Pathological complete response in a case of HER2-positive gastric cancer with peritoneal dissemination treated with trastuzumab in combination with chemotherapy

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Abstract Trastuzumab in combination with cisplatin and capecitabine could be a new standard treatment for patients with HER2-positive advanced gastric cancer. We herein report a case of advanced gastric cancer with peritoneal dissemination that was successfully treated with trastuzumab combined with cisplatin and capecitabine followed by gastrectomy. A 49-year-old man complained of epigastric pain and was diagnosed with advanced gastric cancer. A staging laparoscopy revealed peritoneal dissemination that was overexpressing HER2 protein. After five courses of chemotherapy comprising trastuzumab, cisplatin and capecitabine, laparoscopic restaging was performed. The disseminated nodules had disappeared, and biopsy of the scar of peritoneal seeding and cytology of the peritoneal lavage fluid both found no malignant cells. Therefore, total gastrectomy with D2 lymph node dissection was performed. Pathologically, there were no residual tumor cells in the resected stomach or peritoneal wall. Trastuzumab in combination with chemotherapy may have curative potential for peritoneal dissemination from HER2-positive gastric cancer.

Keywords Gastric cancer · Trastuzumab · Pathological complete response

Introduction

Gastric cancer is a common malignancy and is associated with a high global mortality rate. In 2008, approximately 988,000 new cases were diagnosed, and 736,000 individuals died of gastric cancer worldwide. In particular, gastric cancer is the second leading cause of cancer-related death in East Asia, including Japan, Korea, and China [1]. Peritoneal dissemination is the most common pattern of recurrence or metastasis in gastric cancer [2], and is responsible for approximately 60 % of all deaths from gastric cancer. Although a meta-analysis of phase II and III randomized gastric cancer trials showed that combination chemotherapy results in substantially improved overall survival [3], patients with peritoneal dissemination have very poor prognoses, with a median survival of 3–6 months [4, 5].

Recently, new molecular target therapy agents and combination chemotherapy regimens that are effective against gastric cancer have been developed. Trastuzumab, a monoclonal antibody that targets HER2, induces antibody-dependent cellular cytotoxicity and inhibits HER2-mediated signaling, resulting in tumor cell proliferation, apoptosis, adhesion, migration, and differentiation [6]. In HER2-positive breast cancer, trastuzumab has shown a survival advantage in early and metastatic disease, and is now the standard of care for breast cancer [7, 8]. Recently, the Trastuzumab for Gastric Cancer (ToGA) trial revealed that trastuzumab in combination with chemotherapy could be a new standard treatment option for patients with HER2-positive advanced gastric cancer [9].

We herein present a case of a 49-year-old man with advanced gastric cancer with HER2-overexpressing peritoneal dissemination that was successfully treated with trastuzumab in tandem with current combination

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chemotherapy. The peritoneal dissemination completely disappeared, and the patient then underwent total gastrectomy. To the best of our knowledge, there have been no previous reports of cases that underwent curative-intent surgery after trastuzumab in combination with chemotherapy for peritoneal dissemination.

Case report

A 49-year-old Japanese male complaining of epigastric pain underwent an esophagogastroduodenoscopy (EGD), which revealed an ulcerative lesion on the lesser curvature of the gastric angle (Fig. 1a). Biopsy of the gastric ulcer demonstrated poorly differentiated adenocarcinoma (Fig. 1b). The tumor was strongly positive for HER2 immunohistochemical (IHC) staining (Fig. 1c), and an abdominal ultrasound and computed tomography (CT) scan showed lymph node metastases; however, no obvious peritoneal dissemination was observed. A staging laparoscopy revealed peritoneal dissemination, and both the

biopsy of the peritoneal tumor and peritoneal lavage cytology demonstrated adenocarcinoma, which was also positive for HER2 immunostaining (Fig. 2a, b). The patient received a trastuzumab-based regime, as follows: 8 mg/kg intravenous (i.v.) trastuzumab as the loading dose and 6 mg/kg as the maintenance dose on day 1, 80 mg/m² i.v. cisplatin on day 1, and 2,000 mg/m²/day capecitabine on day 1 to day 14, every 3 weeks. He received five cycles of chemotherapy without suffering from any severe toxicities except for grade 3 neutropenia. Post-treatment imaging studies were performed. EGD showed significant shrinkage of the tumor, and a CT scan revealed the disappearance of metastatic lymph nodes. To evaluate the peritoneal dissemination, staging laparoscopy was performed again. The peritoneal tumors had completely disappeared (Fig. 2c), and biopsy of the scar of the peritoneal tumor and peritoneal lavage cytology both found no malignant cells. Therefore, total gastrectomy with D2 lymph node dissection, reconstructed with Roux-en-Y esophagojejunostomy, was performed (Fig. 3a, b). Pathological examination of the surgical specimen revealed no residual tumor cells

Fig. 1 **a** EGD revealed an ulcerous lesion on the lesser curvature of the gastric angle. **b** Biopsy of the gastric ulcer demonstrated poorly differentiated adenocarcinoma ($\times 40$). **c** The tumor was strongly positive for HER-2 IHC staining ($\times 40$)

Fig. 2 **a** Staging laparoscopy revealed peritoneal dissemination. **b** Biopsy of the peritoneal tumor demonstrated adenocarcinoma that was positive for HER-2 immunostaining ($\times 40$). **c** The peritoneal

tumors completely disappeared, leaving scar tissue that was pathologically free from cancer cells

(Fig. 3c). No tumor tissue was identified in 39 retrieved lymph nodes. He recovered uneventfully after surgery, and was discharged after 15 postoperative days.

Discussion

We herein present a case of gastric cancer with peritoneal dissemination that was successfully treated with trastuzumab plus capecitabine and cisplatin. A pathological complete response was achieved in the resected specimens, which included the primary lesion, lymph nodes, and peritoneal dissemination. There are two case reports suggesting the advantages of combined trastuzumab and chemotherapy in preoperative settings for HER-2-positive locally advanced gastric cancer [10, 11]. Wang et al. [11] and Sbitti et al. [10] reported cases of complete pathological response after neoadjuvant chemotherapy with a trastuzumab-containing regimen for resectable locally advanced gastric cancer overexpressing HER2. However, to our knowledge, there are no previous reports that have demonstrated the complete response of peritoneal

dissemination to a trastuzumab-based regimen, resulting in curative gastrectomy.

Peritoneal dissemination is the most common type of recurrence or metastasis in gastric cancer, and it leads to a poor prognosis [2]. Therefore, it is critical to treat peritoneal dissemination to improve the prognosis of gastric cancer. However, it is often difficult to detect peritoneal dissemination by conventional imaging examination in clinical practice. Staging laparoscopy is very useful for identifying intra-abdominal tumor deposits on the peritoneal surface that are not detectable by preoperative non-invasive imaging. Nakagawa et al. [12] suggested that staging laparoscopy plays two critical roles in cases of advanced gastric cancer; the avoidance of an unnecessary laparotomy in patients with incurable metastatic diseases, and the exact staging of patients for appropriate preoperative treatment. Our indication for staging laparoscopy is large macroscopic type 3 or 4 gastric cancer with serosal invasion without hematogenous or clinically evident peritoneal dissemination, as previously reported [13]. Initially, staging laparoscopy confirmed that our patient had peritoneal dissemination even though peritoneal dissemination was not detected by CT. Using specimens obtained at

Fig. 3 **a, b** Macroscopic findings in the resected stomach. Significant shrinkage of the tumor was observed. **c** Microscopically, no viable cancer cells were observed ($\times 100$)

laparoscopy, the pathological diagnosis of peritoneal dissemination overexpressing HER2 was confirmed by IHC.

The ToGA trial was the first randomized phase III trial to show that trastuzumab plus chemotherapy is superior to chemotherapy alone for HER2-positive advanced or metastatic gastric cancer [9]. Trastuzumab plus 5-fluorouracil or capecitabine and cisplatin has become the standard treatment for patients with HER2-positive metastatic gastric cancer. Either HER2 protein overexpression (as detected by IHC) or gene amplification (detected by fluorescent in situ hybridization, FISH) was observed in 4–28 % of gastric cancer cases [14, 15]. The ToGA trial reported an overall HER2-positive rate of 21.3 % [9]. In this trial, the overall tumor response rate was significantly improved in the trastuzumab plus chemotherapy group compared with the chemotherapy alone group (CR: 5 vs. 2 %, PR: 42 vs. 32 %), corresponding to a 26 % reduction in the death rate [9]. Furthermore, exploratory analysis according to HER2 status suggested that overall survival was longer in patients with high expression of HER2 protein than in patients with low expression. However, there were no other promising factors beyond HER2 status in the exploratory analysis of the ToGA trial. Therefore, further analyses are required to elucidate other molecular biological mechanisms for predicting sensitivity to trastuzumab. In our case, it is possible that the addition of

trastuzumab to 5-fluorouracil or capecitabine and cisplatin is more effective because both the primary tumor and disseminated tumor had strong HER2 expression.

Also, Cavanna et al. [16] investigated HER2 status in both primary and tumor cells in the cerebrospinal fluid using FISH, which allowed intrathecal administration of trastuzumab for leptomeningeal carcinomatosis of gastric cancer. Bozzetti et al. [17] reported that both IHC and FISH indicated a high concordance between HER2 expression on primary tumors and that on corresponding metastases in gastric cancer, suggesting that, in most cases, HER2 status remains unchanged during the metastatic process. In our patient, IHC gave a HER2-positive score of 3+ for both the primary tumor and disseminated tumor.

However, there are a number of issues that need to be resolved in order to determine the exact HER2 status, because there are some differences between surgically resected specimens and biopsy fragments [18]. Therefore, the further development of methodology to assess HER2 status is required so that HER2 expression can be evaluated precisely by methods other than IHC and FISH.

To the best of our knowledge, this patient is the first reported case of curative gastrectomy after trastuzumab plus chemotherapy for peritoneal dissemination. Trastuzumab in combination with chemotherapy may have curative potential for peritoneal dissemination from HER2-positive gastric cancer.

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Conflict of interest We declare that we have no conflict of interest.

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