Improving Perioperative Outcomes in Gastrointestinal Cancer – Personal Highlights

Neoadjuvant therapies have the potential to increase R0 resectability and thereby improving surgical outcomes. Two recent phase II trials, PANDAS/PRODIGE 44 (1) and NICHE-2 (2), investigated neoadjuvant treatment approaches for borderline resectable pancreatic cancer and locally advanced mismatch-repair deficient (dMMR) colon cancer, respectively, with notable implications for clinical practice.

Preoperative modified FOLFIRINOX with or without chemoradiation in borderline resectable pancreatic cancer: Results from the randomized phase II trial PANDAS/PRODIGE 44

Neoadjuvant chemotherapy with modified FOLFIRINOX (mFOLFIRINOX) is currently standard of care for borderline resectable pancreatic cancer and has been shown to increase R0 resectability (3,4). The PANDAS/PRODIGE 44 trial aimed to evaluate the benefit of adding conventional chemoradiotherapy to mFOLFIRINOX in the neoadjuvant treatment of borderline resectable pancreatic cancer. Conducted as a single-center, randomized phase II study, the trial involved 110 patients who received 4 courses of mFOLFIRINOX. Patients were then re-evaluated and randomized 1:1 to receive either two additional courses of mFOLFIRINOX alone (group A) or mFOLFIRINOX followed by conventional radiotherapy (28 x 1.8 Gy over 5 weeks) combined with capecitabine (group B). The primary endpoint was R0 resection rate.

The study results indicated no statistically significant difference in R0 resection rate between the two arms (group A 50% vs. group B 45%, p=0.82). Additionally, there was no observed improvement in overall survival (group A: 32.8 months, group B: 30.0 months, p=0.99), progression-free, loco-regional recurrence-free, or metastasis-free survival. Resection rates were 74% in group A vs. 71% in group B. Patients receiving chemoradiotherapy showed a trend toward higher postoperative disease progression and postoperative mortality (group A: 1% vs. group B: 6%, p=0.10), potentially limiting the initiation of adjuvant chemotherapy. No complete pathologic response was observed in either group. Thus, the PANDAS/PRODIGE 44 trial does not support the addition of conventional radiochemotherapy to mFOLFIRINOX in this setting.

Neoadjuvant immunotherapy in locally advanced MMR-deficient colon cancer: 3-year disease-free survival from NICHE-2

Mismatch-repair deficient (dMMR) colon cancers account for 10-15% of non-metastatic colon cancers. Historically, dMMR colon cancers have been managed similarly to proficient MMR tumors (5). However, dMMR colon cancers have demonstrated good response to immunotherapy (6). The NICHE-2 trial, a non-randomized, multicenter study, investigated neoadjuvant immunotherapy with nivolumab and ipilimumab in patients with locally advanced dMMR colon cancer. Patients received one cycle of nivolumab and ipilimumab, followed by a second nivolumab dose after two weeks, and proceeded to surgery within 6 weeks. The primary endpoints were safety and 3-year disease-free survival (DFS).

Results from the NICHE-2 showed a 3-year DFS rate of 100% in 111 patients (median follow-up: 36.6 months), with only 4% of patients experiencing grade 3 or 4 toxicities and no therapy discontinuations. The trial demonstrated a 98% pathologic response rate and a 68% complete pathologic response rate. Circulating tumor DNA (ctDNA) measurements indicated that 83% of initially ctDNA positive patients converted to negative status before surgery, and all patients were ctDNA negative post-surgery, aligning with a 0% recurrence rate. The NICHE-2 trial provides evidence supporting neoadjuvant immunotherapy in dMMR colon cancer with compelling 3-year DFS and high pathologic response rates, suggesting that immunotherapy may play a critical role in redefining treatment protocols for locally advanced dMMR colon cancer. □

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