Is it Time Yet for Adjuvant Immunotherapy for Patients with DNA Mismatch Repair Deficient Gastric Cancer?

Jennifer R. Eads, MD

Abramson Cancer Center, University of Pennsylvania, Philadelphia, PA

TREATMENT APPROACHES FOR LOCALIZED GASTRIC CANCER

Gastric adenocarcinoma is a tremendous global health problem with more than a million patients diagnosed worldwide in 2020 and more than 768,000 gastric cancer-related deaths.¹ For patients with localized disease, surgical resection is critical but is not enough. Several studies over the past decades have indicated a role for adjuvant chemoradiation, adjuvant chemotherapy, or perioperative chemotherapy. For patients who do not receive any element of neoadjuvant therapy and who undergo a D2 lymphadenectomy during their surgery, adjuvant therapy with either S-1 or capecitabine and oxaliplatin chemotherapy are the treatment standards. In the phase III ACTS-GC trial, 1 year of adjuvant S-1 chemotherapy following gastrectomy inclusive of a D2 lymph node dissection was compared with surgery alone.² A total of 1,059 patients participated in this trial where the 5-year overall survival rate of those receiving S-1 was superior to those undergoing surgery alone (71.7% vs. 61.1%, hazard ratio [HR] 0.669), making adjuvant S-1 use a treatment standard in the Asian countries.^{2,3} In the phase III CLASSIC trial, 1,035 patients with localized stage II–IIIB gastric cancer were randomized to undergo gastrectomy with a D2 lymph node dissection versus the same plus 6 months of capecitabine and oxaliplatin chemotherapy.⁴ This study demonstrated a significant improvement in 3-year, disease-free survival at

74% versus 59% in the surgery-alone group (HR 0.56, $p < 0.0001$), making adjuvant capecitabine and oxaliplatin an alternative adjuvant treatment standard.

Perioperative chemotherapy is the other favored approach for management of patients with localized gastric adenocarcinoma, and the treatment standard is use of the FLOT regimen. In the FLOT4 randomized, phase II/III study, 716 patients with stage cT2 or higher or lymph node-positive, localized gastric adenocarcinoma were randomized to receive either three preoperative and three postoperative cycles of ECF/ECX (epirubicin, cisplatin, and either 5-fluorouracil or capecitabine) or four preoperative and four postoperative cycles of FLOT (5-fluorouracil, leucovorin, oxaliplatin, and docetaxel). Patients who received FLOT had a superior overall survival of 50 months versus 35 months with ECF/ECX (HR 0.77), making this a treatment standard, particularly for fit patients.⁵

CONSIDERATION OF DNA MISMATCH REPAIR IN GASTRIC CANCER

Deficiencies in the DNA mismatch repair (dMMR) mechanism is a molecular feature observed in multiple tumor types and is of particular interest as tumors harboring this deficiency often are sensitive to immune checkpoint inhibitor therapy. Gastric adenocarcinoma is one such disease with dMMR being present in anywhere from 3 to 22% of gastric cancers.⁶ The role of immune checkpoint inhibitor therapy, regardless of MMR status, has been extensively evaluated in the metastatic setting for gastric cancer with positive results and is now indicated for use in the front-line setting for all patients in combination with chemotherapy. This is based on the CHECKMATE 649 trial where patients were randomized to receive one of three regimens—FOLFOX or XELOX (5-fluorouracil or capecitabine plus oxaliplatin) ($n = 833$), FOLFOX/XELOX

plus nivolumab ($n = 789$), or nivolumab plus ipilimumab ($n = 409$).^{7,8} The evaluation of overall survival comparing chemotherapy versus chemotherapy plus nivolumab showed a significant improvement in survival with the addition of nivolumab at 13.8 months versus 11.6 months (HR 0.79) amongst all randomized patients. The comparison of chemotherapy versus nivolumab and ipilimumab, however, did not show a significant survival difference at 11.7 months with nivo/ipi versus 11.8 months with chemotherapy only (HR 0.91). A subgroup analysis of dMMR gastric cancer patients showed much different results but was based on small patient numbers (21 patients received chemotherapy alone, 23 patients received chemotherapy plus nivolumab, and 11 patients received nivolumab plus ipilimumab). In comparisons of survival among dMMR gastric cancer patients only, the addition of nivolumab to chemotherapy was significantly improved at 38.7 months versus 12.3 months with chemotherapy alone (HR 0.38). This also was true for patients receiving nivolumab and ipilimumab versus chemotherapy at a number of months not yet reached versus 10.0 months with chemotherapy alone (HR 0.28).

Defective DNA mismatch repair is seen in colorectal cancers and patients with metastatic disease benefit from treatment with immune checkpoint inhibitor therapy.^{9–11} Notable in colorectal cancer, however, is that patients with early-stage (stage II) dMMR disease do not benefit from adjuvant FOLFOX/XELOX chemotherapy—the same regimens that are indicated for adjuvant gastric cancer treatment.^{12,13} It has been unclear whether adjuvant chemotherapy similarly lacks benefit in early-stage dMMR gastric cancer.

DOES ADJUVANT CHEMOTHERAPY BENEFIT GASTRIC CANCER PATIENTS WITH DEFICIENT DNA MISMATCH REPAIR?

Given the lack of clarity for the use of adjuvant chemotherapy in early-stage dMMR gastric cancer, a meta-analysis was conducted by Nie et al.¹⁴ Investigators conducted an extensive literature review of studies evaluating surgery alone versus surgery plus adjuvant chemotherapy in patients with localized gastric cancer and looked at how the dMMR group compared with the DNA mismatch repair proficient group (pMMR) in terms of survival. They also specifically assessed how dMMR patients fared after receiving adjuvant chemotherapy versus undergoing surgery alone. A total of seven studies—six retrospective and one randomized controlled trial—were used in the analysis, which was conducted at both the study level as well as the individual patient level where feasible. Based on individual patient data, the 3-, 5-, and 10-year disease free survival for

patients with dMMR were 78.4%, 74.2%, and 72.6%, respectively, whereas for patients with pMMR, these disease-free survival rates were 58.0%, 51.5%, and 45.9%. Similar findings were seen in regard to 3-, 5-, and 10-year overall survival at 67.7%, 60.5%, and 56.0% for dMMR versus 57.0%, 49.1%, and 40.2% for those with pMMR. These data confirm what we have believed to be true: patients with dMMR have an overall superior prognosis.

In regard to the role of adjuvant chemotherapy, specifically in dMMR patients, there was a trend toward improved disease-free survival with receipt of adjuvant chemotherapy and a significant improvement in overall survival was observed at 3, 5, and 10 years (80.6%, 73.5%, and 64.0% vs. 65.2%, 59.7%, and 49.9%). These results suggest that unlike for dMMR colorectal cancer, receipt of adjuvant chemotherapy does confer a survival benefit in localized gastric cancer.

INTEGRATION OF BIOMARKERS WITH TREATMENT STANDARDS

A role for immune checkpoint inhibitor therapy has clearly been established for treatment of metastatic colorectal and gastric adenocarcinoma, and results are particularly profound in those patients harboring a dMMR status. In the adjuvant space, while early-stage colorectal cancers that are dMMR do not benefit from chemotherapy, based on the meta-analysis by Nie et al.,¹⁴ it would appear that adjuvant chemotherapy is indicated in the management of localized dMMR gastric adenocarcinoma. The number of dMMR patients in this analysis was small, but findings by the investigators are in line with other reported data in regard to dMMR tumors. The key remaining question is how to further incorporate treatments that are known to be beneficial in the metastatic dMMR setting into current adjuvant treatment strategies; i.e., how do we best incorporate immune checkpoint inhibitor therapy into the treatment paradigm of localized dMMR gastric cancer? Building upon results of the CheckMate 649 trial,^{7,8} meaningful paths forward would include an evaluation of the following—chemotherapy versus chemotherapy plus immune checkpoint inhibitor therapy; chemotherapy versus either single-agent or dual-agent immune checkpoint inhibitor therapy; or perioperative chemotherapy with or without immune checkpoint inhibitor therapy. Key would be that chemotherapy is at a minimum included as a control arm, if not a therapeutic backbone. Such trials are currently underway.

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