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Treatment Options for Metastatic Gastric Cancer After Recurrence Following Perioperative FLOT: A Critical Review

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Abstract

Background: Gastric cancer (GC) recurrence after perioperative FLOT chemotherapy is common, with limited guidance on optimal first-line treatment in the metastatic setting. Despite the survival benefits of FLOT, up to 50% of patients relapse, highlighting the need for effective post-recurrence treatment strategies.

Objective: This manuscript reviews treatment options for patients with recurrent GC after perioperative FLOT, focusing on the impact of prior chemotherapy and the role of key biomarkers such as PD-L1, dMMR/MSI, HER2, and Claudin-18.2.

Results: Post-FLOT recurrence poses challenges due to prior exposure to taxanes, platinum agents, and fluoropyrimidines. Irinotecan-based regimens show promise, though data on optimal treatment are scarce. Biomarkers such as PD-L1, dMMR/MSI-H, and Claudin-18.2 guide targeted therapies, but their efficacy in patients previously treated with FLOT remains unclear.

Conclusion: The management of recurrent GC after perioperative FLOT is complex and should consider performance status, disease burden, prior treatment tolerance, pathological response to FLOT, and molecular profile. Further research is needed to determine the best therapeutic approaches for this population.

Keywords: Metastatic gastric cancer; Perioperative; FLOT; Chemotherapy

Introduction

Gastric cancer (GC) is diagnosed in over one million individuals worldwide annually, accounting for 5.6% of all malignancies and 7.7% of all cancer-related deaths [1]. Due to subtle clinical manifestations in the early stages and the low prevalence of routine screening in Western populations, the majority of patients are diagnosed at advanced stages, when curative treatment is rare [1]. Even among those diagnosed with locally advanced gastric cancer who undergo perioperative or adjuvant chemotherapy and curative-intent surgery, recurrence rates remain high, ranging from 30% to 50% [2].

Two recent phase III trials results show that the addition of pre-operative chemoradiotherapy (CRT) to peri-operative chemotherapy does not improve long-term outcomes in the treatment of operable gastroesophageal adenocarcinoma. While CRT appeared to be effective in targeting and better controlling the local tumour, it did not address distant metastases, which remain the primary cause of mortality [3,4].

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While recent advancements in biomarker-driven therapies have reshaped the treatment landscape for metastatic GC (mGC) [2], their efficacy and role in the locoregional setting remain underexplored.

The combination of chemotherapy with anti-HER2 therapies failed to show consistent benefit in terms of pathological complete response (pCR) [5], was accompanied by high rates of adverse events [6,7] and did not promote survival gains [8]. Anti-angiogenic agents were also not associated with survival benefits but might also be associated with impaired wound healing [9,10]. To date, immunotherapy has shown benefit in disease-free survival (DFS) only for patients with esophageal or gastroesophageal junction (GEJ) tumors who received neoadjuvant treatment with chemoradiotherapy and presented pathological residual disease after surgery [11].

As a result, perioperative chemotherapy using the FLOT regimen (fluorouracil [5- FU]/leucovorin, oxaliplatin, and docetaxel, delivered in four preoperative and four postoperative cycles) remains the standard in many Western countries. This is primarily based on results from the phase II/III FLOT4 trial, which demonstrated that perioperative FLOT improved overall survival (OS) compared to ECF/ECX (epirubicin and cisplatin plus 5-FU or capecitabine) in patients with resectable locally advanced gastroesophageal cancer. The median OS in the FLOT group was 50 months, compared to 35 months in the ECF/ECX group (HR 0.77, p = 0.12) (4). FLOT also outperformed ECF/ECX in secondary endpoints, such as DFS (median 30 vs. 18 months) [12]. An international cohort study utilizing real-world data from patients with locally advanced gastric and GEJ adenocarcinomas across 12 countries revealed that adjuvant FLOT therapy significantly enhances DFS and OS in patients classified as partial responders according to their pathology reports. However, the study demonstrated no improvement in DFS or OS among patients who were minimal or complete responders to treatment [13].

Despite FLOT remaning the standard of care in the curative-intent setting, up to 50% of patients experience disease recurrence, and the optimal first-line systemic treatment for these patients remains uncertain. Given that these patients have already been exposed to platinum agents, fluoropyrimidines, and taxanes, future therapeutic options may be limited. Furthermore, many patients may experience persistent toxicities, such as peripheral neuropathy, which further constrains treatment choices. Notably, the FLOT4 trial did not report outcomes for patients who developed recurrent disease, raising several critical clinical questions:

- Do outcomes differ between patients with upfront metastatic disease and those who relapse after perioperative therapy?
- Does the pathological response to perioperative chemotherapy predict the response to first-line chemotherapy in the metastatic setting?
- How should prior exposure to FLOT components influence future therapeutic choices?
- Is there a time-based threshold, similar to ovarian cancer, that dictates platinum and taxane sensitivity?

Challenges in the Management of Recurrence After FLOT

A retrospective study involving 196 patients who received perioperative FLOT found that 27.6% developed recurrence during the follow-up period, with approximately half experiencing early recurrence, defined as within one year of surgery [14]. The median survival following recurrence was only 4.1 months—substantially lower than expected for patients with de novo metastatic gastric cancer who undergo first-line systemic treatment. This dismal outcome suggests that prior exposure to systemic chemotherapy may limit future therapeutic options, emphasizing the need for novel strategies in managing recurrent disease.

Most phase III studies investigating first-line chemotherapy combinations in metastatic gastroesophageal adenocarcinoma included patients with prior neoadjuvant and/or adjuvant therapy, provided it was completed at least six months prior to randomization [2]. However, these studies generally did not report outcomes separately for chemotherapy-experienced versus chemotherapy-naive patients, leaving a significant gap in our understanding of how prior treatment influences subsequent response rates, as will be further discussed.

Therapeutic Considerations After FLOT Recurrence:

For patients who relapse following perioperative FLOT, the reuse of taxanes may be less effective, particularly since a taxane (docetaxel) was already used during initial therapy. While paclitaxel in combination with ramucirumab remains a standard second- line option for metastatic gastric cancer, the prior use of docetaxel raises concerns about cross-resistance. Although single-agent ramucirumab could be considered in the first- line setting, response rates to monotherapy are low, and combination strategies are generally preferred [15,16].

An alternative strategy could involve the use of irinotecan-based regimens, such as FOLFIRI (5-FU, leucovorin, and irinotecan), which may offer efficacy in patients not previously exposed to irinotecan. Results from the phase II RAMIRIS trial suggest that patients pretreated with docetaxel may derive greater benefit from FOLFIRI combined with ramucirumab compared to paclitaxel and ramucirumab. In this trial, docetaxel- pretreated patients treated with FOLFIRI plus ramucirumab demonstrated higher overall response

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rates (25% vs. 8%) than those treated with paclitaxel and ramucirumab [17]. These findings suggest that irinotecan-based regimens warrant further investigation in the post-FLOT setting.

The Role of Biomarkers in Guiding Treatment Decisions

In patients with recurrent gastric cancer, the utilization of molecular biomarkers has become increasingly important in guiding therapeutic decisions. Biomarker-driven therapies have reshaped the treatment landscape in metastatic gastric cancer (mGC), offering opportunities to tailor therapy based on specific molecular characteristics [2]. Key biomarkers, including HER2 status, microsatellite instability (MSI), mismatch repair (MMR) status, PD-L1 expression, and Claudin-18.2, can provide critical insights into which therapies may offer the greatest benefit.

PD-L1 Expression and the Role of Immunotherapy:

For patients with high PD-L1 expression, defined by a combined positive score (CPS) ≥ 1, immunotherapy has emerged as a promising therapeutic option. Clinical trials such as CheckMate-649 and Keynote-859 demonstrated that the addition of PD-1 inhibitors (nivolumab or pembrolizumab) to chemotherapy significantly improved overall survival (OS) in patients with advanced gastric or gastroesophageal junction cancer, particularly in those with CPS ≥ 5 [18,19]. However, these trials primarily included chemotherapy-naive patients, and the role of immunotherapy in patients who have already received perioperative chemotherapy remains unclear.

For patients who relapse after perioperative FLOT, the decision to pursue immunotherapy combined with chemotherapy requires careful consideration. The question arises whether a patient with a CPS ≥ 1, who did not achieve a pathologic response to FLOT, would benefit from the addition of immunotherapy to standard chemotherapy (e.g., FOLFOX or CAPOX). While PD-1 inhibitors can be highly effective in chemotherapy-naive populations, it is uncertain whether prior exposure to FLOT alters the efficacy of immunotherapy. Therefore, the molecular profile of the tumor, including PD-L1 expression, should guide decision-making, but further research is needed to determine the benefit of combining immunotherapy with chemotherapy in patients who have already received a taxane, platinum, and fluoropyrimidine.

Deficient Mismatch Repair (dMMR) and Microsatellite Instability (MSI):

Deficient mismatch repair (dMMR) and microsatellite instability-high (MSI-H) are well-established predictive biomarkers for response to immune checkpoint inhibitors. dMMR tumors have a high mutation burden, making them more immunogenic and thus more susceptible to immunotherapy. The prevalence of dMMR/MSI-H in gastric cancer ranges between 5% and 10%, and tumors with this biomarker are typically associated with better prognosis and may derive significant benefit from PD-1 inhibitors [2].

In patients with recurrent gastric cancer who harbor dMMR/MSI-H tumors, immunotherapy may be considered even after prior exposure to chemotherapy. Studies such as Keynote-059 have shown that pembrolizumab monotherapy can lead to durable responses in patients with dMMR/MSI-H gastric cancer, regardless of prior treatment history [20]. Therefore, in the metastatic setting, the identification of dMMR or MSI-H should strongly influence the decision to prioritize immune checkpoint blockade over standard chemotherapy, potentially allowing for chemotherapy-free regimens.

Claudin-18.2:

Claudin-18.2 (CLDN18.2) is a tight junction protein expressed in the gastric mucosa and is overexpressed in a significant subset of gastric cancers, making it an attractive target for therapeutic intervention. The expression of CLDN18.2 has been associated with gastric adenocarcinomas, and its targeting has shown promise in clinical trials. Two pivotal trials—Spotlight and GLOW—investigated the addition of zolbetuximab, a monoclonal antibody targeting CLDN18.2, to chemotherapy regimens in patients with advanced gastric cancer [21,22].

In both the Spotlight and GLOW trials, patients with tumors expressing Claudin-18.2 (defined as ≥75% of tumor cells showing moderate-to-strong membranous CLDN18 staining) were treated with zolbetuximab combined with chemotherapy [21,22]. These trials demonstrated that the addition of zolbetuximab significantly improved progression-free survival (PFS) and OS in patients with Claudin-18.2-positive tumors. Importantly, these studies included patients who had received prior neoadjuvant or adjuvant chemotherapy, provided it was completed at least six months before randomization. However, no specific analysis was provided on the outcomes of chemotherapy-pretreated versus chemotherapy-naive patients.

For patients with recurrent gastric cancer after perioperative FLOT, Claudin-18.2 expression should be evaluated, as it may guide the use of zolbetuximab in combination with chemotherapy [21,22]. The identification of this biomarker offers a potential pathway to introduce a novel therapeutic agent that targets an otherwise difficult-to- treat population. Given that FLOT includes a taxane (docetaxel), platinum (oxaliplatin), and fluoropyrimidine (5-FU), the ability to add zolbetuximab to a chemotherapy backbone provides a new option for patients whose tumors express CLDN18.2, potentially enhancing treatment efficacy without relying solely on agents used in the FLOT regimen.

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HER2 Status:

HER2 positivity is another important biomarker in gastric cancer that has led to the development of targeted therapies such as trastuzumab. The ToGA trial was a landmark study that demonstrated the benefit of adding trastuzumab to chemotherapy in patients with HER2-positive metastatic gastric cancer [23]. However, in a subset of patients who had received prior perioperative or adjuvant chemotherapy, no benefit was observed from the addition of trastuzumab [23]. This suggests that prior chemotherapy exposure, particularly in patients who did not achieve a complete pathologic response, may impair the effectiveness of HER2-targeted therapies.

In the setting of recurrent gastric cancer after perioperative FLOT, HER2 status should be assessed, but the potential for benefit from HER2-targeted therapy may be limited if significant resistance to prior chemotherapy has developed. Thus, the integration of HER2-targeted therapies into treatment planning should consider both the molecular characteristics of the tumor and the patient's prior treatment history.

Conclusion

For patients with GC who develop disease recurrence after perioperative FLOT, the optimal first-line regimen in the metastatic setting is likely to depend on several factors, including performance status, disease burden, prior treatment tolerability, pathological response to FLOT, and molecular profile (e.g., HER2 status, MMR status, and CPS). Given the limitations of current trial data, clinicians must carefully weigh the risks of cross-resistance to previously administered agents against the potential benefits of newer treatment strategies. Prospective studies are urgently needed to better define the optimal management of these patients and to clarify the role of biomarkers in guiding therapeutic decision-making.

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