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Esophagogastric cancer

RESECTABLE GASTRIC CANCER: MOVING AWAY FROM ANTHRACYCLINES

Kim Ma, MD, McGill University; **Jamil Asselah, MD, FRCPC,** Medical Oncologist, McGill University Health Centre

TRIAL SUMMARY: The FLOT4 trial

Al-Batran S-E, Homann N, Schmalenberg H, et al. Perioperative chemotherapy with docetaxel, oxaliplatin, and fluorouracil/leucovorin (FLOT) versus epirubicin, cisplatin, and fluorouracil or capecitabine (ECF/ECX) for resectable gastric or gastroesophageal junction (GEJ) adenocarcinoma (FLOT4-AIO): A multicentre, randomized phase 3 trial. Meeting of the American Society for Clinical Oncology, June 4, 2017. Abstract 4004.

Perioperative epirubicin, cisplatin and 5-fluorouracil (ECF) represents the standard of care for resectable esophagogastric cancer. Despite improvement in outcomes, 5-year overall survival (OS) remains poor at 36%.[1] In an effort to improve these results, the FLOT4 trial, a multicentre randomized controlled trial, sought to compare the docetaxel-based triplet (FLOT: 5FU, leucovorin, oxaliplatin, docetaxel) to the standard anthracycline-based ECF regimen.[2] The primary endpoint of the trial was OS.

Of the 716 patients included, 74% were male, median age was 62, and 81% of cases had cT3/4 disease. Although the majority of patients completed the planned preoperative chemotherapy (90% and 91% with ECF and FLOT, respectively), fewer completed postoperative treatment with ECF than FLOT (37% and 50%, respectively). At a median followup of 43 months, median OS was 35 months with ECF and 50 months with FLOT (HR, 0.77; 95% CI, 0.63–0.94; p=0.012). Three-yr OS was 57% with FLOT and 46% with ECF. Progression-free survival (PFS) was also improved with FLOT compared to ECF (30 months vs 18 months, respectively; HR, 0.75; CI, 0.62–0.91; p=0.0004). Postoperative complications were similar in both groups at around 50%. In summary, FLOT improves PFS and OS compared to ECF, with no added toxicity.

COMMENTARY: Esophagogastric adenocarcinoma is a humbling disease. Even patients with completely resected stage I gastric cancer have only a 70%–75% 5-year OS, and this number drops below 40% for stage II disease and beyond.[3] These sobering results have spurred efforts to improve treatment, mainly by optimizing pre- and postoperative therapies. Significant controversy persists regarding perioperative chemotherapy, such as was used in the FLOT4 trial, and adjuvant chemoradiation alone, as studied in the ARTIST and INT0116 trials.[4,5] The debate around perioperative vs solely postoperative treatment in resectable gastric cancer is beyond the scope of this commentary.

In Canada, most physicians favour the use of perioperative chemotherapy in a "sandwich" fashion, with half of systemic therapy delivered prior to surgery and the other half given afterwards. Since its publication in 2006, the MAGIC trial has set the standard of care in resectable esophagogastric cancer: patients were randomized to perioperative ECF and surgery, or surgery alone.[1] Perioperative chemotherapy improved OS, with 5-year OS of 36% with ECF compared to 23% with surgery alone (HR for death 0.75; 95% CI, 0.60–0.93; p=0.009). Since then, little to no advances have been made in the perioperative management of resectable gastric cancer.

The FLOT4 randomized trial presented at ASCO earlier this year, in which anthracycline was substituted with docetaxel, is practice-changing. A near 10% absolute risk reduction for death at 3 years was seen with the FLOT regimen compared to ECF, and represents a major advance in a field that has seen little change over the past decade. Indeed, findings are already being applied in both university and community cancer centers across Canada (personal communications, not published). The FLOT regimen has the added benefit of utilizing easily accessible drugs, and therefore avoiding a common barrier seen with delivering novel therapies outside of clinical trials. Furthermore, the omission of the anthracycline-based component is particularly attractive in older patients with comorbidities who are at increased risk of cardiotoxicity.

Already, the FLOT4 trial has generated further trials, including a phase 2 randomized trial looking at trastuzumab-pertuzumab in combination with FLOT in HER-2-positive gastric cancer.[4] HER-2 inhibitors have already been incorporated into the standard of care in metastatic HER-2 positive gastric cancer; this trial would move trastuzumab-based therapy into the adjuvant and neoadjuvant setting.

This is an exciting time for resectable gastric cancer, in which optimization of systemic therapy and incorporation of targeted therapies are being studied. Nevertheless, there remain several areas of clinical equipoise, including management of poor responders to neoadjuvant chemotherapy. Hopefully, upcoming trials will continue to address these issues.

IN BRIEF

Already known

- Perioperative chemotherapy with epirubicin, cisplatin and 5-fluorouracil (ECF) improves survival over surgery alone and has been the standard of care since 2006.
- Five-year survival of patients with esophagogastric adenocarcinoma remains less that 75% for stage I cancers and falls to 40% for stage II and beyond.

What this study showed

- Pre- and postsurgical treatment with a FLOT (5FU, leucovorin, oxaliplatin, docetaxel) regimen reduced the risk of death at 3 years by 10% compared to ECF
- Omitting anthracyclines is a benefit to patients at risk of cardiotoxicity.

Next steps

- A phase 2 trial is underway to look at trastuzumab-pertuzumab in combination with FLOT in HER-2-positive gastric cancer.
- Further trials are needed to improve the management of poor responders to neoadjuvant chemotherapy.

References:

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