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Case Report

Conversion Surgery for Patients With Stage IV HER2-Positive Gastric Cancer: A Report of 3 Patients

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Gastric cancer is a common malignancy and remains potentially lethal. The prognosis of patients with stage IV gastric cancer is thought to be poor, but new molecular targeted therapy may benefit patients with advanced gastric cancer. Currently, conversion surgery after chemotherapy with a trastuzumab-containing regimen is reported to be effective in these patients. We present 3 patients with human epidermal growth factor receptor 2 (HER2)–positive advanced gastric cancer who underwent conversion surgery after receiving a trastuzumab-containing chemotherapy regimen. Interestingly, the primary lesion acquired resistance to the trastuzumab-containing regimen, although the metastatic lesions maintained a complete response. The reason why the primary lesions became resistant to trastuzumab remains unclear. More studies are needed to clarify the mechanism of resistance. Conversion surgery, made possible by the use of molecular-targeted therapy, may improve the prognosis of patients with stage IV gastric cancer, particularly if metastatic lesions show a complete response to therapy.

Key words: Conversion surgery – Trastuzumab, Her2-positive gastric cancer – Stage IV gastric cancer

The current standard treatment for patients with stage IV gastric cancer is systemic chemotherapy. However, the outcomes remain poor, and complete cure is rarely expected.[1] Conversion surgery is defined as surgical resection after chemotherapy in cases where the tumor was originally considered to be inoperable.[2,3] The ToGA trial demonstrated the efficacy and safety of trastuzumab

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(T-mab)–based chemotherapy in patients with human epidermal growth factor receptor 2 (HER2)–positive metastatic gastric cancer.[4] A previous report described that conversion surgery after chemotherapy with a T-mab–containing regimen might be effective in these patients.[5] We report here 3 patients with stage IV Her2-positive gastric cancer who underwent conversion surgery. There were 2 patients who had multiple liver metastases and 1 who had extensive periaortic lymph node metastases.

Case Presentation

A 68-year-old woman with gastric cancer and liver metastases was treated with a T-mab and XP (capecitabine and cisplatin) regimen. After receiving chemotherapy for 2 years, the liver metastases completely resolved, although the primary gastric lesion was increasing in size (Fig. 1). The patient then underwent total gastrectomy with lymph node dissection.

A 76-year-old man with gastric cancer and liver metastases was treated with a T-mab and XP regimen, but he failed this regimen because of severe side effects and was then changed to weekly paclitaxel with T-mab therapy. After receiving chemotherapy for 3 years, the metastatic lesions in the liver were no longer visible on computed tomography (CT) scan, although the primary lesion showed resistance to chemotherapy (Fig. 2A). He then underwent total gastrectomy with lymph node dissection (Fig. 2B).

A 63-year-old man with gastric cancer and paraaortic lymph node metastases was treated with a T-mab and XP regimen for 2 years. The lymph node metastases decreased in size, and no new metastatic lesions developed. The patient then underwent total gastrectomy with lymph node dissection.

All 3 patients underwent R0 operations. The resected specimens from all 3 patients showed adenocarcinoma with strong membrane HER2 immunoreactivity (Fig. 2C and 2D). Patient 1 is still alive, although a recurrent liver lesion was found 6 months after gastrectomy. Patients 2 and 3 are free of disease more than 1 year after resection without receiving further adjuvant chemotherapy.

Discussion

Gastric cancer currently ranks fourth in cancer-related mortality worldwide.[6] The prognosis of patients with stage IV gastric cancer is very poor.[7] In general, palliative combination chemotherapy has been the mainstay of treatment in the metastatic setting.[8] Newly developed chemotherapeutic agents, especially molecular-targeted therapies, have shown promising results in the treatment of patients with advanced gastric cancer.[9] HER2 is a transmembrane tyrosine kinase receptor involved in cell proliferation, differentiation, motility, and apoptosis.[10] T-mab is a monoclonal antibody that induces antibody-dependent cellular cytotoxicity and inhibits HER2-mediated signaling.[11] The ToGA trial revealed the efficacy of T-mab–based chemotherapy in patients with HER2-positive metastatic gastric cancer,[4] and this molecular targeted therapy may be a new strategy to overcome the poor prognosis in patients with stage IV gastric cancer

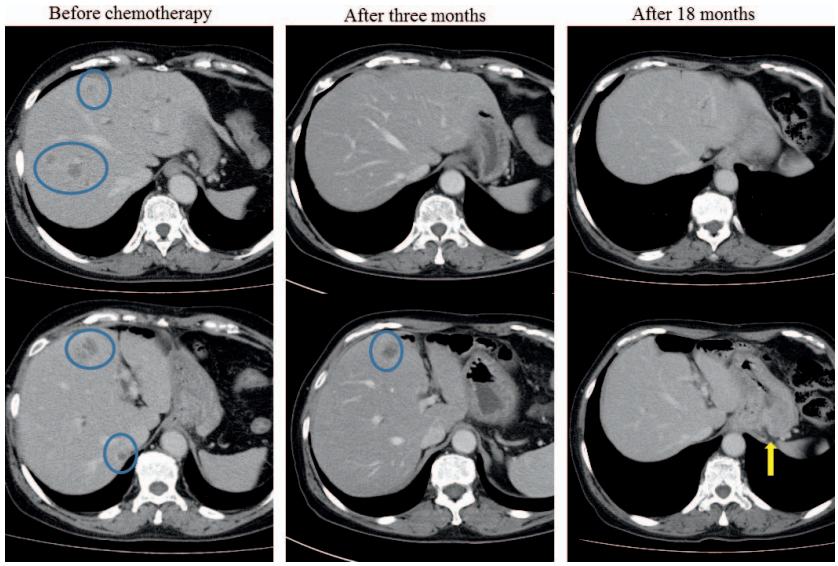

Fig. 1 CT scan findings in a 68-year-old woman with gastric cancer and liver metastases. Multiple liver metastases showed a complete response with administration of T-mab–containing chemotherapy. However, the primary tumor developed resistance to therapy and recurred with progressive growth (arrowhead).

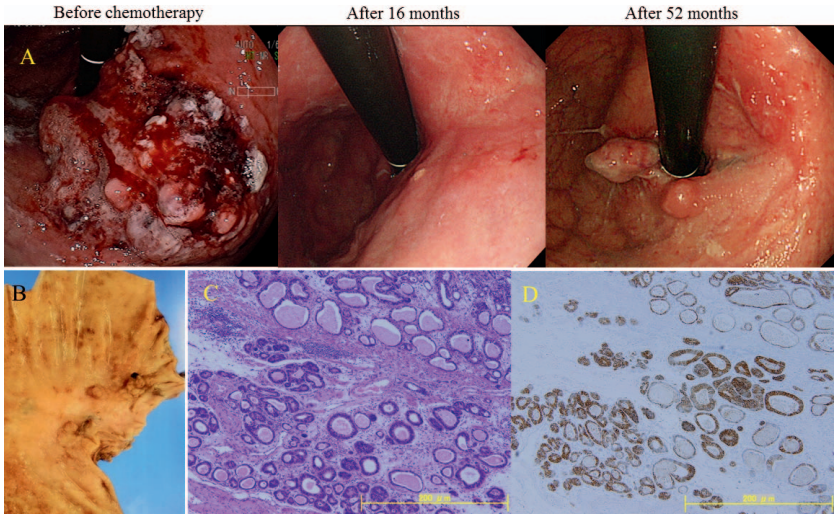

Fig. 2 Endoscopic and pathologic findings in a 76-year-old man with gastric cancer. (A) The primary gastric lesion responded to therapy initially, but then progressed 4 years later. (B) The resected specimen shows an irregular, protruding lesion in the proximal stomach. (C) Pathologic findings show intestinal-type adenocarcinoma (H&E, ×40). (D) The specimen shows strong membranous HER2 immunoreactivity, which is scored as 3+ (HER2 immunohistochemistry, ×40).

if HER2 is overexpressed. The 3 patients reported here with stage IV HER2-positive gastric cancer were able to undergo R0 resections after receiving T-mab–containing chemotherapy.

Previous reports described a very high concordance ratio for HER2 status between primary and parenchymal metastatic or recurrent lesions in gastric cancer.[12] Although the metastatic lesions in all 3 patients responded completely to T-mab–based chemotherapy, the primary lesions progressed. Histopathologically, all 3 resected primary lesions showed grade 0 to 1 effectiveness, with highly positive (3+) staining for HER2 on the tumor cell membranes. It is well known that many patients with HER2-positive breast cancer become resistant to T-mab, and previous reports suggested possible mechanisms of resistance, including upregulation and activation of compensatory signaling pathways through inducing downstream effector pathways.[13] The mechanisms leading to resistance in patients with gastric cancer are yet to be clarified, but similar mechanisms may be responsible, especially in the primary lesions.

Conclusion

Conversion surgery, made possible by the use of molecular-targeted therapy, may improve the prognosis of patients with stage IV gastric cancer, particularly if metastatic lesions show a complete response to therapy.

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