Editorial

Total neoadjuvant therapy for locally advanced gastric cancer: too much of a good thing?

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Gastric cancer (GC) is one of the most common gastrointestinal malignancies and leading causes of cancer-related mortality worldwide (1). While patients with localized disease can be treated with upfront surgery with excellent outcomes, 5-year survival rates are significantly diminished for those with locally advanced disease. The establishment of perioperative chemotherapy as the standard-of-care, first with MAGIC trial which assessed the triplet of epirubicin, cisplatin, and fluorouracil (ECF), has led to substantial improvement in outcomes for patients with more advanced cancers (2). More recently, the FLOT4 regimen has become the new standard-of-care for perioperative therapy in locally advanced, resectable GC, where the triplet of fluorouracil plus leucovorin, oxaliplatin and docetaxel (FLOT) was found to be superior to ECF/epirubicin, cisplatin, and capecitabine (ECX) (3,4). One challenge with perioperative chemotherapy treatment sequencing is completion of intended therapies. Recently, there has been interest in a total neoadjuvant therapy (TNT) approach for patients with stage II/III GC, to address the challenge of patients not completing planned adjuvant therapy, with the goal of ensuring a full chemotherapy course is delivered in the neoadjuvant setting. In both the MAGIC and FLOT4 studies, only ~40% of patients completed their intended chemotherapy cycles, highlighting this difficult clinical challenge. Several recent studies have proposed that TNT may be equivalent (or superior) to perioperative chemotherapy, suggesting that treatment sequencing may need to be reconsidered in these patients (5). Additional advantages to TNT included increasing the likelihood that a tumor is down-staged (thus increasing the number of patients eligible for resection), treatment of micro-metastatic disease, and increased rates of R0 resection.

In a recently published edition of *Journal of Gastrointestinal Oncology*, Yang *et al.* present a retrospective cohort study of patients with GC undergoing TNT or perioperative chemotherapy at Memorial Sloan Kettering Cancer Center (6). The authors identified 121 patients who received perioperative chemotherapy and 28 patients treated with TNT between May 2014 and June 2020, with some variation in chemotherapy regimen received (79% TNT cohort received FLOT *vs.* 31% perioperative therapy cohort). This included highly selected cohort of patients, many of whom had poor histology (diffuse type) and assessed a range of clinical outcomes following the receipt of TNT or peri-operative chemotherapy. Interestingly, they found no significant difference in recurrence-free survival (RFS) or overall survival (OS) between cohorts at 24-month (TNT 77% *vs.* perioperative 85%), despite there being a

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numerically higher proportion of patients receiving TNT who had a pathologic complete response (pCR). The rate of R1 resection was proportionally higher in TNT patients (11%) in comparison to perioperative chemotherapy group (2.5%), though given the small cohort sizes, this data is difficult to interpret—that being said, R1 resections are among the most severe complications from an oncologic standpoint. When patients were then further sub-stratified to perform a direct comparison between TNT and perioperative patients who received FLOT regimen, both RFS and OS were significantly lower in the TNT group. This sub-group comparison may be biased as the patients who received TNT had higher clinical stage and nodal involvement, thus limiting the ability to directly compare these groups. Taken together these findings ultimately bring into questions the benefit of TNT over the current standard-of-care perioperative therapy, though there may be a signal of activity given the increased rates of pCR among TNT patients. Instead, the authors should be applauded for providing hypothesis-generating findings that support the feasibility of TNT in GC.

A notable finding of this study is that TNT appears to be safe—patients did not have a noticeable delay in surgery or increase in morbidity in the perioperative period. While additional cycles were administered for the TNT group, there was no apparent increase in toxicity that led to a delay in surgical treatment, as the median time to surgery was similar. This is notable, particularly as the patients receiving TNT had a poor performance status and more advanced disease. It is unclear based on the current study whether time from diagnosis to surgery has any appreciable impact on oncologic outcomes. One interesting point is that when assessing chemotherapy delivery, patients receiving TNT were more likely to complete the entirety of their chemotherapy cycles with all planned drugs—in the TNT group this exceeded 90% in comparison to 74% in the perioperative group. Additionally, there were over 20% of patients in the perioperative chemo group who did not receive adjuvant therapy, suggesting that these are patients who may have benefited from a TNT approach as it would allow them to receive more total cycles of chemotherapy.

These findings stimulate an important discussion—if TNT allows for safe and timely surgery but does not impact OS or R1 rates, is it just too much of a "good" thing? Is there any benefit of adjuvant systemic therapy after resection or is the impact entirely derived from a dose, regardless of when it is delivered? The NCCN guidelines currently recommend 6–8 cycles of perioperative therapy, distributed before and after surgical resection (7). As we try to further optimize treatment of these patients, other treatment paradigms may also be considered. In other gastrointestinal malignancies, there is also growing support for TNT with incorporation of multi-modal therapies, which could inform ongoing efforts to implementing TNT in GC (8,9). Here, innovative trial designs of TNT approaches incorporating radiation and novel systemic therapies including targeted therapies and immunotherapies seek to build on existing standard therapies to improve efficacy in an adaptive design with evolving arms, while implementing adaptive treatment strategies in response to neoadjuvant therapy-based tumor response criteria into the study design (10,11). Trials are ongoing to assess the incorporation of radiation with a consolidated chemotherapy regimen to assess the rate of pCR following TNT (12). There is also compelling retrospective and phase I/II data on perioperative chemoradiation therapy (CRT) for GC, though this has not been confirmed in randomized phase II trials (13). The future may also be more than just neoadjuvant FLOT with the interim positive results of the addition of immunotherapy to FLOT in localized/locally advanced GC based on the MATTERHORN trial (14,15). The study by Yang *et al.*, justifies prospective study to determine if there is any oncologic benefit to TNT in locally advanced GC and furthermore, which select patients may benefit most from this treatment sequencing.

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Footnote

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aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

References

1. Camargo MC, Anderson WF, King JB, et al. Divergent trends for gastric cancer incidence by anatomical subsite in US adults. Gut 2011;60:1644-9.
2. Cunningham D, Allum WH, Stenning SP, et al. Perioperative chemotherapy versus surgery alone for resectable gastroesophageal cancer. N Engl J Med 2006;355:11-20.
3. Al-Batran SE, Homann N, Pauligk C, et al. Perioperative chemotherapy with fluorouracil plus leucovorin, oxaliplatin, and docetaxel versus fluorouracil or capecitabine plus cisplatin and epirubicin for locally advanced, resectable gastric or gastro-oesophageal junction adenocarcinoma (FLOT4): a randomised, phase 2/3 trial. Lancet 2019;393:1948-57.
4. Kang YK, Cho H. Perioperative FLOT: new standard for gastric cancer? Lancet 2019;393:1914-6.
5. Li SS, Klempner SJ, Costantino CL, et al. Impact of Treatment Sequencing on Survival for Patients with Locally Advanced Gastric Cancer. Ann Surg Oncol 2021;28:2856-65.
6. Yang J, Greally M, Strong VE, et al. Perioperative versus total neoadjuvant chemotherapy in gastric cancer. J Gastrointest Oncol 2023;14:1193-203.
7. Ajani JA, D'Amico TA, Bentrem DJ, et al. Gastric Cancer, Version 2.2022, NCCN Clinical Practice Guidelines in Oncology. J Natl Compr Canc Netw 2022;20:167-92.
8. Kasi A, Abbasi S, Handa S, et al. Total Neoadjuvant Therapy vs Standard Therapy in Locally Advanced Rectal Cancer: A Systematic Review and Meta-analysis. JAMA Netw Open 2020;3:e2030097.
9. Merin G, Borman JB, Aviad I, et al. Double aortic arch associated with coarctation, ventricular septal defect and right ventricular outflow tract obstruction. Successful surgical repair. Am J Cardiol 1972;29:564-7.
10. Rahma OE, Yothers G, Hong TS, et al. Use of Total Neoadjuvant Therapy for Locally Advanced Rectal Cancer: Initial Results From the Pembrolizumab Arm of a Phase 2 Randomized Clinical Trial. JAMA Oncol 2021;7:1225-30.
11. Lopez CD, Kardosh A, Chen EY, et al. NeoOPTIMIZE: An open-label, phase II trial and biomarker discovery platform to assess the efficacy of adaptive switching of modified FOLFIRINOX (mFFX) or gemcitabine/nab-paclitaxel (GA) as a neoadjuvant strategy for patients with resectable/borderline resectable and locally advanced unresectable pancreatic ductal adenocarcinoma (PDAC). J Clin Oncol 2022;40:TPS630.
12. Shi J, Li N, Tang Y, et al. Total neoadjuvant therapy for locally advanced gastric cancer and esophagogastric junction adenocarcinoma: study protocol for a prospective, multicenter, single-arm, phase II clinical trial. BMC Gastroenterol 2022;22:359.
13. Allen CJ, Pointer DT Jr, Blumenthaler AN, et al. Chemotherapy Versus Chemotherapy Plus Chemoradiation as Neoadjuvant Therapy for Resectable Gastric Adenocarcinoma: A Multi-institutional Analysis. Ann Surg 2021;274:544-8.
14. Janjigian YY, Van Cutsem E, Muro K, et al. MATTERHORN: phase III study of durvalumab plus FLOT chemotherapy in resectable gastric/gastroesophageal junction cancer. Future Oncol 2022;18:2465-73.
15. Imfinzi plus chemotherapy significantly improved pathologic complete response in gastric and gastroesophageal junction cancers in MATTERHORN Phase III trial. Press Release. AstraZeneca; June 2nd 2023, 2023. Available online: https://www.astrazeneca.com/media-centre/press-releases/2023/imfinzi-plus-chemotherapy-significantly-improved-pathologic-complete-response-in-gastric-and-gastroesophageal-junction-cancers-in-matterhorn-phase-iii-trial.html

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