

FLOT Regimen Extends Survival in Resectable Gastric Adenocarcinoma

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For patients with locally advanced, resectable gastric or gastro-oesophageal junction (GEJ) adenocarcinoma, selecting the optimal perioperative chemotherapy regimen is crucial for improving long-term outcomes. This study investigates whether a docetaxel-based triplet regimen, FLOT, offers a survival advantage over the established ECF/ECX regimen in this patient population.

KEY TAKEAWAYS

- The Pivot: Perioperative FLOT chemotherapy demonstrated superior overall survival compared to ECF/ECX in resectable gastric/GEJ adenocarcinoma.
- The Data: Median overall survival was 50 months with FLOT versus 35 months with ECF/ECX (HR 0.77; 95% CI 0.63 to 0.94).
- The Action: FLOT should be considered a preferred perioperative chemotherapy option for eligible patients with locally advanced, resectable gastric or GEJ adenocarcinoma.

Background on Gastric and GEJ Adenocarcinoma Management

Gastric and gastro-oesophageal junction (GEJ) adenocarcinomas are aggressive malignancies, and for patients with locally advanced, resectable disease, perioperative chemotherapy followed by surgery is a standard treatment approach. The goal of perioperative chemotherapy is to reduce tumor burden, treat micrometastases, and improve the likelihood of a complete surgical resection, ultimately leading to better survival outcomes. Historically, regimens like epirubicin, cisplatin, and fluorouracil (ECF) or capecitabine (ECX) have been widely used in this setting. However, ongoing research aims to identify more effective chemotherapy combinations that can further enhance patient survival and disease control. Docetaxel-based chemotherapy has shown efficacy in metastatic gastric and GEJ adenocarcinoma, prompting investigation into its role in the perioperative setting for resectable tumors. This study specifically evaluated the safety and efficacy of the docetaxel-based triplet regimen FLOT (fluorouracil plus leucovorin, oxaliplatin, and docetaxel) as a perioperative therapy.

Study Design and Methods

The FLOT4 trial was a controlled, open-label, phase 2/3 randomized study conducted across 38 German hospitals and with practice-based oncologists. The trial enrolled 716 patients with histologically-confirmed advanced clinical stage cT2 or higher or nodal positive stage (cN+), or both, resectable gastric or GEJ adenocarcinoma, with no evidence of distant metastases. Patients were randomly assigned via a central interactive web-based response system to one of two treatment groups. The control group received three preoperative and three postoperative 3-week cycles of ECF/ECX, consisting

of 50 mg/m² epirubicin and 60 mg/m² cisplatin on day 1, plus either 200 mg/m² fluorouracil as a continuous intravenous infusion or 1250 mg/m² capecitabine orally on days 1 to 21. The experimental group received four preoperative and four postoperative 2-week cycles of FLOT, comprising 50 mg/m² docetaxel, 85 mg/m² oxaliplatin, 200 mg/m² leucovorin, and 2600 mg/m² fluorouracil as a 24-hour infusion on day 1. The primary outcome of the trial was overall survival, analyzed in the intention-to-treat population, with a superiority hypothesis for the FLOT regimen. The trial is registered with ClinicalTrials.gov, number NCT012166441.

Key Findings: Overall Survival Benefit

Between August 8, 2010, and February 10, 2015, a total of 716 patients were randomized, with 360 assigned to the ECF/ECX group and 356 to the FLOT group. The primary endpoint analysis revealed a significant improvement in overall survival for patients treated with perioperative FLOT compared to ECF/ECX. The median overall survival in the FLOT group was 50 months (95% confidence interval [CI] 38.33 to not reached), whereas in the ECF/ECX group, it was 35 months (95% CI 27.35 to 46.26). This translated to a hazard ratio (HR) of 0.77 (95% CI 0.63 to 0.94) in favor of FLOT, indicating a 23% reduction in the risk of death with the FLOT regimen¹.

Safety Profile and Tolerability

The safety profiles of both regimens were generally comparable. The number of patients experiencing related serious adverse events, including those occurring during hospitalization for surgery, was similar between the two groups: 96 patients (27%) in the ECF/ECX group and 97 patients (27%) in the FLOT group. Toxic deaths were rare and occurred in two patients (1).

Clinical Implications for Practice

The results of the FLOT4 trial provide compelling evidence that perioperative FLOT chemotherapy significantly improves overall survival in patients with locally advanced, resectable gastric or GEJ adenocarcinoma compared to the ECF/ECX regimen. This finding suggests that FLOT should be considered a preferred standard of care for eligible patients in this clinical setting. The observed median overall survival of 50 months with FLOT represents a substantial improvement, offering a more optimistic prognosis for patients facing these challenging cancers.

Why this matters for clinical practice today: For clinicians managing gastric and GEJ adenocarcinoma, this study offers clear guidance on optimizing perioperative chemotherapy. The FLOT regimen, with its demonstrated survival benefit and comparable safety profile to ECF/ECX, provides a strong evidence base for its adoption. Integrating FLOT into treatment protocols for appropriate patients could lead to better long-term outcomes, emphasizing the importance of multidisciplinary team discussions to ensure optimal patient selection and management. This shift in practice could impact patient counseling, treatment planning, and ultimately, the trajectory of disease for many individuals.

Limitations and Next Steps

While the FLOT4 trial provides robust evidence, it is important to consider its limitations. The study was open-label, which could introduce some bias, although the primary endpoint of overall survival is less susceptible to subjective interpretation. The study was conducted primarily in German hospitals, and while the findings are likely generalizable, further research in diverse populations could confirm these results. Future research could also focus on identifying specific patient subgroups who might benefit most from FLOT, exploring biomarkers for treatment response, and investigating potential long-term toxicities or quality-of-life impacts associated with the regimen. Additionally,

comparisons with other emerging perioperative strategies or combinations with targeted therapies could further refine treatment approaches for gastric and GEJ adenocarcinoma.

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