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MINIREVIEWS

Current trends in perioperative treatment of resectable gastric cancer

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Abstract

In the last few decades, the treatment strategy for locally advanced resectable gastric cancer (GC) has shifted to a multimodal approach, which potentially decreases recurrence risk and improves survival rates. Perioperative therapy leads to downstaging, increased curative resection rates, and prolonged disease-free and overall survival, by preventing micrometastases in patients with resectable GC. Application of neoadjuvant therapy provides information about tumor biology and *in vivo* sensitivity. A consensus regarding the therapeutic approach for non-metastatic GC does not exist, and many clinical trials aim to clarify this aspect. Advances in precision medicine and the role of immunotherapy have been the focus of research in GC treatment. Herein, the current status and possible future developments of perioperative therapy for locally advanced resectable GC are reviewed, based on the most recent randomized clinical trials.

Key Words: Perioperative treatment; Immunotherapy; Neoadjuvant; Chemotherapy; Gastric cancer; Adjuvant

Core Tip: The results of the most recent randomized studies have led to a shift from traditional care concepts towards evidence-based multimodal treatment strategies for gastric cancer (GC). Perioperative chemotherapy has become the standard of care for resectable GC. Molecular-based modifications of the backbone treatment increase the efficacy of therapy.

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INTRODUCTION

Gastric cancer (GC) includes histologically heterogeneous and microscopically distinct cell types and can be classified using various systems such as the Lauren and the World Health Organization (WHO) classifications[1,2]. According to the Lauren classification, GC is categorized into two subtypes: Intestinal and diffuse. The WHO classification defines five different subtypes, *i.e.*, papillary, tubular, mucinous, poorly cohesive, and mixed adenocarcinoma.

Recently, molecular classification systems were published by the Cancer Genome Atlas (TCGA) and Asian Cancer Research Group, providing a molecular subtyping structure, as well as a guide to targeted agents[3,4]. TCGA identifies a comprehensive set of genetic changes associated with GC and further classifies GC into four subtypes: Chromosomal instability (CIN) (50%), microsatellite instability (MSI) (22%), genomically stable (GS) (20%), and Epstein-Barr virus-positive (EBV) tumors (9%). The EBV subtype has an excellent prognosis, whereas patients with the CIN subtype achieve the greatest benefit following adjuvant chemotherapy [hazard ratio (HR) = 0.39; 95% confidence interval (CI): 0.16-0.94; P = 0.03][5]. However, patients with the GS subtype are characterized by poor chemotherapy benefit and worse prognosis. MSI-high (MSI-H) GC is considered a distinct subtype and has higher mutation rates with unique DNA methylation patterns. Both EBV and MSI-H GC patients are highly responsive to immune checkpoint inhibitors (ICIs)[6].

Despite the significant progress in the therapeutic strategies and surgical techniques for GC in the last decade, the number of patients experiencing relapse and dying after being diagnosed with localized GC remains rather high, even in the early stages. Adjuvant chemotherapy, chemoradiotherapy, and perioperative chemotherapy are different approaches that are proven to improve survival compared with surgery alone. The administration modality and chemotherapy protocols differ between Eastern and Western countries. In Asia, Europe and Northern America adjuvant chemotherapy is administered after surgery; after preoperative chemotherapy and surgery (perioperative chemotherapy) an in combination with radiotherapy (chemoradiotherapy), respectively. Since the onset of the fluorouracil, leucovorin, oxaliplatin, docetaxel (FLOT)4-AIO trial[7], perioperative FLOT administration has become the new standard of care for locally advanced gastric and gastroesophageal junction [GC/esophagogastric junction (EGJ)] cancers. Advances in precision medicine and the role of immunotherapy have been the focus of GC treatment research. In this review, the current status and possible future developments of perioperative chemotherapy or resectable GC are summarized.

MANAGEMENT OF RESECTABLE GC

Upper endoscopy, endoscopic ultrasound, contrast-enhanced computed tomography (CT) and positron emission tomography are the main tools for staging. Peritoneal carcinomatosis can be identified in approximately 20% of patients without radiological evidence[8]. It is more frequently encountered in diffuse-type GC[9]. Thus, staging laparoscopy with peritoneal washing should be utilized to screen for peritoneal disease in these patients who are candidates for perioperative CT (Figure 1). Endoscopic resection is recommended in early GC with intestinal histotype, according to Lauren's classification, T1a, < 2 cm, well-differentiated, non-ulcerated, and without clinically suspected lymph node involvement[10]. Standard surgery is defined as total or subtotal gastrectomy with D2 lymph node dissection and recommended in cases with ≥ cT1b or cN+ and M0 GC. According to the National Comprehensive Cancer Network (NCCN) guidelines, perioperative chemotherapy (category 1) or preoperative chemoradiation (category 2B) followed by surgery should be offered to resectable ≥ T2 disease in appropriate candidates[10].

Adjuvant treatment

Adjuvant CT alone is the standard of care in Eastern Asia, due to its improved survival benefits reported in the CLASSIC[11] and ACTS-GC[12] trials (Table 1). A large meta-analysis of randomized

Table 1 Landmark trials of perioperative treatment in gastric cancer

Treatment	Study	Arms	*n*	R0	pCR	PFS	HR (*P* value)	OS	HR (*P* value)	Ref.
NAC	EORTC 40954	PF-S	72	82%			NA	2-yr: 73%	0.84 (0.47)	[18]
		S alone	72	67%				2-yr: 70%		
	OEO2	PFx2-S	400	60%			NA	5-yr: 23%	0.84 (0.03)	[17]
		S alone	402	54%				5-yr: 17%		
	OE05	PFx2-S	451	59%	3%			3-yr: 39%	0.90 (0.19)	[19]
		ECXx4-S	446	66%	11%			3-yr: 42%		
NACRT	CROSS	RT + pacli-carbo, w-S	180	92%	29%	5-yr: 44%	0.61 (0.006)	5-yr: 47%	0.68 (0.003)	[21]
		S alone	188	69%		5-yr: 27%		5-yr: 33%		
Perioperative CT (+/-targeted)	MAGIC Trial	ECFx3-S-ECFx3	250	74%	8%	NR	0.66 (< 0.001)	5-yr: 36%	0.75 (0.009)	[22]
		S alone	253	68%		NR		5-yr: 23%		
	FNLCC/FCCD	PFx2-S-PFx4	113	84%	3%	5-yr: 34%	0.65 (0.003)	5-yr: 38%	0.69 (0.02)	[23]
		S alone	111	73%		5-yr: 19%		5-yr: 24%		
	The FLOT-4	FLOTx4-S-FLOTx4	356	84.0%	15.6%			5-yr: 45%	0.77 (0.012)	[7]
		ECX/ECFx3-S-ECX/ECFx3	360	77%	5.8%			5-yr: 36%		
	ST03	ECXx3-S-ECXx3	533	64%	8%			3-yr: 50.3%	1.08 (0.36)	[35]
		ECXx3 + BV-S-ECXx3 + BV	530	61%	11%			3-yr: 48.1%		
	PETRARCA (abstract only, ESMO 2020)	FLOTx4-S-FLOTx4	41	90%	12%	26 mo	0.57 (0.114)			[32]
		FLOT + T + Px4-S-FLOT + T + Px4 + 9 (T + P)	40	93%	35%	NR				
	RAMSES[36] (abstract only, ESMO 2020)	FLOTx4-S-FLOTx4	90	83%	30%					
		FLOT + RAM x4-S-FLOT + RAM x4 + 16 RAM	90	97%	27%					
NAC, adjuvant CT -/+ RT	CRITICS	ECXx3-S-ECXx3	393			5-yr: 39%	0.99 (0.9)	5-yr: 42%	1.01 (0.9)	[24]
		ECXx3-S-CRT	395			5-yr: 38%		5-yr: 40%		
Perioperative CT *vs* adjuvant CT	RESOLVE	S-XELOXx8	345	NR		3-yr: 51.1%	0.86 (0.17) (SOX *vs* XELOX)			[28]
		S-SOXx8	337	NR		3-yr: 56.5%				
		3SOX-S-3SOX	365	NR		3-yr: 59.4%	0.77 (0.03) (SOX *vs* XELOX)			
NAC *vs* CRT	PRODIGY	DOSX3-S-S1x8	266	95%	10%	3-yr: 66.3%	0.70 (0.023)			[29]
		S-S-1x8	264	84%		3-yr: 60.3%				
	POET	PFLX3-RT (30 Gy)/C-S	62	71%	15.6%	3-yr: 47.4%	0.67 (0.07)	5-yr: 39.5%	0.65 (0.055)	[66]
		PFL2-S	64	69%	2%	3-yr: 22.7%		5-yr: 24.4%		
	NEORES	CF-RT (40 Gy)-S	91	87%	28%			3-yr: 47%	(0.77)	[64]

		CF-S	90	74%	9%			3-yr: 49%		
Adjuvant CRT	INT-0116 trial	5FU/LVx1-CRT-5FU/LVx2	281			3-yr: 48%	0.66 (0.001)	3-yr: 50%	0.74 (0.005)	[14]
		S alone	275			3-yr: 31%		3-yr: 41%		
	CALGB 80101 Trial	5FU/LVx1-CRT-5FU/LVx2	280			3-yr: 46%	1.00 (0.99)	3-yr: 50%	1.03 (0.80)	[71]
		ECFx1-CRT-ECFx2	266			3-yr: 47%		3-yr: 52%		
	ARTIST trial	XPx2-XRT-XP2	230			3-yr: 78%	0.74 (0.09)	5-yr: 75%	1.13 (0.53)	[15]
		XPx6	228			3-yr: 74%		5-yr: 73%		
	ARTIST trial-2	S-1 (x12 mo)	182			3-yr: 65%	0.69 (0.04) (S-1 *vs* SOX)	NR	NR	[16]
		SOX (x6 mo)	181			3-yr: 74%	0.72 (0.07) (S-1 *vs* SOXRT)	NR	NR	
		SOXRT	183			3-yr: 73%	0.97 (0.88) (SOX *vs* SOXRT)	NR	NR	
Adjuvant CT	ACTS-GC trial	S1 (12 mo)	529			5-yr: 65%	0.65	5-yr: 72%	0.67	[14]
		S alone	530			5-yr: 53%		5-yr: 61%		
	CLASSIC trial	XELOXx8 (6 mo)	520			5-yr: 68%	0.58 (< 0.0001)	5-yr: 78%	0.66 (0.53)	[11]
		S alone	515			5-yr: 53%		5-yr: 69%		

5FU: 5-fluorouracil; BV: Bevacizumab; CF: Cisplatin and 5-fluorouracil; CRT: Chemoradiotherapy; CT: Chemotherapy; DOS: Docetaxel, oxaliplatin, S-1; ECF: Epirubicin, cisplatin, fluorouracil; ECX: Cisplatin, epirubicin, and capecitabine; ESMO: European Society for Medical Oncology; FLOT: Fluorouracil, leucovorin, oxaliplatin, docetaxel; HR: Hazard ratio; LV: Leucovorin; NA: Not available; NAC: Neoadjuvant chemotherapy; NACRT: Neoadjuvant chemoradiation; NR: No response; OS: Overall survival; pacli-carbo: Paclitaxel and carboplatin; pCR: Pathological complete response; PF: Cisplatin and fluorouracil; PFL: Cisplatin, fluorouracil, leucovorin; PFS: Progression-free survival; RAM: Ramucirumab; RT: Radiotherapy; S: S-1; SOX: S-1 and Oxaliplatin; T + P: Trastuzumab + pertuzumab; w-S: Followed by surgery; XELOX: Capecitabine and oxaliplatin; XP: Capecitabine and cisplatin.

controlled trials investigating the impact of postoperative CT *vs* surgery alone in GC reinforced the survival impact of adjuvant CT[13]. The United States Intergroup-0116 trial (SWOG 9008/INT-0116) indicated improved disease-free survival (DFS) and overall survival (OS) with adjuvant chemoradiotherapy compared to those with surgery alone[14]. The drawbacks of this trial were substantial rates of acute toxicity (33% had ≥ grade 3 gastrointestinal toxicity) associated with CRT, low rates and extent of nodal dissection (D2 dissection in 10%), relatively simple (and currently outdated) radiotherapy techniques and choice of CT regimen. It has been concluded that adjuvant CRT was only effective in patients who underwent limited (D1 or less) lymph node dissection and were compensated for poor surgery. Additionally, the high toxicity rates have limited the use of postoperative CRT in Europe, and a particular CT regimen is no longer preferred in the United States either.

The Adjuvant chemoRadioTherapy In Stomach Tumors (ARTIST-1) trial investigated the role of adjuvant CRT in GC patients after D2 gastrectomy[15]. Although radiotherapy did not demonstrate significant survival benefit, it reduced the rate of local recurrence by 6%. Subgroup analysis suggested that lymph node positivity and intestinal subtype were the independent factors for survival benefit with adjuvant radiotherapy. In the ARTIST-2 trial[16], adjuvant oxaliplatin combined with S-1 (SOX) and SOXRT were associated with a reduced hazard of recurrence risk compared to S-1 monotherapy in patients with D2-resected stage II or III lymph node-positive GC with no survival benefits. The addition of radiotherapy to SOX did not significantly reduce the rate of recurrence after D2 gastrectomy compared to SOX alone. DFS between patients treated with adjuvant CT and CRT was similar across all subgroups.

Neoadjuvant CT

A significant number of patients are diagnosed at advanced stages owing to the asymptomatic nature of GC. Neoadjuvant CT (NAC) helps to achieve better control of tumor progression with improved therapeutic response and treatment tolerance in patients with GC. NAC potentially improves OS by downstaging, increasing pathological response rates and reducing the risk of relapses by eradicating the micrometastatis. The trials on NAC for GC have revealed conflicting results. First, the United Kingdom Medical Research Council Esophageal Cancer Trial (OEO2) randomly assigned both patients with adenocarcinoma (67%) and squamous cell carcinoma (SCC) (33%) into two treatment groups: Surgery

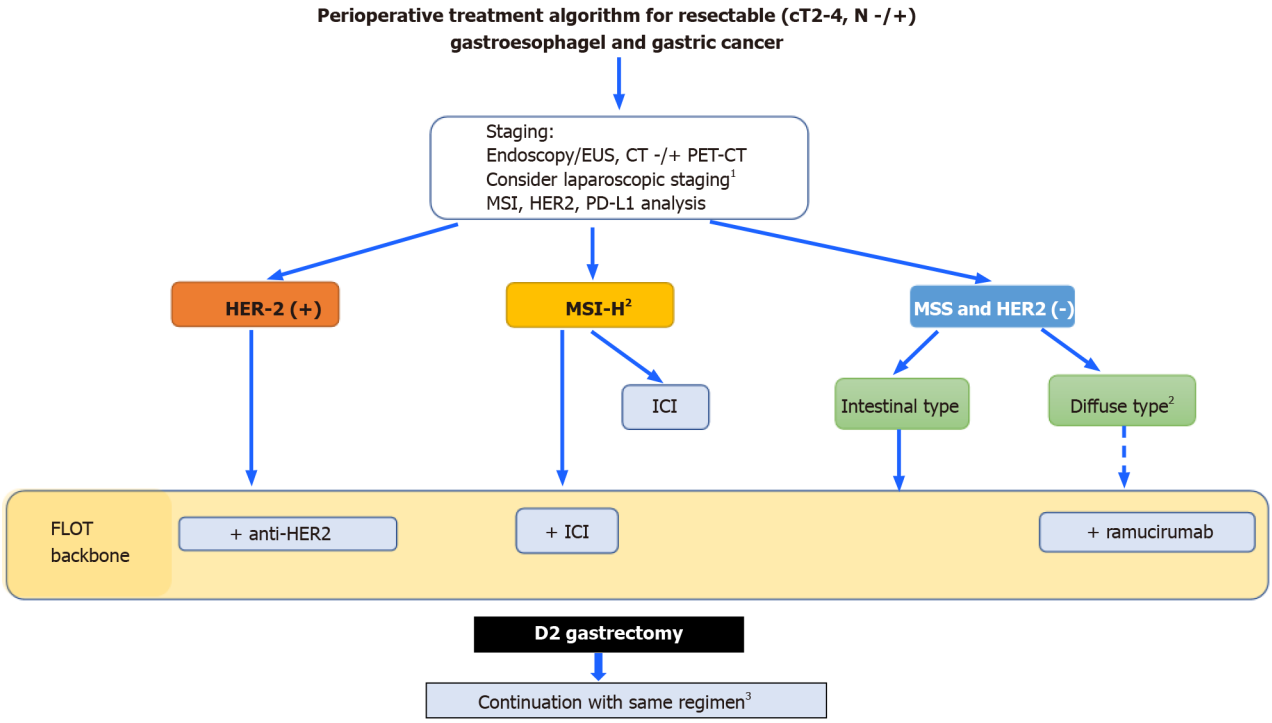

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Figure 1 Perioperative algorithm for resectable gastric cancer. [1]Strongly recommended for diffuse type gastric cancer. [2]Upfront surgery may be recommended. [3]Radiotherapy for R1/2 resection. CT: Computed tomography; PET-CT: Positron emission tomography computed tomography; EUS: Endoscopic ultrasound; FLOT: Fluorouracil, leucovorin, oxaliplatin, docetaxel; MSI: Microsatellite instability; HER2: Human epidermal growth factor 2; ICI: Immune checkpoint inhibitor; MSI-H: High microsatellite instability; MSS: Microsatellite stability; PD-L1: Programmed death-ligand 1.

plus preoperative CT [two cycles of cisplatin and fluorouracil (CF)] and surgery alone[17]. In this study, the R0 resection rates (60% *vs* 54%) and 5-year OS (23% *vs* 17%) data favored the NAC arm. In the European Organization for Research and Treatment of Cancer (EORTC-40954) trial, patients with locally advanced adenocarcinoma of the stomach or EGJ[18] were randomized to the preoperative CF and upfront surgery arms. Although neoadjuvant therapy improved the radical resection rates (82% *vs* 67%, $P = 0.036$), it did not improve survival.

The United Kingdom Medical Research Council OE05 trial compared the triplet cisplatin, epirubicin, and capecitabine or 5-fluorouracil (ECX/ECF) regimen with the CF regimen and reported that the intensified triplet regimen did not increase survival in EGJ cancers[19]. Despite the increased rates of toxicity, the ECX group had a higher R0 resection rate and pathological complete response (pCR); however, the addition of epirubicin to cisplatin and fluoropyrimidine backbone did not provide any survival benefit.

Neoadjuvant CRT

Several trials evaluated whether neoadjuvant chemoradiation (NACRT) followed by surgery would improve survival compared to surgery alone; however, most of the early studies were small case series that were underpowered[20]. The pivotal Chemoradiotherapy for Oesophageal Cancer Followed by Surgery (CROSS) trial established the benefit of neoadjuvant taxane-based chemoradiation for patients with ≥ T2 esophageal or EGJ cancer patients (75% adenocarcinoma)[21]. Complete resection (R0) was achieved in 92% of the CRT-surgery group *vs* 69% of the surgery group ($P < 0.001$). The median OS (mOS) was 49 and 24 mo in CRT and surgery alone groups, respectively [HR = 0.66; $P = 0.003$ and 5-year OS: 47% *vs* 34%]. Postoperative complications were similar in both groups. The survival benefit was highest in the SCC subgroup, with mOS of 81.6 mo in the NACRT plus surgery group and 21.1 mo in the surgery alone group (HR = 0.48; $P = 0.008$). Patients with SCC also had a higher rate of pathologic complete response (49%) compared to patients with adenocarcinoma (23%, $P = 0.008$).

Perioperative CT

The MAGIC trial is unquestionably a milestone in the development of perioperative GC treatment[22]. In this trial, ECF therapy was evaluated as a perioperative treatment compared with surgery alone in patients with resectable stages II and III adenocarcinoma of the stomach (74%), EGJ (11%-12%), and lower esophagus (14%-15%). The results showed that preoperative NAC significantly increased the R0 resection rate (79% *vs* 70%) and increased pathological response compared to surgery alone. The OS rate (5-year OS: 36% *vs* 23%; $P = 0.009$) and PFS rate after the perioperative regimen were improved

compared to those after surgery alone. Postoperative morbidity and mortality were similar in both arms.

In contrast, the FNCLCC/FFCD ACCORD (French) trial evaluated the role of perioperative treatment compared to surgery alone in 224 patients with operable adenocarcinoma of the stomach (25%), EGJ (64%), and lower esophagus (11%)[23]. A significant increase in the R0 resection rates (84% *vs* 73%, P = 0.04) were achieved in the neoadjuvant group compared to the surgery alone group, in addition to improved OS (38% *vs* 24%, P = 0.02) and 5-year DFS (34% *vs* 19%, P = 0.01).

The MAGIC trial predominantly recruited patients with GC, whereas the French study primarily included patients with proximal tumor. Therefore, the perioperative treatment approach may be considered as evidence-based for both tumor sites. The limitation in both trials was the lack of standard D2 lymph node dissection in the majority of cases, causing a heterogeneous patient population. The German cancer research group recently showed the efficacy of NAC in patients undergoing D2 lymph node dissection in the FLOT4 trial[7].

The FLOT4 trial included patients with locally advanced gastric and EGJ adenocarcinoma. The perioperative FLOT regimen increased the R0 resection rate and prolonged the median PFS and mOS compared to the ECF/ECX regimen. The pCR in the FLOT perioperative group was significantly improved compared to that in the perioperative ECF/ECX group (16% *vs* 6%). Notably, patients in the FLOT arm showed higher 5-year OS rates (45% *vs* 36%). The success of this trial was attributed to the use of docetaxel in the FLOT regimen instead of epirubicin used in the ECF/ECX regimen.In the FLOT trial, D2 resection was performed in most patients with GC. The FLOT regimen caused lower grade 3 or 4 non-hematological toxicities. Conversely, grade 3 or 4 neutropenia, diarrhea, and neuropathy were more often observed with FLOT than with ECF/ECX.

In the MAGIC, FCCD/FNCLCC, and FLOT trials, approximately 10% of the patients could not complete preoperative CT, and approximately 50% were unfit for postoperative CT. Perioperative treatment should be considered beforehand for resectable GC because of the reduced patient compliance with adjuvant treatment. Perioperative CT is recommended by both the NCCN and European Society for Medical Oncology guidelines to treat ≥ T2 GC, regardless of lymphatic involvement[10,24].

Role of adjuvant chemoradiation in the perioperative approach

The CRITICS study was designed to compare the OS between the perioperative CT (ECX/epirubicin, oxaliplatin, capecitabine) with preoperative CT and postoperative CRT[25]. Postoperative CRT did not improve OS compared to postoperative CT. However, recent long-term follow-up results of the trial, including per-protocol analysis of patients who started the allocated postoperative treatment, showed better 5-year OS rates with postoperative CT (57.9% *vs* 45.5%, P = 0.0004)[26].

Perioperative vs adjuvant treatment alone

A meta-analysis of 2093 patients with GC randomized in 14 clinical trials reported remarkable results favoring perioperative treatment[27]. The global analysis showed a significant benefit of OS (HR = 0.48, P < 0.001), PFS, and R0 resection rates for the perioperative arm compared to those of the adjuvant-only arm. In the RESOLVE trial[28], 1094 patients who underwent D2 gastrectomy for locally advanced GC were randomly assigned to either the perioperative SOX arm or the postoperative adjuvant CT with SOX or capecitabine and oxaliplatin arm. Perioperative SOX was superior to postoperative capecitabine and oxaliplatin in terms of the 3-year DFS. In addition, postoperative SOX showed equivocal results compared with postoperative capecitabine and oxaliplatin. The PRODIGY study[29], a phase III randomized clinical trial from South Korea, investigated the outcomes of perioperative CT with docetaxel, oxaliplatin and S-1 against adjuvant S-1 for resectable GC. Significant tumor downstaging and improved PFS (HR = 0.70; P = 0.023) were observed in the perioperative arm, whereas OS was similar regardless of the treatment modality (HR = 0.84; P = 0.338).

Perioperative CT plus targeted therapy/immunotherapy

Experimental research is focused on biomarkers that may be valid for the selection of patients who may benefit from further treatment (*i.e.*, conventional chemotherapeutic agents, immunotherapies and targeted therapies) besides surgery. The identification of different molecular subtypes of GC has greatly accelerated this process.

Several regimens including cytotoxic agents plus targeted molecules or ICIs have been tested as neoadjuvant and adjuvant approaches. Due to their established efficacy in metastatic disease, human epidermal growth factor 2 (HER2) and vascular endothelial growth factor-targeted agents were explored in perioperative regimens with the FLOT backbone.

Anti-HER2

HER2 overexpression or amplification is recorded in approximately 15%-20% of gastric and EGJ adenocarcinomas. It is more common in intestinal type and EGJ cancers than in diffuse/mixed-type cancers and cancers of the gastric body. HER2-positivity is defined by the presence of 3+ immunohistochemical score or 2+ score with positive fluorescence *in situ* hybridization test.

In patients with metastatic HER2-positive GC, the addition of trastuzumab to platinum-based chemotherapy as a first-line treatment has been proven to increase the mOS compared to chemotherapy alone in the landmark ToGA study[30]. Trastuzumab plus chemotherapy is now the standard first-line therapy for patients with HER2+ advanced-stage G/EGJ cancers. New HER2- targeted agents and combinations have been developed to overcome intrinsic and acquired resistance. In a randomized phase II trial (DESTINY-Gastric01)[31], medically compromised patients with HER2+ advanced-stage G/EGJ cancers who had received at least two previous lines of therapy, trastuzumab deructexan, demonstrated a significantly higher response rate and longer OS than those who had received chemotherapy.

Limited data exist on the efficacy of anti-HER2 targeted therapy in the perioperative setting. In the phase II PETRARCA trial (presented at the European Society for Medical Oncology 2020), the addition of trastuzumab and pertuzumab to perioperative FLOT regimen increased the pCR rates (35% *vs* 12%) and nodal response (68% *vs* 39%) in HER2- positive resectable EGJ cancer[32]. The R0 resection (90% *vs* 93%) and surgical morbidity (43% *vs* 44%) and mortality (2.5% *vs* 2.5%) rates were comparable. More adverse events of grades > 3 were reported with trastuzumab and pertuzumab, especially diarrhea (5% *vs* 41%) and leukopenia (13% *vs* 23%). However, large-scale phase III randomized controlled studies are warranted to confirm the efficacy.

HER2-targeted agents may upregulate the expression of programmed death cell 1 (PD-1) or programmed death cell ligand 1 (PD-L1), increase the extent of tumor immune cell infiltration and promote antigen presentation *via* dendritic cells, all of which could enhance the efficacy of anti-PD-1/anti-PD-L1 antibodies[33]. A randomized phase III trial evaluating the efficacy of pembrolizumab plus trastuzumab and chemotherapy is currently ongoing (KEYNOTE-811)[34]. The first interim analysis of KEYNOTE-811 showed that adding pembrolizumab to standard therapy with trastuzumab and chemotherapy results in a meaningful improvement in objective response rate as first-line treatment of HER2-positive GC.

Anti-vascular endothelial growth factor

The United Kingdom Medical Research Council ST03 trial compared perioperative ECX with ECX plus bevacizumab in patients with locally advanced resectable gastric, esophageal, and EGJ adenocarcinoma [35]. The 3-year OS and DFS rates were comparable between the combined bevacizumab and control groups. The incidence of impaired wound healing and anastomotic leakage was higher in the bevacizumab group.

The randomized phase II/III RAMSES/FLOT7 trial (presented at the European Society for Medical Oncology 2020) evaluated the addition of the vascular endothelial growth factor-R2 inhibitor, ramucirumab, to the FLOT regimen for resectable GC patients in the perioperative setting[36]. In the phase II of this trial, the addition of ramucirumab to perioperative FLOT significantly improved R0 resection rates (97% *vs* 83%, $P = 0.0049$) with similar complete/near-complete pathologic response (30% *vs* 27%) and operative morbidity. In the subgroup analysis, the relative benefit of FLOT-ramucirumab on the R0 resection rate was more pronounced in the cT4 (25% *vs* 100%) and diffuse-/mixed-type histology groups (77% *vs* 95%). Even though the anti-angiogenic therapy seems favorable and was successfully used for clinical purposes, further prospective randomized studies are needed to evaluate the use of the drugs included as part of this therapy for localized disease. Additionally, some of these agents have been associated with serious safety issues. Because angiogenesis is an important step in the healing process, agents targeting the angiogenesis pathway may interfere with wound healing, thus increasing the risk of surgical complications, bleeding, and infection.

Immunotherapy

The inhibition of PD-1/PD-L1 interactions, through the use of ICI, is able to reactivate immune response against cancer and has changed the treatment landscape of GC, especially in the metastatic phase. Higher PD-L1 expression, assessed according to the combined positivity score (CPS), is associated with better response to ICI in advanced GC, as observed for other tumors[37].

In advanced GC adenocarcinoma, the combination of nivolumab and chemotherapy improved OS in tumors with PD-L1 CPS ≥ 5 in CheckMate-649 trial[38] and pembrolizumab plus chemotherapy (with PDL-1 CPS ≥ 10) in KEYNOTE-590 trial[39], as first-line treatment. Nivolumab demonstrated superior OS regardless of PD-L1 expression as third-line therapy in Attraction-02[40] trial and pembrolizumab prolonged the duration of response in PD-L1 positive patients with CPS ≥ 1 (KEYNOTE-059)[41].

ICI therapies have been the standard of care for the treatment of advanced MSI-H tumors. MSI is characterized by high mutation rates and the generation of frameshift-peptide neoantigens, which foster a highly immunogenic environment with increased peritumoral and tumor-infiltrating lymphocytes [42]. The incidence of MSI in G/EGJ cancers varies between 5% and 20%[43]. MSI-H GC has unique clinical characteristics, including a distal location, high frequency of intestinal-type histology, lower stage and a good prognosis[44].

MSI-H status has been confirmed as a biomarker for pembrolizumab therapy in patients with advanced G/EGJ cancers regardless of the previous lines of therapies. In a *post hoc* cohort analysis of three trials (KEYNOTE-059, KEYNOTE-061, and KEYNOTE-062) including 84 of 1614 patients with confirmed MSI-H advanced G/EGJ cancers, treatment with pembrolizumab therapy alone or in

combination with CT was associated with improved OS, PFS, and durable response[45]. The effect of ICI treatment in the perioperative setting is under investigation in several clinical trials (Table 2). Durvalumab (NCT04592913), pembrolizumab (NCT03221426), atezolizumab (NCT03421288), and avelumab (NCT03399071) studies evaluated the efficacy and safety of ICI plus CT (FLOT) compared to CT alone as a perioperative treatment for localized G/EGJ adenocarcinoma regardless of the PD-L1 status. Although MSI is a strong predictor of response to ICI treatment, the clinical value of PD-L1 expression is still under investigation[46].

Recent studies have shown that tumor mutational burden is a predictive factor of survival in GC patients receiving ICIs[47,48]. In June 2020, the Food and Drug Administration granted accelerated approval for the treatment of patients with unresectable or metastatic tumor mutational burden-high (≥ 10 mutations per megabase) solid tumors who progressed after prior treatment. The efficacy of immunotherapy was also shown in MSI-H metastatic GC, however currently, no phase III data are present for patients with resectable GC. Promising results have been observed in two latest phase II studies, GERCOR NEONIPIGA and DANTE trials[49,50].

Neoadjuvant nivolumab plus ipilimumab plus adjuvant nivolumab were evaluated in the phase II GERCOR NEONIPIGA study in patients with localized dMMR esophagogastric adenocarcinoma[49]. Neoadjuvant therapy with nivolumab and ipilimumab was feasible and associated with a high pCR rate in patients with MSI/dMMR resectable esogastric adenocarcinoma. Among 29 patients with localized MSI/dMMR disease, a pCR rate of 59% was reached, whereas, normally, a pCR rate of about 10% would be expected with platinum- and fluoropyrimidine-based NAC in this particular molecular subtype. DANTE trial evaluated atezolizumab in the perioperative treatment of resectable G/EGJ cancers in combination with FLOT[50]. Higher pCR rates were observed in the ICI arm (50% *vs* 27%).

The benefit of perioperative CT is unclear in MSI-H GC. In a large study, 5-fluorouracil-based adjuvant CT improved DFS (P = 0.002) in microsatellite stable/MSI-low group but showed no benefit in the MSI-H group[51]. In the CLASSIC trial[52], patients with MSI-H GC had no survival benefit from adjuvant CT. In the MAGIC trial[53], which evaluated the role of perioperative CT in resectable GC, MSI-H status was associated with worse survival in the CT-plus-surgery arm compared to microsatellite stable/MSI-low GC. A meta-analysis of pooled data from the CLASSIC, MAGIC, ARTIST, and ITACA-S trials, which compared different curative multimodal treatments for GC, revealed that MSI-H status was associated with longer OS but reported no benefit from perioperative or adjuvant CT[54]. Thus, some centers currently recommend upfront surgery for patients with MSI-H tumors and consider perioperative immunotherapy for advanced locoregional disease.

The CheckMate 577 study[55] investigated the role of adjuvant immunotherapy in residual disease after NACRT in esophageal cancers. Patients with esophageal adenocarcinoma (EAC) and esophageal squamous cell carcinoma or EGJ cancer received NACRT followed by adjuvant nivolumab for up to 1 year in case of residual pathologic disease (ypT+ and/or ypN+; R0 resection). Adjuvant nivolumab provided superior DFS with a 31% reduction in recurrence risk or death and doubled the median DFS.

CHALLENGING ASPECTS AND FUTURE PERSPECTIVES

Impact of histology

The impact of histological subtypes on decision-making of perioperative treatment is neglected in international guidelines. However, tumor histology is an essential denominator for treatment response and its subsequent outcomes. A multicenter phase II study of perioperative CT for GC reported a significantly longer OS and an improved PFS for patients with intestinal-type tumors compared to non-intestinal-type tumors[56]. Homann *et al*[57] reported that the pCR rate was the highest with intestinal-type tumors (30.8%) and the lowest with diffuse/mixed-type tumors (0%). Al-Batran *et al*[58] also found that the tumor regression grade was significantly better in intestinal GC than diffuse GC after NAC with FLOT or ECF.

A previous study showed that NAC conferred better outcomes, although the therapeutic response was relatively weak for gastric signet ring cell carcinoma (SRCC)[59]. Conversely, other studies suggested that NAC provided no survival benefit in this population[60,61]. Another recent analysis confirmed the poor outcomes associated with signet ring cell histology in terms of R0 resection and histopathological response in GC and EGJ cancer patients undergoing NAC[62]. Despite the lack of validated approaches for GC treatment according to histotype, CT seems to be a feasible approach for diffuse GC with SRCC. Nevertheless, these results imply the need for dedicated clinical trials focusing on operable diffuse and/or SRCCs. In the PRODIGE19 trial, presented in the American Society of Clinical Oncology (ASCO) 2019, a perioperative approach with ECF *vs* an upfront surgery followed by adjuvant treatment for resectable gastric SRCC was assessed[63]. Resection and median survival rates were higher with perioperative chemotherapy [R0, 88% *vs* 78%; 2-year OS, 60% *vs* 53%; median survival, 39 *vs* 28 mo (HR = 0.71; 95%CI: 0.40-2.64)]. Consequently, a diagnosis of SRCC does not change the indication of perioperative treatment in patients with locally advanced GC.

Table 2 Overview of ongoing trials of biological and immunological agents in the perioperative treatment for gastric cancer

NCT	Agent	Target structure	Trial	Phase	Study design	Primary endpoint	Ref.
NCT04592913	Durvalumab	PD-L1	Matterhorn	III	FLOT + durvalumab	EFS	[72]
					FLOT + placebo		
NCT03221426	Pembrolizumab	PD-1	Keynote-585	III	CF/FLOT + pembrolizumab	pCR, OS, EFS	[73]
					FLOT + placebo		
NCT03421288	Atezolizumab	PD-L1	Dante	II	FLOT + atezolizumab	DFS	[50]
					FLOT + placebo		
NCT03399071	Avelumab	PD-L1	Iconic	II	FLOT + avelumab	pCR	[74]
NCT05504720	Pembrolizumab + trastuzumab	PD-1/HER2	PherFlot	II	FLOT + pembrolizumab + trastuzumab	DFS, pCR	[75]
NCT02205047	Trastuzumab +/- pertuzumab	HER2	Innovation	II	CT	pCR	[76]
					CT + trastuzumab		
					CT + trastuzumab + pertzumab		

CF: Cisplatin and 5-fluorouracil; CT: Chemotherapy; DFS: Disease free survival, EFS: Event free survival; FLOT: Fluorouracil, leucovorin, oxaliplatin, docetaxel; HER: Human epidermal growth factor; OS: Overall survival; pCR: Pathological complete response; PD: Programmed cell death; PDL: Programmed cell death ligand.

EGJ tumors

The treatment options for resectable adenocarcinoma of EGJ include perioperative CT and NACRT. FLOT has been the standard perioperative CT protocol for resectable EGJ and GC. The preference between NACRT and CT alone in EGJ cancer is challenging. Head-to-head comparisons are lacking, and cross-trial comparisons are limited because of the heterogeneities in patient characteristics and surgical management. Although radiosensitivity of SCC and adenocarcinoma are different, previous studies usually analyze these two histological subtypes in a single group[21,64]. Certainly, patients with SCC achieved more benefit from CRT in the CROSS trial. While the FLOT trial included no SCC patients, an exploratory network meta-analysis revealed no significant difference between the CROSS and FLOT trials in terms of OS[64]. In a current meta-analysis, NACRT provided a higher R0 resection and pCR rates and lower local recurrence and distant metastasis rates compared to NAC[65]. NACRT may be particularly preferred for SCC histology because of its increased radiosensitivity, and for bulky adenocarcinomas, where achieving an R0 margin is a prior concern.

Likewise, other studies revealed that NACRT and NAC are comparable in terms of OS[64,66]. The NeoRes trial randomized 181 patients with esophageal cancer to receive preoperative CF with or without concurrent radiotherapy[64]. Although pCRs (the primary endpoint) and R0 resection rates were higher with NACRT, there were no significant differences in PFS or OS. Moreover, subgroup analysis showed no relation in terms of tumor histology (adenocarcinoma *vs* SCC). The POET trial compared NAC to NACRT followed by surgery and included only locally advanced adenocarcinomas of the EGJ (Siewert types I and II)[66]. Although the study was terminated early due to relatively higher in-hospital mortality in the NACRT group (10.2% *vs* 3.8%), the mOS and median PFS were similar in both arms.

Both the NeoRes and POET trials have used regimens that are no longer standard of care for EGJ tumors and were underpowered to detect differences in OS. Recent trials have aimed to compare current NAC (FLOT) and CRT (CROSS) regimens in phase III studies (Neo-AEGIS[67], ESOPEC[68], TOPGEAR[69]). In the Neo-AEGIS trial in which the preliminary results were presented at the ASCO 2021, 377 patients with adenocarcinoma of the esophagus or EGJ were randomized to perioperative CT (ECF/ECX or FLOT) regimen *vs* NACRT based on the CROSS regimen[67]. At a median follow-up of 24.5 mo, there were 143 deaths at the second futility analysis (60% of planned events), with a 3-year estimated survival probability of 56% and 57%, respectively. The R0 resection rates (95% *vs* 82%) and pCR (16% *vs* 5%) data favored the NACRT arm. Anastomotic leak and postoperative in-hospital mortality were comparable.

The use of trastuzumab in combination with NACRT for HER2-overexpressing EAC was evaluated in the NRG Oncology/RTOG 1010 study[70]. The addition of CRT failed to meet the primary endpoint of DFS. The median DFS was 19.6 mo with CRT and trastuzumab *vs* 14.2 mo with CRT alone (HR = 0.99; 95%CI: 0.71-1.39).

The CRITICS study showed no benefit of the addition of postoperative radiotherapy, which may be partially attributed to poor patient compliance with the adjuvant treatment[25]. Therefore, subsequent studies have focused on the optimization of preoperative treatment strategies. Determining the clinical value of adding further systemic perioperative CT to NACRT was addressed in the TOPGEAR study [69], which studied the responses in patients with operable GC and gastroesophageal cancer randomized to either perioperative CT or preoperative CT and CRT, followed by adjuvant CT.

Future directions

G/EGJ cancers have high levels of both genomic and phenotypic variability even within individual tumors, and this underlying heterogeneity is considered to be the major reason for the failure of biomarker-based clinical trials. Currently, only the following three biomarkers are routinely used in GC: HER2, PD-L1, and MSI. Other potential targetable genetic alterations, including fibroblast growth factor receptor 2 amplification, epidermal growth factor receptor amplification, MET amplification, Claudin 18.2 expression and NTRK fusion are being tested in ongoing trials in advanced GC. Despite a lack of clinically relevant biomarkers, many clinical trials are underway to study the expression of biomarkers that could provide insight to intratumoral heterogeneity conditioning of the response to treatment. This could lead to an improvement in selection of patients candidates for targeted therapies.

There is little data to support the routine use of molecular therapies or immunotherapy in resectable GC. Nevertheless, the results of early studies on anti-HER2 targeted therapies and ICIs are promising. However, anti-HER2 therapies may improve the response rate, but no survival benefit has been demonstrated yet. In the GERCOR NEONIPIGA trial, the high pCR rates with neoadjuvant ICI are promising, on the perioperative use of immunotherapies in resectable MSI-H GC. The preliminary results of the DANTE study also showed that adding ICI to FLOT therapy in the perioperative setting, regardless of PD-L1 status, may be a very rational approach. The results of these studies can help optimize the selection of patients to receive targeted therapies, thereby facilitating precision medicine approaches for patients with G/EGJ cancers.

In determining patients who are most likely to benefit from immune therapies, a more accurate definition of potential patients who will benefit from chemotherapy, might improve outcomes in the near future, when used along with novel biomarkers, such as MSI and EBV.

CONCLUSION

Appropriate treatment modalities should be planned by a multidisciplinary team specialized in the management of GC because of the complex nature of the disease. Perioperative treatment has become the major denominator of multimodal treatment, as the current standard of care for resectable GC. Biomarkers, MSI, PD-L1, tumor mutational burden, HER2, and genomic subtypes help determine the immunotherapy and targeted therapy options to consolidate the efficacy of the backbone treatment.

FOOTNOTES

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