Neoadjuvant Treatment With Trastuzumab and FOLFOX Induces a Complete Pathologic Response in a Metastatic \textit{ERBB2} (HER2)-Amplified Duodenal Cancer

Ahmad Hamad, MD; Aatur D. Singhi, MD, PhD; Nathan Bahary, MD; Kevin McGrath, MD; Rula Amarin, MD; Herbert J. Zeh, MD; and Amer H. Zureikat, MD

Abstract

Overexpression of HER2 protein and amplification of the \textit{ERBB2} gene has been observed in various adenocarcinomas, providing a therapeutic target that can be used to extend the survival of a select cohort of patients. Anti-HER2 therapy has been successfully applied to gastric and colorectal cancers, but its use and potential benefit in small intestinal carcinomas is not well characterized. We applied anti-HER2 therapy to an \textit{ERBB2}-amplified advanced duodenal adenocarcinoma, adding trastuzumab to FOLFOX in the neoadjuvant setting. A 61-year-old woman with an advanced duodenal cancer harboring an \textit{ERBB2} amplification received preoperative trastuzumab and FOLFOX. Restaging revealed significant tumor downstaging with no metastasis. After multidisciplinary assessment, she underwent pancreaticoduodenectomy. Final pathologic analysis revealed no residual invasive adenocarcinoma, consistent with a complete neoadjuvant treatment response. This case report emphasizes the need for further molecular characterization of small bowel cancers; genetic alterations may provide therapeutic targets to improve the prognosis of these rare and aggressive malignancies.


Small bowel adenocarcinoma (SBA) is a rare tumor that accounts for 37\% of small bowel malignancies and <2\% of all gastrointestinal tumors.\(^1\) Although surgery remains the mainstay of therapy, most patients present with advanced disease, and 5-year overall survival (OS) rates range from 26\% to 40\%.\(^2\) Because of its low incidence and lack of available trials, current chemotherapy regimens used for adjuvant or metastatic SBA are extrapolated from colorectal cancer (CRC) and gastric cancer, with poor results.\(^3\) Overexpression of the HER2 protein and amplification of the \textit{ERBB2} gene has been observed in various adenocarcinomas, providing a therapeutic target that can be used to extend the survival of a select cohort of patients. Anti-HER2 therapy has been successfully applied to gastric cancer and CRC, but its use and potential benefit in small intestinal carcinomas is not well characterized.\(^4,5\) We applied anti-HER2 therapy to an \textit{ERBB2}-amplified advanced duodenal adenocarcinoma, adding trastuzumab to FOLFOX in the neoadjuvant setting, to achieve a complete pathologic response (cPR) in the resected specimen.

Case Report

A 61-year-old woman of Middle Eastern descent known to have hypertension, hyperlipidemia, and gastroesophageal reflux disease presented with a 4-month history...
of epigastric discomfort. Due to persistent symptoms, she underwent a right upper-quadrant ultrasound that demonstrated a distended gallbladder without stones, and a markedly dilated common bile duct with no stones or filling defects (Figure 1). These findings prompted an MRI, which revealed a dilated intrahepatic and extrahepatic biliary tree, dilation of the common bile duct to the preampullary region, no pancreatic mass, and possible duodenal wall thickening. Subsequent upper endoscopy demonstrated a malignant-appearing, fungating, ulcerated, and partially obstructive circumferential mass in the second and third portions of the duodenum (Figure 2).

Biopsies of the abnormal duodenal mucosa revealed an invasive, moderately differentiated adenocarcinoma. Molecular analysis of the duodenal biopsy demonstrated the tumor to be HER2-positive (immunohistochemistry [IHC] +2 with 50% staining of tumor cells and fluorescence in situ hybridization [FISH]–amplified), microsatellite stable, and negative for ALK and PD-L1 (Figure 3). Further molecular testing using next-generation sequencing identified no mutations in BRAF, HRAS, KRAS, NRAS, and PIK3CA. A colonoscopy showed a tubular adenoma, which was resected. A staging CT scan of the chest, abdomen, and pelvis showed irregular thickening involving parts of the second and third parts of the duodenum and multiple enlarged regional lymph nodes, but no evidence of metastatic disease. Laboratory studies revealed a normal CBC count, metabolic profile, liver function tests, CA19-9, and carcinoembryonic antigen (CEA) levels.

The patient was recommended to undergo a robotic-assisted classic pancreatoduodenectomy (Whipple) procedure at the University of Pittsburgh Medical Center. At laparoscopy, exploration revealed the presence of a segment 4B subcentimeter liver lesion. Frozen section analysis confirmed it to be metastatic duodenal adenocarcinoma and the resection was aborted. No other lesions were noted on laparoscopy. Molecular analysis of the liver biopsy was consistent with the primary tumor, demonstrating it to be microsatellite stable, PD-L1 expression–negative, ALK-negative by IHC, and HER2-positive (IHC +2 with 50% staining of tumor cells, and FISH-positive).

After multidisciplinary discussion, and due to the presence of an ERBB2 amplification, the patient was recommended to undergo treatment with 6 cycles of FOLFOX and trastuzumab, followed by a potential pancreatoduodenectomy in the absence of new metastatic disease on restaging. Because the management of SBA is mostly extrapolated from CRC, the rationale was to treat this oligometastatic SBA with “neoadjuvant”/definitive chemotherapy followed by resection in the absence of new metastasis; a strategy analogous to the treatment of metastatic CRC. Before initiation of therapy, a PET scan confirmed the FDG-avid duodenal primary with regional lymphadenopathy and no metastasis. The patient commenced therapy with FOLFOX (oxaliplatin, 85 mg/m²; leucovorin, 400 mg/m²; 5FU bolus, 400
mg/m²; and infusional 5FU, 2,400 mg/m² on days 1 and 14) and trastuzumab (6 mg/kg loading dose on day 1 of the first cycle followed by 4 mg/kg on day 1 and 14 days from the second cycle onwards). Notably, the trastuzumab dose used in this patient was lower than that used in the ToGA trial (8 mg/kg loading, followed by 6 mg/kg maintenance every 3 weeks) due to the 2-weekly FOLFOX treatment schedule as opposed to the 3-weekly capecitabine/cisplatin schedule, respectively. Therapy was interrupted due to the need for a duodenal stent placement for obstructive symptoms and removal of her subclavian chemotherapy port due to catheter tip thrombosis. After 4 cycles of FOLFOX and trastuzumab, restaging PET/CT revealed a marked decrease in the thickening and FDG avidity of the duodenal primary, resolution of FDG avidity of the regional lymph nodes, and no evidence of metastatic disease. After multidisciplinary discussion, a decision was made to reexplore and resect the primary tumor.

At exploration, no metastases were identified, and the patient underwent a robotic-assisted classic pancreaticoduodenectomy with resection of the segment 4B liver scar (old biopsy site). Final pathologic analysis revealed no residual invasive adenocarcinoma, consistent with a complete neoadjuvant treatment response (Figure 4). All surgical margins were free of neoplasia, and 39 resected lymph nodes were benign. The liver segment was also free of neoplasia, and final stage was ypT0N0. Her postoperative course was uneventful, and she was discharged on the seventh postoperative day.

Discussion

SBA is a rare aggressive malignancy with a poor prognosis. Although surgical resection represents the best chance for cure, most patients present with advanced disease; in a large study, 40.6% and 24% presented with T4 tumors or distant metastasis, respectively.¹ In the absence of randomized clinical trials, treatment options for advanced and metastatic SBA have been extrapolated from CRC, with poor results. Although several studies have reported improved response rates using 5FU in combination with oxaliplatin, irinotecan, or cisplatin, complete responses are rare and OS remains poor (Table 1). Moreover, although molecular profiling has allowed the application of targeted therapeutics in CRC, a significant lag in the molecular understanding of SBA remains, highlighting the need to identify target pathways that could improve patient prognosis.₆,₇ In this novel case report, we successfully used preoperative trastuzumab in combination with FOLFOX in an ERBB2-amplified metastatic duodenal cancer to achieve a cPR in the surgical specimen. Although the contribution of anti-HER2 therapy to this patient’s favorable PR is difficult to quantify, it is noteworthy that complete tumor regression was observed after only 4 cycles of trastuzumab and FOLFOX.

Anti-HER2 therapy is being increasingly used in various gastrointestinal malignancies. As a member of the epidermal growth factor receptor family, HER2 is located on chromosome 17q21 and acts as a proto-oncogene. It is a cell membrane receptor tyrosine kinase that is activated following ligand binding and receptor dimerization.⁸ Dimerization
causes transphosphorylation of the receptor kinase domains, which recruits molecules responsible for downstream signaling pathways. These receptors function through different pathways to regulate cell motility, proliferation, differentiation, migration, and apoptosis. Amplification of \( \text{ERBB2} \) has been implicated in the development of gastric, ovarian, breast, prostate, lung, and colorectal cancers. 

A recent trial examining the combination of trastuzumab with chemotherapy (cisplatin and 5FU or capecitabine) in patients with \( \text{HER2} \)-positive metastatic gastric cancer (ToGA trial) showed improved median OS compared with chemotherapy alone (13.8 vs 11.1 months, respectively; \( P = .0046 \)). More recently, the HERACLES trial showed that 30% of pretreated patients with \( \text{HER2} \)-mutated metastatic CRC achieved an objective response, whereas 59% achieved disease stabilization after treatment with trastuzumab and the tyrosine kinase inhibitor lapatinib. 

However, although \( \text{HER2} \) protein overexpression has been reported in 8.2% to 53.4% of gastric adenocarcinomas (ToGA trial: gastric, 21%; gastroesophageal, 2%) and 5% of CRCs, its frequency in small intestinal adenocarcinomas is only approximately 2.1%. In a study by Overman et al, only 1 of 54 cases of small intestinal adenocarcinoma ex-
hhibited HER2 protein expression. Likewise, Chan et al\textsuperscript{15} reported that 47 of 49 tumors completely lacked HER2 protein expression by IHC. Although the remaining 2 cases showed a 1+ HER2 staining pattern, none exhibited HER2 gene amplification by FISH. In 51 cases of small intestinal adenocarcinomas, Aparicio et al\textsuperscript{14} found that only 2 cases showed HER2 expression, and both were located in the ileum, whereas 32 patients with duodenal adenocarcinoma lacked any HER2 expression.

Despite the low incidence of ERBB2 amplification in SBA, the increased availability and feasibility of molecular testing coupled with potential therapeutic benefits of targeted therapy may be worthwhile in this genetically defined subgroup, particularly in the absence of large trials to guide therapy. In our patient, testing for ERBB2 amplification expression was performed because none of the other known drivers of SBA where found in her primary lesion. Therefore, our report highlights the need to molecularly profile select SBAs and to test for ERBB2 amplification, particularly when known mutations are not implicated in the pathogenesis. cPR to neoadjuvant therapy in resected duodenal cancer is uncommon; however, neoadjuvant therapy in this disease entity is not widely used compared with other gastrointestinal cancers. Onkendi et al\textsuperscript{16} reviewed the Mayo Clinic experience with salvage neoadjuvant therapy for unresectable/recurrent (nonmetastatic) duodenal adenocarcinoma and observed a cPR in 2 of 10 cases, whereas Kelsey et al\textsuperscript{16} observed a cPR in 2 of 11 patients treated with neoadjuvant chemoradiation for localized duodenal cancer. In our patient, because the added benefit of anti-ERBB2 therapy in achieving this patient’s cPR remains unknown, she was recommended to undergo postoperative therapy with FOLFOX and trastuzumab, followed by trastuzumab monotherapy at a dose of 6 mg/kg every 3 weeks for a total of 1 year (extrapolated from the adjuvant treatment of breast cancer). Notably, at 6 months post resection, her CT scan showed no evidence of recurrent disease.

Conclusions

This case report emphasizes the need for further molecular characterization of small bowel cancers; genetic alterations may provide therapeutic targets to improve the prognosis of these rare and aggressive malignancies.

References


