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Case report

Gastric cancer patient with c-MET amplification treated with crizotinib after failed multi-line treatment: A case report and literature review

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Abstract: Gastric cancer is one of the most common gastrointestinal tumors. Most patients have been in advanced stage at diagnosis and lack effective treatment. Molecular targeted drugs have become new therapeutic strategies. MET is an important driving gene for the development of gastric cancer. MET gene amplification and protein over-expression are closely related to the invasion and metastasis, late stage and poor prognosis of gastric cancer. Crizotinib is a small molecule inhibitor against MET. There are few reports of crizotinib in gastric cancer patients with c-MET amplification. This article reports a case of c-MET gene amplification in advanced gastric cancer with liver metastases. After 2 months of treatment with crizotinib, liver lesions were completely relieved and progression-free survival lasted for up to 20 months.

Keywords: gastric cancer; c-MET; crizotinib

1. Introduction

Gastric cancer is one of the most common digestive tract tumors, ranking fifth in cancer incidence worldwide. Additionally, gastric cancer is the third most common cancer leading to cancer-related deaths [1]. Although the level of diagnosis has been enhanced in recent years, the characteristics of gastric cancer itself, such as the lack of typical clinical manifestations in the early stage, causes most patients to be newly diagnosed in the advanced stage [2]. The survival time of patients with advanced gastric cancer is generally less than 12 months, and the 5-year survival rate is less than 10% [3,4].

At present, the treatment methods for gastric cancer mainly include surgery, adjuvant and

palliative chemotherapy, biological therapy, targeted therapy and radiation therapy [5]. However, most of the gastric cancer patients have lost the chance of surgery at the time of diagnosis. The traditional radiotherapy and chemotherapy have low efficacy, and the molecular targeted drugs of gastric cancer are also limited. Therefore, the screening of novel targets and the development and verification of targeted drugs are particularly in urgent need. The mesenchymal epidermal transforming factor receptor (MET) is a member of the receptor tyrosine kinase (RTK) family. Studies have shown that MET is an important driving gene for the development of gastric cancer, and 50%–60% of advanced gastric cancer over-expressed MET [6]. MET gene amplification and protein over-expression are closely related to the invasion and metastasis, late stage and poor prognosis of gastric cancer. Therefore, targeted drugs for MET is highly expected in the treatment of gastric cancer [7,8].

Crizotinib is an oral small molecule inhibitor that targets both ALK receptor tyrosine kinase (ALK) and MET gene loci and shows great potential in ALK or ROS proto-oncogene 1 (ROS1) rearrangement or MET amplification of non-small cell lung cancer (NSCLC) treatment [9]. Both experiments in vitro and in vivo have shown that MET-amplified gastric cancer cells and organoids are very sensitive to crizotinib therapy [10–12]. There are few reports of crizotinib in gastric cancer patients with c-MET amplification. Now we report a case of advanced gastric cancer patients with positive c-MET gene amplification and liver metastases treated with crizotinib until progression. After 2 months of treatment with crizotinib, the liver lesions were completely relieved and progression free survival lasted up to 20 months. This article reports on its clinical features, diagnosis and treatment through case review.

2. Case report

Male, aged 51 years old, was diagnosed with metastatic adenocarcinoma of the abdominal and posterior peritoneal lymph nodes in our hospital in October 2014. Lymph node biopsy (F14-27377): lymph node metastatic medium-poorly differentiated adenocarcinoma. Immunohistochemistry: CK7 (+), CK20 (+), CK19 (+), CDX2 (+, most), C-erbB-2 (2+, uncertain), Ki67 (+, 60%), TTF-1 (−), PsAP (−), GATA-3 (−), PAX-8 (−), AR (−), CEA (+), Syn (+, small amount). The results of immunohistochemical examination suggested that the source of the digestive system was first considered. Pathological results (T2014-26478): EGFR gene 18, 19, 20, 21 exons and KRAS gene 2, 3, 4 exons and NRAS gene 2, 3, 4 exons see no sure mutation. FISH detects the Her-2 gene with amplification (+). According to the patient's imaging characteristics and immunohistochemical pathological results, the source of the primary gastric system was the most likely one. The choice of chemotherapy regimen depended on the patient's physical condition, age, and underlying disease. The patient, male, aged 51y old, had good physical condition and a large tumor burden (wide abdominal and retroperitoneal lymph node metastasis). In order to improve the therapeutic effect, we choose three drugs combined with trastuzumab. It was recommended that oxaliplatin + Docetaxel+ Capecitabine chemotherapy regimen relate to Trastuzumab targeted therapy. Then successfully completed six cycles of systemic chemotherapy during the period of 2014.11.06-2015.02.21 and the specific program was: oxaliplatin 150mgd1 + Docetaxel 80mgd1 + Capecitabine 2gd1-14 + Trastuzumab 490mgd1.

After six cycles of chemotherapy, the abdominal and retroperitoneal metastatic lymph nodes were significantly reduced. Monthly review indicated that the condition was stable and no progress,

while very unfortunately, review in June 2015 showed that abdominal lymph nodes were significantly increased after chemotherapy. Oxaliplatin + S-1 chemotherapy regimen combined with Trastuzumab targeted therapy was recommended. Two cycles of systemic chemotherapy were carried out in 2015.6.24 and 7.15. The specific protocol was: S-1 60 mg po bid d1- 14+ oxaliplatin 236mgd1 + Trastuzumab 420mgd1 q3w. The patient was presented with regional recurrence and good physical tolerance, and was given concurrent chemoradiotherapy. During the period of 2015.8.4-2015.9.8, radiotherapy was conducted in gastric micro-bend and retroperitoneal lymph node, DT50Gy/25F, combined with Capecitabine (early 3# night 2# d1-5 qw). After synchronous chemoradiotherapy, the lymph nodes in the peritoneal and retroperitoneum were significantly smaller than before. Very unfortunately, in December 2015, the patient reviewed the abdominal CT (CT-548428): the VI segment of the right lobe of the liver showed a slightly low-density shadow of the round shape and the long diameter was about 10 mm, which was slightly strengthened after enhancement and metastasis possibly. Family members of the patient intended to use apatinib and signed the informed consent. Then the patient received targeted therapy with apatinib (500mg/d) during the period of 2015.12.16–2016.1.28. Patient accepted magnetic resonance of upper abdomen in 2016.1.26 (MR-158924): liver metastasis carcinoma, a total of 16 lesions, increased, compared with the previous lesions and the lymph node next to the gastric cardia swollen. The treatment with apatinib was not effective. The patient's second-generation sequencing results showed MET gene amplification about 4.1 times, ERCC2 (excision repair cross-complementing rodent repair deficiency gene 2) gene amplification about 2.2 times (GENESEEQ，14-27377E). So, the patient started crizotinib 250mg bid targeted therapy in 2016.1.29. Two months later (2016.3.21), review of upper abdomen MR (MR-158924): no clear metastatic tumor in the liver, the lymph node next to the gastric cardia was slightly smaller than before. It suggested that liver metastases were completely relieved. Although there were drug side effects of bradycardia and multi-source atrial premature beats during treatment, the limits could be accepted.

From 2016.5.3, due to the drug side effects, the amount of crizotinib was reduced to 200mg po bid, and the disease was stable and no progress when reviewed in 2016.5.23, 2016.7.25, 2016.12.16, 2017.3.14, 2017.6.9, 2017.8.29, 2017.11.24. The liver parenchyma signal was uniform and no obvious abnormal signal was observed. Death of the patient with advanced gastric cancer was difficult to avoid, and the patient eventually died because abdominal lymph node metastasis oppressed the biliary tract leading to obstructive jaundice, secondary sepsis, and eventually multiple organ failure. However, the use of crizotinib alone resulted in complete remission of liver metastases, and patients with progression-free survival lasted up to 20 months. Disease progression in patients with advanced gastric cancer was difficult to avoid, but until 20 days before the patient died, the examination of the upper abdomen CT (CT-548428, 2018.6.11) suggested: the liver surface was smooth, split liver was not wide, hepatic lobe proportional coordination, no abnormal density in the liver. Although the disease progressed, no metastases were found again in the liver parenchyma.

3. Discussion

Due to the atypical symptoms, gastric cancer patients are mostly in the advanced stage of diagnosis, the median survival time is generally no more than 12 months, and the 5-year survival rate is extremely low [3,4]. The current treatment options for advanced gastric cancer are still very limited. The combination of commonly used chemotherapy drugs is inefficient, and the application

of targeted drugs may be one of the most potential directions for improving the efficacy of gastric cancer. Trastuzumab, ramucirumab, apatinib, and PD-1 monoclonal antibody pembrolizumab have been approved for advanced gastric cancer, but efficacy is still limited [13–16]. Therefore, it is imperative to explore new targets for gastric cancer, screen new targeted drugs, or expand the range of applications of original targeted drugs.

The c-MET gene is located on the long arm of human chromosome 7 and contains 21 exons. c-MET is a tyrosine kinase receptor for hepatocyte growth factor (HCG) and consists mainly of three domains: the extracellular domain, the transmembrane domain, and the intracellular domain. The combination of HCG and c-MET intensifies downstream signaling pathways, which are involved in promoting tumor cell growth, invasion and angiogenesis [17]. Aberrant activation of the c-MET pathway mainly includes three types of c-MET 14 exon skip mutation, c-MET amplification and c-MET protein over-expression [18]. MET protein is encoded by the proto-oncogene c-MET, which inhibits tumor cell apoptosis, promotes its proliferation, migration and differentiation, and participates in multiple processes of tumorigenesis, development and metastasis [6,19]. Over-expression of c-MET was detected in various tumors, and c-MET over-expression was found to be closely associated with local tumor invasion, distant metastasis, and poor prognosis [20–23]. Positive expression of c-MET often indicates a poor prognosis, and its possible causes are as follows: First, c-MET is involved in tumor migration and invasion [24]. Second, c-MET is involved in tumor angiogenesis, which is beneficial to tumor blood supply and tumor metastasis [25]. Third, c-MET can induce the production of matrix degrading enzymes, which can promote the invasion and metastasis of cancer by destroying the basement membrane and increasing proteolysis [26]. c-MET may be a potential tumor marker and therapeutic target, and inhibition of c-MET expression is expected to inhibit tumor growth invasion and metastasis [27,28].

In recent years, studies have found that the expression rate of c-MET in gastric cancer tissues is high, and it is related to invasion, metastasis and poor prognosis of gastric cancer, but it is not related to the sex age, tumor size, location and differentiation degree of patients [29–31]. Studies have shown that the expression rate of c-MET in gastric cancer tissues is significantly higher than that in other tissues, and the expression rate of lymph node metastasis in gastric cancer tissues is significantly higher than that in non-metastatic patients [32]. Sotoudeh et al found that over-expression of c-MET is associated with lymph node metastasis and vascular invasion in gastric cancer [33]. The results of Ha et al. suggested that the overall survival and disease-free survival of patients with c-MET over-expressing gastric cancer are shorter than those without over-expression [31]. Similarly, Peng et al. showed that MET gene amplification is one of the poor prognostic factors in patients with gastric cancer, and the overall survival and disease-free survival of MET gene-expanding gastric cancer patients are significantly shortened [34].

Crizotinib, a multi-target protein kinase inhibitor that acts on MET/ALK/ROS signaling pathway, is the only small molecule inhibitor currently available for MET. It has been approved by the FDA for advanced non-small cell lung cancer with ALK-positive/ROS-1 positive/MET expansion. However, as for patients with gastric cancer who have over-expressed or mutated c-MET, there is no consistent conclusion on the therapeutic effect. Okamoto et al. used crizotinib to feed gastric cancer mouse models. The results indicated that mice with positive c-MET amplification showed tumor suppression after feeding the drug, while mice negative for c-MET showed no obvious efficacy [11]. Lennerz et al. studied 4 patients with advanced gastric cancer treated with crizotinib. Two patients had disease progression after treatment. The other two patients showed clinical symptom

improvement after treatment, mainly characterized by better appetite, pain relief, and mass reduced and the effect is maintained for about 4 months [35].

In this case, though the malignant pathological results of gastric tissue were not obtained at the beginning, combined with the imaging characteristics at the time and the pathological results of immune histochemistry, it was considered that the primary tumor is the most likely source of gastric origin. Subsequent systemic treatment according to gastric cancer, the disease was relieved. Due to the disease progressed, palliative surgery for gastric cancer was carried out, and the pathological findings of gastric tissue suggested poorly differentiated adenocarcinoma. The patient developed lymph node metastasis at the time of the visit, which was already advanced gastric cancer with a poor prognosis, and the patient eventually died from the onset to last less than four years. After the patient's first chemotherapy combined with targeted therapy, progression-free survival lasted 4 months. After the second radiotherapy and chemotherapy combined with targeted therapy, progression-free survival lasts about 3 months. Followed by patients with liver metastases, the use of apatinib did not control the progression of the disease. After crizotinib was used alone for 2 months, the liver metastases were completely relieved, and the metastatic lymph nodes were slightly reduced. Moreover, the progression-free survival lasted up to 20 months and there was no recurrence of liver metastases during regular review. Disease progression in patients with advanced gastric cancer was difficult to avoid, but no metastases were found in the liver parenchyma until the patient died. One study found that in advanced gastric cancer, platinum + docetaxel + capecitabine chemotherapy regimen was about 68% effective, with a median progression-free survival of 7.6 months [36]. Even if the patient was combined with trastuzumab -targeted therapy, progression-free survival was only 4 months in the case. Oh, S.Y. et al. found the median progression-free survival of S-1+ oxaliplatin (SOx) chemotherapy regimen was 4.6 months in advanced gastric cancer [37]. However, the patient's progression-free survival was approximately 3 months after SOx combined with targeted therapy and radiation therapy in the case.

Apatinib is the first small molecule anti-angiogenic targeting drug in the world that has been proven to be safe and effective in advanced gastric cancer. It is also the best single-agent after failure of standardized treatment for advanced gastric cancer. One study showed a median progression-free survival was 2.6 months after treatment with apatinib in advanced gastric cancer [38]. However, application of apatinib was not effective and the disease progressed further in this case. The patient's gene sequencing showed MET gene amplification, followed by the use of a small molecule inhibitor against MET-crizotinib. After 2 months, liver metastases were in complete remission and progression-free survival lasted for up to 20 months, which indicated that crizotinib has a unique effect in gastric cancer patients with positive MET amplification. In addition, the ERCC2 gene amplification in this patient may cause over-expression of ERCC2 protein, enhance the ability of tumor cells to repair damaged DNA, and participate in the resistance of tumor cells to platinum, fluorouracil and taxane chemotherapy drugs. It also partly explained the shorter progression-free survival of the patient after twice systemic chemotherapy.

In summary, for gastric cancer patients with positive c-MET amplification, the targeted therapy with crizotinib is effective, and adverse reactions are within acceptable limits. It is recommended that the c-MET gene test can be routinely used as a routine examination for patients with gastric cancer, and patients with conditions can be treated with crizotinib. In clinical research, it is necessary to further expand the sample size and screen the dominant population to benefit more patients. Our case provides evidence that crizotinib is useful in the treatment of gastric cancer patients with MET gene amplification.

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Conflict of interest

The authors declare that there are no actual or potential conflicts of interest in relation to this article.

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