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EDITORIAL

Perioperative chemotherapy for resectable gastric cancer: MAGIC and beyond

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Abstract

Over the last 15 years, there have been major advances in the multimodal treatment of gastric cancer, in large part due to several phase Ⅲ studies showing the treatment benefits of neoadjuvant and adjuvant chemotherapy and chemoradiation protocols. The objective of this editorial is to review the current high-level evidence supporting the use of chemotherapy, chemoradiation and anti-HER2 agents in both the neoadjuvant and adjuvant settings, as well as to provide a clinical framework for use of this data based on our own institutional protocol for gastric cancer. Major studies reviewed include the SWOG/INT 0116, Medical Research Council Adjuvant Gastric Infusional Chemotherapy (MAGIC), CLASSIC, ACTS-GC, Adjuvant Chemoradiation Therapy in Stomach Cancer (ARTIST) and Trastuzumab for Gastric Cancer trials. Although these studies have demonstrated that multiple approaches in terms of the timing and therapy for gastric cancer are effective, no standard of care is widely accepted and questions regarding the optimal timing of chemotherapy, the benefit of radiotherapy, the minimum required extent of lymphadenectomy and optimal chemotherapy regimen still exist. Protocols from the upcoming ARTIST Ⅱ, CRITICS, TOPGEAR, Neo-AEGIS and MAGIC-B studies are outlined, and results from these studies will provide critical information regarding optimal timing and treatment regimen. Additionally, the future directions of gastric cancer research predicated on molecular profiling and tailored therapies based on targetable genetic alterations in individual patient's tumors are addressed.

Key words: Gastric cancer; Neoadjuvant therapy; Adjuvant therapy; Chemotherapy; Chemoradiation

Core tip: Although multiple phase Ⅲ trials have been performed around the world, no standard of care exists for the treatment of gastric cancer. We reviewed the existing high-level evidence supporting the use of neoadjuvant and adjuvant chemotherapy, chemoradiation, and anti-HER2 therapies in gastric cancer, as well as provide a clinical framework for the treatment of gastric cancer patients at our institution

based on these studies. Also highlighted in this editorial are current clinical trials in progress and future directions of gastric cancer research based on next generation sequencing data.

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Major advances in the multimodal treatment strategy for gastric cancer have changed clinical management of the disease over the last 15 years, with multiple phase Ⅲ trials showing survival benefit for several perioperative chemotherapy and adjuvant treatment strategies (Table 1). Despite high-level evidence supporting the use of adjuvant therapy after curative-intent surgery, questions regarding the optimal timing of chemotherapy, the benefit of radiotherapy, the minimum required extent of lymphadenectomy and optimal chemotherapy regimen still exist. As a result, there is no global standard of care for adjuvant therapy in gastric cancer, but rather local standards that exist according to the phase Ⅲ trials that were conducted in those regions. The two major studies of adjuvant therapy in Western populations are the Intergroup 0116 (INT 0116) trial and the Medical Research Council Adjuvant Gastric Infusional Chemotherapy (MAGIC) trial. Despite level 1 evidence from these phase Ⅲ studies demonstrating survival benefit leading to category 1 recommendations in the NCCN Guidelines[1], utilization of these approaches has been reported to be surprisingly low in the United States. A recent study of the Surveillance, Epidemiology, and End Results (SEER)-Medicare database suggests that the number of gastric cancer patients eligible for additional treatment who actually received adjuvant therapy is quite low, and the number receiving perioperative chemotherapy is even lower[2]. From 2002-2009, only 25% of eligible patients received adjuvant chemoradiation and only 3% received perioperative chemotherapy, though this proportion steadily increased with time[2].

Prior to the publication of INT 0116 in 2001, high-level evidence supporting adjuvant chemoradiation was lacking and in fact argued against such an approach[3]. INT 0116 finally demonstrated significantly improved overall survival (OS) and 3-year recurrence-free survival (RFS) in patients receiving bolus 5- fluorouracil (5-FU) plus leucovorin with radiation therapy after surgical resection compared to those receiving surgery alone[4]. Because this trial was conducted at a time when modified D2 lymphadenectomy was not routinely performed in the United States, 90% of the patients underwent D0 or D1 lymphadenectomy. This led to routine criticism that the improved survival observed in the chemoradiation group was due to multimodality therapy compensating for inadequate surgical clearance of involved lymph nodes. While the median 10-year follow-up data from the study showed continued benefit in the chemoradiation group irrespective of extent of lymphadenectomy, it is difficult to draw definitive conclusions on the benefit of chemoradiation in patients with D2 lymphadenectomy due to the small number of patients (n = 54)[5].

The Adjuvant Chemoradiation Therapy in Stomach Cancer (ARTIST) trial aimed to address the question of whether adjuvant chemoradiation benefits patients who already have adequate surgical lymph node clearance. Korean patients undergoing curative-intent gastrectomy with D2 lymphadenectomy were randomized either to surgery followed by chemotherapy or surgery followed by chemoradiation. On initial reporting, 3-year disease-free survival (DFS) was similar between the two groups[6]. The exception was an unplanned subgroup analysis of node-positive patients, where 3-year DFS favored the chemoradiotherapy group (P = 0.0365). These hypothesis-generating results suggest that radiation therapy is beneficial for locoregional control and that perhaps only node-positive patients may benefit from adjuvant chemoradiation. This will be further tested in ARTIST-Ⅱ, which will randomize only node-positive patients to one of two adjuvant chemotherapy arms or a third arm that includes adjuvant chemoradiation. Additionally, it is unclear whether the ARTIST data can be extrapolated to Western populations because results from Asian gastric cancer trials have consistently shown improved outcomes compared to Western studies. Those disparities may represent a difference in biology or regional treatment patterns. Gastric cancers in Asia tend to be intestinal type, located in the distal stomach, compared to more diffuse tumors located in the proximal stomach and gastroesophageal junction in the West. Additionally, the impact of diet and active gastric cancer screening programs in Asia may also play a role in the difference in outcomes. Fortunately, the upcoming results of the Dutch ChemoRadiotherapy after Induction chemoTherapy in Cancer of the Stomach (CRITICS) trial may provide additional information regarding the benefit of chemoradiation in a Western population that has received perioperative chemotherapy (Table 1)[7]. This study is designed to provide neoadjuvant chemotherapy to all randomized patients who are then assigned to either adjuvant chemotherapy or chemoradiation after surgical resection.

Apart from the controversy regarding the addition of radiation therapy in gastric cancer, current trials are still addressing the optimal timing of adjuvant therapy. The two major trials showing survival benefit for postoperative chemotherapy are the Japanese ACTS-GC trial and the Korean CLASSIC trial[8,9]. While

Table 1 Completed and ongoing phase Ⅲ trials of perioperative chemotherapy and chemoradiation in gastric cancer

	Timing, intervention	Treatment arms (*n*)	Results
INT0116[4] United States	Adjuvant, chemoradiation	Surgery alone (*n* = 275)	Median OS: 27 mo HR = 1.35, 95%CI: 1.09-1.66 (*P* = 0.005)
		Surgery + 5-FU/LV/RT (*n* = 281)	Median OS: 36 mo
ARTIST[6] South Korea	Adjuvant, chemoradiation	Surgery (D2 resection) + capecitabine/cisplatin (*n* = 228) Surgery (D2 resection) + capecitabine/cisplatin/RT (*n* = 230)	3-yr DFS: 74.2% 3-yr DFS: 78.2% (*P* = 0.08)
ARTIST Ⅱ[28] South Korea	Adjuvant, chemoradiation	Surgery (D2 resection, node-positive only) + capecitabine/cisplatin Surgery (D2 resection, node-positive only) + capecitabine/cisplatin/RT	In progress
ACTS-GC[9] Japan	Adjuvant, chemotherapy	Surgery alone (D2 resection) (*n* = 30) Surgery (D2 resection) + oral S-1 postop (*n* = 529)	5-yr OS: 61.1% 5-yr OS: 71.7 HR = 0.67, 95%CI: 0.54-0.83
CLASSIC[8] South Korea	Adjuvant, chemotherapy	Surgery alone (D2 resection) (*n* = 515) Surgery (D2 resection) + 8 cycles oral capecitabine + Ⅳ oxaliplatin (*n* = 520)	3-yr DFS: 59% (53%-64%) 3-yr DFS: 74% (69%-79%) HR = 0.56, 95%CI: 0.44-0.72 (*P* < 0.0001)
MAGIC[10] United Kingdom	Perioperative, chemotherapy	Surgery alone (*n* = 253) 3 cycles ECF preop + surgery + 3 cycles ECF postop (*n* = 250)	5-yr OS: 23% 5-yr OS: 36% HR = 0.75, 95%CI: 0.60-0.93 (*P* = 0.009)
FNCLCC/FFCD[11] France	Perioperative, chemotherapy	Surgery alone (*n* = 111) 5-FU/cisplatin preop + surgery + 5-FU/cisplatin postop (*n* = 113)	5-yr OS: 24% 5-yr OS: 38% HR = 0.69, 95%CI: 0.50-0.95 (*P* = 0.02)
POET[15] Germany	Neoadjuvant, chemoradiation	2.5 cycles PLF preop + surgery (*n* = 59) 2 cycles PLF then PLF/RT preop + surgery (*n* = 60)	3-yr OS: 27.7% 3-yr OS: 47.4% HR = 0.67, 95%CI: 0.41-1.07 (*P* = 0.07)
CRITICS[7] The Netherlands	Perioperative, combination	3 cycles ECX/EOX preop + surgery + capecitabine/cisplatin/RT postop 3 cycles ECX/EOX preop + surgery + 3 cycles ECX/EOX postop	In progress
TOPGEAR[12] Australia/New Zealand/ Europe/Canada	Perioperative, combination	3 cycles ECF preop + surgery + 3 cycles ECF postop 2 cycles ECF with 5-FU/RT preop + surgery + 3 cycles ECF postop	In progress
Neo-AEGIS[13] Ireland	Perioperative, combination	3 cycles ECF preop + surgery + 3 cycles ECF postop Carboplatin/paclitaxel/RT preop + surgery	In progress
MAGIC-B[22] United Kingdom	Perioperative, chemotherapy	3 cycles ECX preop + surgery + 3 cycles ECX postop 3 cycles ECX with lapatinib or bevacizumab preop + surgery + 3 cycles ECX with lapatinib or bevacizumab postop	In progress

OS: Overall survival; DFS: Disease-free survival; 5-FU: 5-Fluorouracil; LV: Leucovorin; RT: Radiotherapy; ECF: Epirubicin/cisplatin/5-FU; PLF: Cisplatin/fluorouracil/leucovorin; ECX: Epirubicin/cisplatin/capecitabine; EOX: Epirubicin/oxaliplatin/capecitabine.

these well-conducted studies have led to postoperative chemotherapy being adopted as the major adjuvant modality in Asian countries following surgery with D2 lymphadenectomy, the question of applicability of these studies to a Western population persist. Although most patients in the United States receive chemoradiation in the adjuvant setting, a perioperative treatment strategy emerged as an alternate standard of care following the publication of the MAGIC trial in 2006. The results showed that the 5-year survival for patients randomized to perioperative epirubicin, cisplatin, and fluorouracil (ECF) was significantly improved compared to those undergoing surgery alone (36% *vs* 23%, *P* = 0.009)[10]. Of note, 40% of these patients underwent D2 lymphadenectomy and 42% of patients were able to complete all 6 planned cycles of chemotherapy. Results of the MAGIC trial and the smaller French FNCLCC/FFCD trial[11] have solidified perioperative chemotherapy as an acceptable treatment strategy in the US. The use of upfront chemotherapy has several potential benefits including the early treatment of micrometastases, higher dose intensity of delivered chemotherapy prior to the morbidity of surgery, improved chance of complete pathologic response and curative resection, and the ability to assess biological response to a particular chemotherapy regimen that may affect the choice of postoperative regimen. However, with currently published studies, pathologic complete response remains dismally low with 0% in the MAGIC trial and 3% in the French FNCLCC/FFCD trial demonstrating pathologic T0 disease in their surgical specimens. Furthermore, patients in both studies received the same post-surgery chemotherapy regimens despite lack of a pathologic response in the majority of cases, and as such there is currently no data to indicate choosing a differing postoperative

regimen will be of benefit.

These issues and questions still remain to be addressed, though further evaluation and refinement of this treatment strategy continues in global prospective trials. In addition to the upcoming CRITICS trial which is investigating the addition of adjuvant chemoradiotherapy, the Australian Trial of Preoperative Therapy for Gastric and Esophagogastric Junction Adenocarcinoma (TOPGEAR) trial is also evaluating a perioperative treatment approach by assigning patients to either perioperative ECF or perioperative ECF with neoadjuvant chemoradiation (Table 1)[12]. The Irish ICORG 10-14 or Neo-AEGIS trial is randomizing patients with esophageal and gastroesophageal tumors to perioperative ECF or neoadjuvant concurrent weekly carboplatin and paclitaxel with radiotherapy as established to be superior to surgery alone in the Dutch CROSS trial[13,14]. A neoadjuvant chemoradiotherapy approach has been suggested to be beneficial when investigated in the German POET trial. This study aimed to establish if the addition of neoadjuvant chemoradiotherapy to neoadjuvant chemotherapy improves survival outcomes for patients with adenocarcinomas of the gastroesophageal junction[15]. The chemoradiotherapy group demonstrated an improvement in median survival compared to the chemotherapy alone group (3-year survival 47.4% *vs* 27.7%), though this did not meet their prespecified boundary for statistical significance (P = 0.07). Likely a large component for the lack of statistical significance was due to poor accrual, with the study only randomizing 126 patients out of its target accrual of 354 patients. However, benefit from the addition of chemoradiotherapy was also suggested by a higher rate of post-therapy pathologic complete response in the surgical specimens (15.6% *vs* 2.0% in the chemotherapy alone group). In a retrospective case series of 235 patients with cancers of the esophagus and gastroesophageal junction treated at MD Anderson, achievement of a complete pathologic response after chemoradiotherapy was a highly favorable prognostic factor[16]. Five-year overall survival was doubled when compared to the presence of post-therapy residual carcinoma (65% *vs* 29%, P = 0.003), and the authors conclude pathologic complete response may be an attractive surrogate for survival in future prospective trials. These upcoming trial results will be met with great interest as they may address ongoing questions regarding the benefit of chemoradiation and the optimal timing of perioperative chemotherapy or chemoradiation.

Since the publication of the Trastuzumab for Gastric Cancer (ToGA) trial, the use of the monoclonal antibody trastuzumab has become a standard option for patients with HER2-overexpressing gastric cancer. This study randomized patients to receive either chemotherapy alone (capecitabine plus cisplatin or fluorouracil plus cisplatin) or chemotherapy in combination with trastuzumab. The chemotherapy plus trastuzumab group demonstrated a median overall survival of 13.8 mo compared to 11.1 mo in the chemotherapy alone group (P = 0.0046)[17]. Currently there are several ongoing trials investigating the efficacy of targeting HER2-overexpressing tumors in the perioperative setting. Pertuzumab, a monoclonal antibody that recognizes a different epitope of HER2 than trastuzumab, has been shown to provide more comprehensive inhibition of HER2 signaling in preclinical xenograft models when combined with trastuzumab[18]. In addition to trials examining the combination in the metastatic setting such as the phase Ⅲ JACOB trial (NCT01774786)[19], a 3-arm, randomized phase Ⅱ trial is being conducted by the EORTC (European Organization for Research and Treatment of Cancer) to evaluate if neoadjuvant dual HER2-blockade with chemotherapy may lead to higher pathologic complete response rates than trastuzumab and chemotherapy or chemotherapy alone in resectable gastric cancer (NCT02205047)[20]. For patients who have undergone upfront resection, the phase Ⅱ TOXAG study is assessing the safety, tolerability, and early efficacy of adding trastuzumab to adjuvant capecitabine and oxaliplatin chemotherapy and chemoradiation (NCT01748773)[21]. The MAGIC-B trial is also investigating the addition of the HER2 tyrosine kinase inhibitor lapatinib to perioperative ECX (epirubicin, cisplatin, capecitabine) chemotherapy in the subset of patients whose tumors demonstrate HER2 overexpression[22].

Lastly, the future direction of gastric cancer trials will likely be supported by information gleaned from next-generation sequencing and bioinformatic technologies. Recently published data from The Cancer Genome Atlas (TCGA) project classifies gastric cancers into four major subtypes on the basis of molecular and genetic data: (1) Epstein-Barr virus (EBV)-associated tumors; (2) microsatellite unstable tumors; (3) genomically stable tumors; and (4) tumors with chromosomal instability[23]. Many tumors in these major subcategories were found to harbor targetable genetic mutations, providing a necessary research platform to enhance novel drug development efforts and guide the design of prospective perioperative or neoadjuvant chemotherapy protocols. For example, EBV-associated tumors demonstrated *PIK3CA* mutations, and amplification of *JAK2*, *ERBB2*, *CD274,* and *PDCD1LG2*, of which the latter two encode the immune checkpoint inhibitor targets PD-L1 and PD-L2, respectively. Tumors with chromosome instability demonstrated genomic amplification of several receptor tyrosine kinase signaling mediators, including the gene encoding the proangiogenesis ligand VEGFA. Currently, the MAGIC-B trial is randomizing patients to receive the perioperative regimen administered in the original MAGIC trial with or without the VEGFA inhibitory monoclonal antibody bevacizumab[22]. The availability of both pre-treatment biopsies and paired surgically-resected specimens will hopefully provide the necessary tissues to find predictive biomarkers that may identify patients who will derive the greatest benefit from the use of perioperative bevacizumab.

This will be especially critical in the event this study does not meet its prespecified endpoint for a molecularly unselected patient population in light of the negative results of the AVAGAST trial, which investigated the use of bevacizumab in an advanced unresectable gastric cancer population[24]. Further suggestion that disease biology may trump clinical factors such as nodal staging stems from longer term follow-up of the ARTIST trial[25]. With a median 7 years of follow-up no difference in OS was seen with the addition of chemoradiotherapy, paralleling the lack of difference in DFS in the intent to treat population. Patients with Lauren classification diffuse histology, however, also appeared not to demonstrate any benefit from the addition of chemoradiation in contrast to the patients with intestinal subtype tumors. In the TCGA dataset, cancers with Lauren diffuse histology predominantly were classified as genomically stable tumors that demonstrated infrequent targetable genetic alterations other than *RHOA* mutations and *CLDN18-ARHGAP6* or *ARHGAP26* fusions. These genes are implicated in cellular adhesion and motility and their dysregulation is consistent with the pathologic behavior of diffuse subtype tumors. Follow-up mechanistic studies to confirm that these alterations are driver mutations and drug development efforts that may inhibit these oncogenic events are desperately needed if perioperative or adjuvant treatment outcomes are to improve with this poor prognostic subset of patients.

At our institution, patients amenable to curative surgical resection are discussed in a multidisciplinary fashion and are either offered upfront surgery or perioperative chemotherapy based on currently published data. For those patients who have significant nodal disease on clinical staging or elect to proceed with perioperative chemotherapy, we utilize modifications of the ECF regimen such as EOX (epirubicin, oxaliplatin, capecitabine), which is deemed acceptable in the NCCN guidelines and proven to be non-inferior for locally-advanced disease in the REAL2 trial[26]. For elderly patients or patients with significant comorbidities who we feel would poorly tolerate a 3-drug regimen, we feel utilization of a fluoropyrimidine and a platinum-based drug alone is acceptable given the positive survival outcome with this approach based on the French FNCLCC/FFCD perioperative chemotherapy trial. Our preferred regimen in this situation would be modified infusional FOLFOX6 (fluorouracil, leucovorin, oxaliplatin) given its close approximation to the FLO regimen. This regimen demonstrated a survival benefit in comparison to infusional 5-FU and cisplatin on subset analysis of patients older than 65 years of age in a phase Ⅲ trial for advanced gastric cancer conducted by the German AIO study group[27]. In patients who have upfront surgery, D2 lymph node dissection is routinely performed at our institution. For patients who do not exhibit pathologic lymph node involvement we would prescribe 6 mo of modified FOLFOX6 or capecitabine and oxaliplatin as per the design of the phase Ⅲ CLASSIC trial. For patients who have pathologically-involved nodes within the D2 lymph node dissection specimen, we would also incorporate adjuvant chemoradiation, as this is suggested to be of benefit in that subgroup of patients within the ARTIST trial.

In summary, ongoing prospective randomized trials may help better refine clinical factors to best determine timing of chemotherapy and radiation in relation to surgery for gastric cancer. Further molecular characterization of gastric cancers will likely help identify additional targets to evaluate in prospective biomarker-driven trials to define subgroups of patients who will benefit from targeted therapies based on the genetic makeup of their tumors. Better understanding of disease biology and predictive biomarkers will help refine molecular factors to optimize radiation timing, choice of chemotherapy and/or molecularly targeted therapy and the overall possibility of long-term cure for our patients.

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