

CLINICAL VIGNETTE

Could Perioperative Immunotherapy Replace Chemotherapy for Mismatch Repair Deficient Gastric Cancer?

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Case Report

An 84-year-old woman presented with abdominal pain and vomiting. At presentation she was severely anemic, requiring transfusion of three units of packed red blood cells. Computed tomography (CT) scans revealed a suspicious thickening of the gastric body. Esophagogastroduodenoscopy (EGD) with endoscopic ultrasound (EUS) showed a submucosal narrowing and circumferential ulceration at the antrum extending to the pylorus. In addition, a few < 1 cm peri-aortic suspicious lymph nodes were visualized. Biopsy revealed a moderate to poorly differentiated adenocarcinoma with lymphovascular invasion. There was no distant disease on whole body imaging, so she was diagnosed with clinical stage III (T3N1) gastric adenocarcinoma.

Molecular testing of the tissue revealed loss of nuclear expression of MLH1 and PMS2, intact expression of MSH2 and MSH6, MLH1 promoter methylation, and no mutations in *BRAF*. Therefore, she was deemed to have sporadic microsatellite instability (MSI-H) / mismatch repair deficiency (dMMR) not due to hereditary Lynch syndrome. Tumor testing also revealed lack of HER2 overexpression and a PD-L1 combined positive score of 15 (1-2+ intensity). Germline genetic testing of 85 genes (including *BRCA1* and *BRCA2*) revealed no pathogenic mutations.

Given the favorable prognosis and potential response to immunotherapy in MSI-H solid tumors, she received neoadjuvant pembrolizumab over three months with minimal side effects. She then underwent laparoscopic partial gastrectomy and was found to have a pathologic complete response with no residual carcinoma and zero out of thirty-seven lymph nodes positive for carcinoma. Most studies utilizing neoadjuvant immunotherapy have continued immunotherapy for some duration after surgery to consolidate the response, so she was treated with an additional three months of adjuvant pembrolizumab.

Discussion

Despite recent advances in the treatment of gastric cancer, outcomes for these patients remains relatively poor. Amongst gastric cancers, 5-10% have dMMR/MSI-H, and these tend to be exceptionally responsive to immunotherapy. Cancers with dMMR (due to damage to *MLH1*, *MSH2*, *MSH6*, or *PMS2*) are unable to correct damaged DNA, and this results in hundreds to thousands of mutations in coding regions and instability in

repetitive DNA regions known as microsatellites. The extraordinarily high number of mutations in dMMR/MSI-H leads to vast amounts of neoantigens, which in turn trigger an immune response. Pembrolizumab is an antibody which acts as an immune checkpoint inhibitor by inhibiting the programmed cell death protein 1 (PD-1) to release the brakes on T cells, thus allowing cell-mediated immune response against the cancer cells. Single-agent pembrolizumab has been demonstrated to be effective against dMMR cancers, regardless of site or tissue of origin. In a study of previously treated patients with 12 different metastatic cancer types with dMMR, the objective radiographic response rate to treatment with pembrolizumab was 53%, with 21% of patients obtaining a complete response.¹

For locoregional gastric cancer, combined modality treatment has been demonstrated to significantly increase overall survival in patients with stage II or higher gastric cancer.² The preferred perioperative chemotherapy regimen for most patients is fluorouracil, leucovorin, and oxaliplatin (FOLFOX), or fluorouracil, leucovorin, oxaliplatin, and docetaxel (FLOT) in select patients with good performance status. The patient discussed in this paper was elderly and frail, and therefore a poor candidate for FLOT and a suboptimal candidate for FOLFOX chemotherapy. After multidisciplinary discussion, the decision was made to pursue perioperative immunotherapy.

Early results from a small phase II study for select patients with locally advanced gastric cancer treated with single-agent pembrolizumab found that 33% (two out of six) patients with MSI-H tumors achieved a pathologic complete response.³ In that study, patients received adjuvant chemoradiation with pembrolizumab followed by pembrolizumab for up to one year. Another recently published phase II study in patients with locally unresectable or high risk resectable solid tumors with dMMR found that pembrolizumab was safe and efficacious when given for 6 months preoperatively with the option to continue for 12 months after surgery.⁴ Out of thirty-two treated patients, the overall response rate was 77%. Among the six patients who underwent surgery, 50% achieved a pathologic complete response.

Several questions remain in the consideration of perioperative immunotherapy, such as the duration of neoadjuvant and adjuvant PD-1 blockade. Given the lack of large prospective trials with long-term follow-up to guide this decision, three

months pre- and post-surgery was chosen in this patient. The rationale was to use a duration of treatment similar to that used for patients with gastric cancer treated with perioperative FLOT or FOLFOX chemotherapy. The aforementioned studies utilizing immunotherapy as well as trials in other tumor types, such as triple negative breast cancer (as in the pivotal KEYNOTE-522 trial), have tended to utilize up to one year of adjuvant immunotherapy. An argument could be made for this longer duration of adjuvant therapy based upon the tolerability of immunotherapy. However, it is not clear if any additional benefit will be outweighed by the risk of potential irreversible toxicities such as thyroid dysfunction. Hopefully future studies will clarify the characteristics of patients who will be most likely to obtain a pathologic response, and for whom the side effect/clinical benefit ratio is favorable.

This patient had a complete response without chemotherapy with very minimal side effects. Currently, the National Cancer Comprehensive Network (NCCN) includes the use of pembrolizumab for dMMR/MSI-H gastric cancers in the metastatic setting. This is based on the first ever site and tissue agnostic approval by the US Food and Drug Administration (FDA) for pembrolizumab for metastatic dMMR/MSI-H cancers. Ongoing prospective trials are investigating the use of immunotherapy in the perioperative setting for dMMR/MSI-H tumors (IMHOTEP, NCT04795661; NEONIPIGA, NCT04006262). These studies may help address whether immunotherapy could be a first-line option in operable dMMR/MSI-H cancers and reduce the toxicity and complications associated with chemotherapy.

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