohistochemistry. The patient survived little longer than one year since the diagnosis.

The case presents several points that deserve to be discussed:

1. *The combination of FOLFOX + onartuzumab appeared quite active in this patient, although the final results of the randomized trial demonstrated that onartuzumab does not add any benefit to chemotherapy. This should prevent us to advocate the use of new treatments without solid evidence of efficacy. The time to progression (TTP) after FOLFOX + onartuzumab was about 11 months which is higher than the median TTP of 7.1 months described in the paper by De Vita et al.[1] with FOLFOX alone as first line treatment in patients with gastric cancer; however, the overall survival of this patient, slightly longer than one year, is consistent to the result of De Vita et al. that observed a median survival of 12.7 months (95% CI 10.7-15.6) in the patients who received a second line therapy.*
2. *Although overexpression of c-Met is certainly prognostic in many tumors, it is debatable if c-Met represents an useful target for antitumor therapy. In addition, the methodology for assessing c-Met overexpression and the corresponding interpretation vary a lot and this may led to misclassification in many cases.*
3. *The discrepancy of HER2 status between immunohistochemistry and FISH reminds us that the appropriate handling of the sample, the correct testing procedures and interpretation of the results are extremely important when the administration of an effective treatment is at stake. This should dictate periodic quality control assessment and certification of the laboratories.*

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