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TOPIC HIGHLIGHT

2016 Gastric Cancer: Global view

Advanced gastric cancer: Current treatment landscape and future perspectives

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Abstract

Gastric cancer currently ranks fourth in cancer-related mortality worldwide. In the western world, it is most often diagnosed at an advanced stage, after becoming metastatic at distant sites. Patients with advanced disease (locally advanced or metastatic) have a somber prognosis, with a median overall survival of 10-12 mo, and palliative chemotherapy is the mainstay of treatment. In recent years, novel approaches using inhibition of human epidermal growth factor receptor 2 (HER2) have demonstrated significant improvements in progression-free and overall survival, compared with chemotherapy alone, in first-line treatment of patients with overexpression of HER2. In addition, both second-line chemotherapy and treatment with the vascular endothelial growth factor receptor-inhibitor ramucirumab demonstrated significant benefits in terms of overall survival, compared with best supportive care, in randomized studies. Moreover, ramucirumab in combination with chemotherapy demonstrated further significant benefits in terms of progression-free and overall survival, compared with chemotherapy alone, in second-line treatment for patients with metastatic gastric cancer. A recently published molecular classification of gastric cancer is expected to improve patient stratification and selection for clinical trials and provide a roadmap for future drug development. Nevertheless, despite these developments the prognosis of patients with advanced gastric cancer remains poor. In this review we discuss current standards of care and outline major topics of drug development in gastric cancer.

Key words: Gastric cancer; Phase Ⅲ; Clinical trials; Chemotherapy; Targeted therapy; Perspectives

Core tip: With the integration of both ramucirumab and transtuzumab, treatment options for advanced gastric cancer have increased significantly in recent years. Therefore, a reconsideration of treatment options and results for gastric cancer is necessary. This paper discusses results of phase Ⅲ trials for both standard

chemotherapy and targeted treatments in metastatic gastric cancer. Furthermore, results of selected early-phase clinical trials, for example on immune checkpoint inhibitors, are discussed.

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INTRODUCTION

Gastric cancer (GC) currently ranks fourth in cancer incidence worldwide and is the most common type of cancer among Japanese men[1,2]. In the last few decades, epidemiological changes in the anatomical distribution have converged with a decline in the incidence of distal (non-cardia) GC, notably in developed countries, and an increase in the incidence of adenocarcinoma of the proximal stomach. The origins of these changes are probably multifactorial and linked to many risk factors, including *Helicobacter pylori* (*H. pylori*) infection incidence, dietary factors, and obesity[3].

GC has a routine appearance of adenocarcinoma in 90% of cases and is divided into intestinal and diffuse types according to the Lauren classification[4]. The intestinal type is associated with *H. pylori* infection and dysplastic changes, whereas the diffuse type is characterized by sheets of cells without gland formation and occasionally signet ring cells[5]. Diffuse-type GC can also be associated with *H. pylori* infection, but not with intestinal metaplasia, as a precursor and is known to have a poorer prognosis.

Several attempts have been made to develop a molecular classification of GC based on genomic alterations. In 2012, Deng *et al*[6] identified 5 subgroups of GC defined by signature genomic alterations: *FGFR-2* (9% of tumors), *KRAS* (9%), *EGFR* (8%), *ERBB-2* (7%) and *MET* (4%). Interestingly, about 37% of GC had genomic alterations in the receptor of the tyrosine kinase RAS.

Recently, the Cancer Genome Atlas Research Network identified four molecular subtypes of GC by analyzing data from 295 primary tumors in six molecular platforms: (1) EBV-infected tumors (9%); (2) microsatellite unstable tumors (22%); (3) genomically stable tumors (20%); and (4) chromosomally unstable tumors (50%). The researchers confirmed that every subtype has distinct genomic features. For example, EBV-infected tumors frequently contain mutations in the *PIK3CA* gene (80% *vs* 3%-42% in the other subtypes), amplifications of the *JAK2* gene, and elevated expression of PD-L1. In this context, PIK3CA inhibitors and PD-L1 antagonists merit further investigation[7].

Tumors classified as chromosomally unstable are predominantly localized at the cardia or the gastrointestinal junction. This subtype is enriched for TP53 mutations and RTK-RAS activation. The microsatellite unstable subtype accounts for 22% of GC cases and is significantly associated with *MLH1* silencing and genomic hypermutation. Moreover, the vascular endothelial growth factor A (*VEGFA*) gene is amplified in this subtype, suggesting that it may respond to anti-angiogenic therapy. Finally, the fourth subtype, the "genomically stable", is histologically associated with diffuse-type cancer, as well as *CDH1* and *RHOA* mutations.

Despite these major advances in our understanding of the biology of GC, the median survival rate of patients with advanced GC is still less than 12 mo, and the development of personalized treatment strategies is the principal challenge. The primary aim of this review is to summarize data from recent phase Ⅲ clinical trials on both chemotherapy and targeted therapies in advanced GC and to discuss their impact on current clinical practice. Furthermore, we discuss recent phase Ⅱ trials of special interest.

FIRST-LINE TREATMENT

Before any systemic treatment for GC is initiated, the status of the human epidermal growth factor receptor 2 (HER2) is determined. Treatment options for the approximately 20% of patients with HER2-positive GC are discussed in the paragraph on targeted therapies. The following section discusses the treatment options for patients with HER2-negative GC.

Chemotherapy is the standard first-line treatment for patients with advanced GC and a good performance status. Available data from randomized clinical trials clearly demonstrate a statistically significant advantage of palliative chemotherapy, compared with best supportive care (BSC), in terms of palliation of symptoms and improvement of survival for patients with advanced GC[8].

In contrast, the benefit of combination - compared with single-agent - chemotherapy is much smaller: A meta-analysis published in 2010 indicated a modest survival benefit (approximately 1.5 mo) for combination chemotherapy over single-agent chemotherapy. Of note, the combination chemotherapy regimens included in this analysis were mostly "older" regimens (combination of 5-FU/anthracyclines) and therefore might not have had optimal efficacy[9]. For example, in the Japanese phase Ⅲ "SPIRITS" trial, 305 patients were randomly assigned to S-1 (40-60 mg/m^2 twice-daily on days 1-21 and cisplatin 60 mg/m^2 on day 8 every 5 wk) or S-1 alone (40-60 mg/m^2 twice-daily on days 1-28 every 6 wk). Both progression-free survival (PFS) (6 *vs* 4 mo) and overall survival (OS) (13 mo *vs* 11 mo, HR = 0.77; 95%CI: 0.61-0.98) were significantly improved by the combination regimen[10]. However, the Japanese phase Ⅲ JCOG 9912 trial,

which compared a continuous infusion of 5-FU (800 mg/m^2 per day on days 1-5 every 4 wk) with the combination of intravenous irinotecan (70 mg/m^2 per day on days 1 and 15) and cisplatin (80 mg/m^2 on day 1) every 4 wk and with oral S-1 alone (40 mg/m^2 twice-daily on days 1-28 every 6 wk), did not confirm the superiority of this combination. While S-1 alone was non-inferior to 5-FU, patients receiving the combination of irinotecan plus cisplatin did not have a survival improvement as compared to the treatment with S-1 alone[11].

More than 50 years since its development, infusional 5-FU remains the backbone of most combination chemotherapy regimens in advanced GC. However, in recent years, two oral fluoropyrimidines - capecitabine and S-1 - were shown to be at least equal in efficacy to 5-FU. Capecitabine was shown to be non-inferior in two phase Ⅲ trials.

Kang *et al*[12] conducted a randomized phase Ⅲ trial comparing cisplatin (80 mg/m^2 on day 1) plus capecitabine (1000 mg/m^2 twice-daily on days 1-14) in a 21-d cycle to cisplatin plus 5-FU (800 mg/m^2 per day as a continuous infusion on days 1-5). The trial met its primary endpoint and demonstrated the non-inferiority of cisplatin plus capecitabine, compared with cisplatin plus 5-FU. Although patients receiving capecitabine had a better response rate (RR) than those receiving 5-FU (41% *vs* 29%), PFS, RRs, and toxicity profiles were similar.

The oral fluoropyrimidine S-1 is a widely accepted treatment option, as a single agent or in combination chemotherapy, for advanced GC in Japan. S-1 is a combination of tegafur with two enzyme inhibitors: 5-chloro-2,4-dihydroxypyridine (CDHP), a reversible inhibitor of dihydropyrimidine dehydrogenase, and potassium oxonate (Oxo). CDHP enhances the anticancer activity of tegafur by increasing its half-life, and Oxo reduces the gastrointestinal toxicity of tegafur. Because CYP2A6, which converts tegafur to 5-FU, is highly active in Caucasians, separate studies in Caucasian populations were necessary before registration of S-1 in Europe and the United States.

The pivotal trial, which evaluated S-1 in a Western population, is the randomized phase Ⅲ "FLAGS" trial. This trial compared a regimen of cisplatin (75 mg/m^2 on day 1) plus S-1 (25 mg/m^2 twice-daily on days 1-21) with cisplatin (100 mg/m^2 on day 1) plus 5-FU (1000 mg/m^2 per day for 5 d) over a 28-d cycle. Although the comparison of the two fluoropyrimidines in this trial is limited by the different doses of cisplatin, the cisplatin/S-1 combination was as effective as the cisplatin/5-FU combination (OS 8.6 mo *vs* 7.9 mo for S-1 *vs* 5-FU). Importantly, patients receiving 5-FU experienced significantly more side effects than did patients treated with S-1: rates of grade 3/4 neutropenia were 32.3% *vs* 63.6%, rates of complicated neutropenia were 5.0% *vs* 14.4%, and rates of stomatitis were 1.3% *vs* 13.6%[13].

Platinum derivatives - alternatives to cisplatin

Several recent studies explored whether oxaliplatin can replace cisplatin for GC. Cisplatin-free regimens represent a more convenient therapeutic approach, which avoids the necessary hyperhydration and decreases the risk of renal and ototoxicity associated with cisplatin, but at the price of increased neurotoxicity. Two phase Ⅲ trials demonstrated a non-inferiority of oxaliplatin, compared with cisplatin, in the treatment of advanced GC, and a third trial observed comparable results.

In a randomized phase Ⅲ study conducted in Japan, the standard SP regimen (S-1 40 mg/m^2 twice-daily on days 1-21 and cisplatin 60 mg/m^2 on day 8 for 5 wk) was compared to SOX (S-1 40 mg/m^2 twice-daily on days 1-14 and oxaliplatin 100 mg/m^2 on day 1 for 3 wk). A total of 685 patients participated in the study, which reached its primary endpoint by showing a non-inferiority of SOX in PFS. As expected, serious adverse events occurred more often in the patients treated with SP (29.3% *vs* 37.9%). Furthermore, the rate of treatment-related deaths was twice as high in the patients treated with SP (2.4% *vs* 1.2%)[14].

Al-Batran *et al*[15] compared biweekly infusional fluorouracil and leucovorin, either in combination with oxaliplatin (FLO) or cisplatin (FLP). This trial confirmed the better tolerability of oxaliplatin. While median OS (10.7 mo *vs* 8.8 mo) showed no significant differences between the two groups, a trend towards better PFS was observed in the patients treated with FLO. However, as expected, the rates of peripheral neuropathy were significantly higher in the patients treated with FLO (63% *vs* 22%). Interestingly, a subgroup analysis of patients older than 65 years indicated that FLO exhibited a significantly superior RR and OS (13.9 mo *vs* 7.2 mo), forming the basis for the widespread use of this combination in elderly patients.

In the landmark REAL-2 trial, patients were randomized into four groups [epirubicin, oxaliplatin and capecitabine (EOX); epirubicin, oxaliplatin and 5-FU (EOF); epirubicin, cisplatin and 5-FU (ECF); and epirubicin, cisplatin and capecitabine (ECX)] in a two-by-two factorial design. The results of this trial confirmed that oxaliplatin was non-inferior to cisplatin in combination with epirubicin and either 5-FU or capecitabine. Furthermore, apart from the expected differences in toxicities between the two agents, fewer thromboembolic events (7.6% *vs* 15%) were observed in the patients treated with oxaliplatin, compared with cisplatin[16].

Irinotecan is another alternative to platinum derivatives that has been evaluated in several randomized trials. In 2008, Dank *et al*[17] published the results of a phase Ⅲ trial comparing irinotecan/5-FU to cisplatin/5-FU. Although irinotecan/5-FU did not show an improvement in time-to-progression, the combination was better tolerated, as a lower rate of patients discontinued treatment due to toxicity (10%

vs 22%). This observation has been confirmed in other randomized phase Ⅱ trials[18].

For these reasons both oxaliplatin and irinotecan are adequate substitutes for cisplatin in combination with fluoropyrimidines.

What is the role of taxanes in GC?

In the V-325 study, published by Van Cutsem *et al*[19], 445 patients were treated with cisplatin/5-FU with or without docetaxel as a first-line therapy. Although the RR (37% *vs* 25%), time-to-progression (5.6 mo *vs* 3.7 mo) and 2-year OS rate (18% *vs* 9%) were improved by the addition of docetaxel, the absolute benefit in terms of survival was less than 4 wk, and was counterbalanced by a significant increase in grade 3-4 adverse events.

In view of the significant toxicities associated with this regimen, especially in the elderly population, several "modified DCF" regimens have been developed. One example is FLOT (docetaxel 50 mg/m^2, infusional 5-FU 2600 mg/m^2, leucovorin 200 mg/m^2, oxaliplatin 85 mg/m^2) every 2 wk. A randomized phase Ⅱ study (n = 143) by Al-Batran *et al*[15] specifically addressed the question whether the addition of docetaxel to the combination of FLO is feasible in fit patients older than 65 years. Significantly more grade 1-4 adverse events such as neutropenia, alopecia and diarrhea were observed in the FLOT group, but there were no differences between the two groups in terms of serious adverse events, discontinuation for toxicity or toxicity-related deaths[20]. Thus, the FLOT regimen was feasible in the selected fit elderly patients. However, quality-of-life was decreased in the patients treated with FLOT, compared with the patients treated with FLO. Although the FLOT group demonstrated an improved RR (49% *vs* 28%) and a trend towards a better PFS (9.0 mo *vs* 7.1 mo, P = 0.79), there was no significant benefit in median OS (17.3 mo *vs* 14.5 mo, P = 0.39). For this reason, the authors concluded that "this study confirms the role of the doublet combination FLO as a tolerable and active treatment option for older adult patients with metastatic gastric cancer". Interestingly, subgroup analyses indicated that patients with locally advanced (non-metastatic) tumors and patients younger than 70 years benefited more from FLOT than FLO. However, this result needs prospective confirmation in further trials.

The phase Ⅲ "START" trial, which compared S1/docetaxel (S-1 at 80-120 mg/d on days 1-14 of a 21-d cycle with docetaxel 40 mg/m^2 every 21 d) *vs* S-1 alone (days 1-28 of a 42-d cycle) in 635 Japanese and Korean patients, showed a significant benefit in terms of PFS (5.3 mo *vs* 4.2 mo) and OS (12.5 *vs* 10.8 mo) in favor of the combination. While the RR in the combination group was 38.8% (26.8% in the single-agent group), 58% of the patients presented at least one grade 3 toxicity in the combination group[21].

Another recent randomized phase Ⅱ trial addressed whether 5-FU can be replaced by capecitabine in a three-drug regimen including docetaxel and oxaliplatin[22]. The patients treated with the combination of docetaxel, oxaliplatin and 5-FU (TEF) had a significantly better OS (14.6 mo *vs* 11.3 mo), PRS (7.6 mo *vs* 5.5 mo) and RR (46.6% *vs* 25.6%) compared with the docetaxel, oxaliplatin and capecitabine group (TEX). Furthermore, the TEF regimen was associated with a better toxicity profile.

Is triplet superior to doublet chemotherapy in advanced GC?

When discussing triplet *vs* doublet chemotherapy regimens, we need to address the regimens, the outcomes and the patients.

Regarding the regimens: a superiority in terms of survival for 5-FU, an anthracycline and cisplatin (ECF) over the same regimens without the anthracycline or cisplatin was demonstrated in our meta-analyses published in 2006 and 2010[8,9]. However, those trials were conducted more than 10 years ago, when second-line therapy was not generally available. At present, second-line treatment is routinely administered: up to 50% of patients in European studies[23,24] and 80% of patients in Asian trials are treated with second-line chemotherapy. The recently published phase Ⅲ trial by Guimbaud *et al*[23], which compared the three-drug regimen of ECX in first line to FOLFIRI *vs* the reverse sequence, did not observe a survival benefit for patients treated with ECX, compared with FOLFIRI. Furthermore, there were no differences in quality-of-life between study arms, and FOLFIRI was better tolerated. Other triplet chemotherapy regimens, such as DCF and FLOT, which were discussed previously, have not demonstrated convincing benefits in terms of survival, but instead increased toxicity rates. Therefore, these regimens are not generally accepted as standards of care. Results for other outcomes, such as quality-of-life, were contradictory for different regimens: whereas treatment with DCF resulted in a significant delay in the deterioration of quality-of-life, compared with CF, a higher rate of patients treated with FLOT (47.5%), as compared to FLO (20.5%) experienced a > 10 point deterioration of quality-of-life global health scores after 8 wk of treatment[24,25].

The question whether subgroups, such as patients with locally advanced or limited metastatic disease, may have a benefit from these combinations, is currently under investigation.

Second-line and beyond: As much as for first-line treatment, the aim of second and later lines of treatment in advanced GC is to increase survival and control the clinical symptoms of the disease, with as little toxicity as possible and no negative impact on quality-of-life. Several phase Ⅲ clinical trials and a recent meta-analysis demonstrated a modest but significant survival benefit of chemotherapy in this

setting for patients with good performance status[26,27]. Single-agent therapy with irinotecan or taxanes have been shown to be effective. Therefore, the choice of the regimen should be guided by the previous lines of therapy and eventual residual toxicities (*e.g.*, neurotoxicity).

In a German (AIO) phase Ⅲ study containing patients with advanced GC and a performance status of 0-2 who had failed first-line treatment, irinotecan (250 mg/m^2 on day 1 of a 21-d cycle, to be increased to 350 mg/m^2 based on tolerance) showed a significant benefit in terms of OS (4 mo *vs* 2.4 mo, P = 0.012) and RR (44% *vs* 5%), compared with BSC. Although the study was closed due to poor accrual after inclusion of 40 patients, a significant improvement in tumor-related symptoms was noted in 50% of the patients treated with irinotecan, compared with 7% of the patients treated with BSC[28].

The survival benefit of second-line or third-line chemotherapy was confirmed in a Korean phase Ⅲ trial in patients with advanced GC and a good performance status after failure of fluoropyrimidines and platinum. In this trial (n = 202), patients were randomized in a 2:1 ratio to receive either chemotherapy (docetaxel or irinotecan) or BSC. Median OS was improved significantly in patients treated with chemotherapy (5.3 mo *vs* 3.8 mo with BSC). The efficacies of irinotecan and docetaxel were comparable[26].

Finally, the recently published phase Ⅲ trial "COUGAR-02" confirmed that docetaxel significantly increased OS in patients with a performance status of 0-2 after progression to previous platinum/fluopyrimidine chemotherapy. In this trial, 168 patients were treated with active symptom control with or without docetaxel (75 mg/m^2 in a 21-d cycle)[29]. Although only 23% of the patients received 6 cycles of docetaxel, and only 7% presented an objective response to docetaxel, a modest but significant benefit in OS (5.2 mo *vs* 3.6 mo, P = 0.01) was observed. Moreover, despite the fact that 21% of patients treated with docetaxel presented grade 4 toxicities, significantly less pain and a trend for less dysphagia and nausea were reported. Global quality-of-life scores were similar between the two groups.

With the publication of this well-conducted, large, randomized trial, the benefit of docetaxel as a second-line treatment, in terms of improvement in tumor-related symptoms and survival, has clearly been established. For this reason, all patients in good performance status should be offered second-line chemotherapy.

The activities of weekly paclitaxel (80 mg/m^2 on days 1, 8, and 15 every 4 wk) and irinotecan (150 mg/m^2 on days 1 and 15 in 28-d cycles) as second-line treatments were determined in a recent Japanese randomized phase Ⅲ study in 223 patients with advanced GC that had progressed after fluoropyrimidine plus platinum chemotherapy[30]. Irinotecan was not superior to taxane monotherapy in terms of median PFS (2.3 mo *vs* 3.6 mo with paclitaxel, P < 0.33) and OS (8.4 mo *vs* 9.5 mo, P = 0.38), and treatment-related toxicity was comparable in both arms. Interestingly, third-line chemotherapy was administered in 97 patients (89.8%) after paclitaxel treatment and in 80 patients (72.1%) after irinotecan treatment (P = 0.001). Thus, we agree with the author's conclusion that both regimens are valid choices for second-line treatment.

Is combination better than single-agent chemotherapy in second-line treatment?

Recently, a Japanese phase Ⅲ trial conducted by the Tokyo Cooperative Oncology Group evaluated single-agent (irinotecan) *vs* combination (irinotecan/cisplatin) chemotherapy as a second-line treatment in patients refractory to S-1-based chemotherapy[31]. Interestingly, the combination of cisplatin/irinotecan demonstrated a PFS benefit without an OS improvement. Thus, according to this trial, there is no evidence for a benefit of combination *vs* single-agent chemotherapy in second-line treatment.

TARGETED THERAPIES

Approximately 20% of GC are characterized by overexpression or/and amplification of the *HER2* gene. HER2 overexpression is more common in intestinal GC than diffuse GC, and more common in GEJ GC than distal GC. Currently, the prognostic value of HER2 in GC is controversial[32]. Combining chemotherapy with trastuzumab results in a significant improvement in survival in HER2-positive GC.

In the international phase Ⅲ "ToGA" trial, 594 previously untreated patients with advanced HER2-positive (either IHC 3+ or IHC 2+ and FISH+) GC were randomized to chemotherapy (cisplatin 80 mg/m^2 on day 1 and either capecitabine 1000 mg/m^2 twice-daily on days 1-14 every 3 wk or 5-FU 800 mg/m^2 per day continuously for 3 wk) with or without trastuzumab (8 mg/kg loading dose, followed by 6 mg/kg every 3 wk). Compared with chemotherapy alone, the combination of chemotherapy plus trastuzumab resulted in a statistically significant and clinically relevant improvement in RR and OS. The combination did not raise any new safety concerns; notably, the incidence of cardiotoxicity was equal in the 2 arms[33]. Recently, an HRQol analysis showed that the time to deterioration of HRQoL was prolonged in the combination arm[33,34].

Up to now, this is the only prospective randomized phase Ⅲ trial exploring trastuzumab in combination with chemotherapy in GC, although phase Ⅱ data with XELOX and in combination with S-1 and cisplatin have shown interesting clinical activities[35,36]. Therefore, the benefit of trastuzumab in combination with other chemotherapeutic regimens needs further investigation. A non-interventional register studying

the addition of trastuzumab to different first-line chemotherapies found comparable results in terms of median PFS (6.8 mo) for other chemotherapy-trastuzumab combinations, although the final results are pending. Importantly, pharmacokinetic data suggested that the above-mentioned dose of trastuzumab might not be optimal in combination with capecitabine and cisplatin. Therefore, a currently ongoing phase Ⅲ trial named HELOISE (NCT 01450696) is exploring two different doses of trastuzumab (8 mg/kg loading dose, followed by 6 mg/kg or 10 mg/kg every 3 wk) in combination with cisplatin (80 mg/m^2 on day 1) and capecitabine (800 mg/m^2 twice-daily on days 1-14). Furthermore, the clinical value of the continuation of trastuzumab beyond first progression - a strategy with proven value in HER2-positive breast cancer - needs to be defined[37].

Second-line treatment for HER2-positive GC

Lapatinib is a small molecule TKI that binds reversibly to EGFR-1 and EGFR-2 (HER2) and blocks the activation of downstream second messengers. Lapatinib is approved for second-line treatment of HER2-positive advanced breast cancer[38].

The phase Ⅲ clinical trial, "TyTAN", evaluated the efficacy of lapatinib in combination with paclitaxel in the second-line setting in Asian patients with HER2-positive advanced GC. A total of 261 HER2-positive (by FISH) patients were randomized to lapatinib plus chemotherapy *vs* chemotherapy alone[39]. According to the results of this trial, the overall RR was significantly higher in patients treated with lapatinib, but median PFS and OS rates were unchanged. However, in subgroup analyses, patients with an IHC score of 3+ and patients younger than 60 years benefited from the addition of lapatinib to paclitaxel.

The limited efficacy of lapatinib was confirmed in the first-line setting for GC in the phase Ⅲ "LOGIC" trial, which investigated the activity of lapatinib in combination with capecitabine/oxaliplatin and demonstrated a non-significant prolongation of OS[40].

Future perspectives for HER2-positive GC

Currently, pertuzumab, a monoclonal antibody that binds to the dimerization domain of the HER2/HER3 receptors, is being investigated in GC. In HER2-positive metastatic breast cancer, a recently published phase Ⅲ trial comparing docetaxel in combination with trastuzumab and either pertuzumab or placebo demonstrated an OS benefit of 16 mo (!) for patients treated with pertuzumab, without significant differences in toxicity, especially cardiac toxicity[41]. Preclinical data indicate that targeting the dimerization domain of HER2/HER3 has antitumoral activity in GC as well, although the serum clearance of the antibody seems to be higher in this setting[42]. On the basis of a randomized phase Ⅱ a trial (n = 30) exploring two different dose schedules of pertuzumab (840 mg for cycle 1 and 420 mg for cycles 2-6 *vs* 840 mg in cycles 1-6) in combination with chemotherapy, the dose of 840 mg pertuzumab was selected for the ongoing international randomized phase Ⅲ "JACOB" trial (NCT 01774786). This trial is exploring the role of pertuzumab, in combination with trastuzumab and chemotherapy, in advanced GC. Of note, RRs for patients treated with pertuzumab, in combination with trastuzumab and chemotherapy, were 86% and 55% for the two doses in the above-mentioned phase Ⅱ a trial[43].

In analogy to the "EMILIA" trial (a randomized phase Ⅲ trial comparing T-DM1 (trastuzumab emtansine, an antibody-drug conjugate linking trastuzumab to the microtubule inhibitor DM1, a maytansine derivative) to the combination of and capecitabine) in pretreated, HER2-positive breast cancer, the ongoing phase Ⅲ GATSBY trial (NCT01641939) is evaluating T-DM1 *vs* a taxane (docetaxel or paclitaxel) in previously treated metastatic HER2-positive GC.

Targeting EGFR1 in advanced GC

Despite the high (approximately 50%) rate of EGFR expression in GC, targeting EGFR has not proven to be a successful strategy, at least in unselected GC patients. The so-called "EXPAND" trial, which evaluated the addition of cetuximab to first-line chemotherapy with capecitabine or 5-FU in patients with advanced GC, failed to improve PFS or OS, independent of the expression of EGFR[44].

The ineffectiveness of targeting EGFR in a non-selected population of patients with GC was confirmed in the phase Ⅲ REAL 3 trial. In this trial, panitumumab or placebo was added to first-line chemotherapy with EOX[45]. The study was terminated prematurely due to a significantly worse median OS (8.8 mo *vs* 11.3 mo) in the patients treated with EOX and panitumumab. Predictive biomarkers for the efficacy of panitumumab (mutations in KRAS, BRAF, PIK3CA or loss of PTEN expression) could not be identified.

Nevertheless, in patients with advanced NSCLC, high EGFR expression (IHC score > 200) was found to be a predictor of survival for patients treated with the combination of first-line chemotherapy plus cetuximab[46]. Currently, data for patients with GC and high tumor EGFR expression is pending. However, a small randomized phase Ⅱ trial demonstrated that in a subgroup of patients with IHC 2+/3+ EGFR metastatic GC, adding the EGFR monoclonal antibody nimotuzumab to irinotecan might improve the antitumoral activity[47]. Based on these results, a randomized phase Ⅲ trial (ENRICH trial, NCT 01813253) investigating this combination as a second-line regimen in EGFR-overexpressing GC is ongoing in Japan and South Korea.

Role of angiogenesis

Angiogenesis has become an important target in the

treatment of several solid tumors. In GC, increased VEGF-A expression has been correlated with a poor prognosis. Therefore, several studies tried to explore the role of anti-angiogenic therapies in this context[48,49].

Results from the international phase Ⅲ "AVAGAST" study, which assessed the benefit of adding bevacizumab, a monoclonal antibody targeting VEGF, to a cisplatin/capecitabine combination chemotherapy regimen[50], showed only a modest improvement in PFS (6.7 mo *vs* 5.3 mo), without an OS benefit (12.1 mo *vs* 10.1 mo). Nevertheless, in an unplanned subgroup analysis, OS was significantly improved in non-Asian patients, in patients with the diffuse subtype, and in patients with distal GC. Furthermore, recent data demonstrated a clear benefit of targeting angiogenesis in the second-line setting. In contrast to bevacizumab, ramucirumab is an Ig1 monoclonal antibody and antagonist of the VEGF receptor 2, blocking the binding of VEGF A, C and D. The phase Ⅲ "REGARD" trial evaluated ramucirumab monotherapy (8 mg/kg every 15 d) *vs* placebo in 355 patients[51] after failure of first-line chemotherapy. Ramucirumab increased median OS by 37% (5.2 mo *vs* 3.8 mo, HR = 0.776, 95%CI: 0.603-0.998) as well as PFS (2.1 mo *vs* 1.3 mo, HR = 0.483, 95%CI: 0.376-0.620). Importantly, ramucirumab was well-tolerated, with hypertension (8% with grade ≥ 3) being the most important side effect. Rates of grade > 3 arterial and venous thromboembolism were 1% *vs* 0% and 1% *vs* 4%, respectively, in the patient groups[43].

The activity of ramucirumab, in combination with chemotherapy, in second-line treatment of GC was confirmed by the phase Ⅲ "RAINBOW" trial. In this study, 665 patients were randomized to receive paclitaxel (80 mg/m^2 on days 1, 8 and 15), with or without ramucirumab (8 mg/kg every 15 d). Patients treated with ramucirumab had significant improvements in median OS (9.6 mo *vs* 7.4 mo, HR = 0.807, 95%CI: 0.678-0.962), PFS (4.4 mo *vs* 2.9 mo, HR = 0.635, 95%CI: 0.539-0.752, $P < 0.0001$) and RR (28% *vs* 54%, $P = 0.0001$)[52].

These proof-of concept trials for the inhibition of angiogenesis in metastatic GC were confirmed by another phase Ⅲ trial evaluating apatinib, the oral VEGR-2 tyrosine kinase inhibitor, after failure of second-line chemotherapy[53]. In this study, 293 heavily pretreated Chinese patients were randomized to apatinib (850 mg/d) *vs* placebo. Although median PFS (as assessed by the investigators) was 2.6 mo in the experimental group and 1.8 mo in the placebo group (HR = 0.44), median OS was 6.5 and 4.7 mo, respectively (HR = 0.71). However, objective RRs were 3% *vs* 0%. Furthermore, 9% of the patients treated with apatinib developed a hand-foot syndrome of grade 3/4.

These data confirm the importance of angiogenesis as a pathway and support further development of anti-angiogenic treatments for GC.

FUTURE PERSPECTIVES

For the moment, several novel targets are under investigation (Table 1). For example, the PI3K/AKT/mTOR pathway plays a crucial role in multiple cellular functions including proliferation, angiogenesis and cell growth. The results of a phase Ⅲ trial, GRANITE-1, were recently released. The study compared everolimus, a mTOR inhibitor, to placebo in pretreated advanced GC and did not show an improvement in OS (5.4 mo *vs* 4.3 mo)[54].

Hepatocyte growth factor (HGF), as well as its receptor mesenchymal epithelial transition factor (MET), play key roles in GC[55,56]. Rilotumumab, a fully human IgG2 monoclonal antibody against HGF, demonstrated promising preliminary results in combination with EOX in a randomized phase Ⅱ study[57]. Furthermore, recent data showed that MET-positive patients respond better to the combination of rilotumumab and ECX than do MET-negative patients[58]. Due to the increased toxicity and treatment-related deaths in the combination group in RILOMET-1, all clinical trials investigating the role of rilotumumab in GC - including the phase Ⅲ RILOMET-1 (with ECX) and RILOMET-2 (with cisplatin and capecitabine) trials - have been terminated. Results of the RILOMET-1 trial have been presented at the ASCO 2015 Annual Meeting; both OS and PFS were statistically worse in the rilotumumab arm, independent of MET expression[59]. In addition, preliminary results of a phase Ⅱ trial evaluating onartuzumab, another monoclonal antibody designed specifically to target the MET receptor, failed to show a PFS benefit when added to mFOLFOX in a first-line setting in patients with HER2-negative metastatic GC[60].

Cancer immunotherapy has seen major advances in the last 10 years. Checkpoint inhibitors have become the cornerstone in the treatment of melanoma and - compared with docetaxel - demonstrated a significant improvement in OS in a randomized phase Ⅲ trial in NSCLC[61]. Early results of "KEYNOTE-012" a phase Ib trial evaluating pembrolizumab, a humanized anti-PD-1 monoclonal antibody, were initially presented at the 2015 ASCO Gastrointestinal Cancers Symposium, and update data was reported at the ASCO 2015 Annual Meeting. In this trial, 39 chemotherapy-refractory patients with advanced GC, good PS and either distinctive stromal or ≥ 1% of tumor nest cell PD-L1-staining were treated with pembrolizumab (10 mg/kg every 2 wk) until complete response, disease progression, or unacceptable toxicity[62]. With a 22.2% objective RR, as assessed by central review after a median follow-up of 8.8 mo, pembrolizumab demonstrated promising anticancer activity in this heavily pretreated population. Thirteen patients (33%) remain on therapy. A total of 53.1% of patients with measurable disease displayed some degree of tumor shrinkage from baseline. At 6 mo, 69% of patients

Table 1 Novel targets are investigation

Name of trial	Regimen		No. of patients	Primary endpoint	NCT number	Country
GO2 - Alternative chemotherapy for frail or elderly patients with advanced gastric or oesophageal cancer	Best supportive care: Participants will be treated according to local policy. OxCap 100%: oxaliplatin 130 mg/m^2 on day 1, capecitabine 625 mg/m^2 twice-daily for 21 d. OxCap 80%: oxaliplatin 104 mg/m^2 on day 1, capecitabine 500 mg/m^2 twice-daily for 21 d. OxCap 60%: oxaliplatin 78 mg/m^2 on day 1, capecitabine 375 mg/m^2 twice-daily for 21 d.	http://www.isrctn.com/ISRCTN44687907?q=gastric cancer phase III&filters=&sort=&offset=4&totalResults=29&page=1&pageSize=10&searchType=basic-search	530	Chemotherapy intensity comparison: Progression-free survival Chemotherapy *vs* best supportive care comparison: Overall survival		United Kingdom
Efficacy and Safety Study of Olaparib in Combination With Paclitaxel to Treat Advanced Gastric Cancer	Olaparib 100 mg tablets orally twice-daily throughout each cycle (28 d); once paclitaxel dosing is stopped, the olaparib dose will be 300 mg twice-daily. Paclitaxel 80 mg/m^2 *iv* infusion over 1 h on days 1, 8 and 15 of a 28-d cycle.	https://www.clinicaltrials.gov/show/NCT01924533	500	Overall survival	NCT01924533	China, South Korea, Japan, Taiwan
HELOISE - A Study of Herceptin (Trastuzumab) in Combination With Cisplatin/Capecitabine Chemotherapy in Patients With HER2-Positive Metastatic Gastric or Gastro-Esophageal Junction Cancer	Capecitabine 1600 mg/m^2 orally daily on days 1-14 of each 3-wk cycle (6 cycles) Cisplatin 80 mg/m^2 *iv* on day 1 of each 3-wk cycle (6 cycles). Trastuzumab (Herceptin) 8 mg/kg *iv* loading dose, followed by 6 mg/kg *iv* every 3 wk.	https://www.clinicaltrials.gov/show/NCT01450696	400	Overall survival	NCT01450696	25 countries worldwide
A Study of Trastuzumab Emtansine Versus Taxane in Patients With Advanced Gastric Cancer	Standard taxane (docetaxel or paclitaxel) according to investigator choice. Trastuzumab emtansine 3.6 mg/kg or 2.4 mg/kg once- wk every 3 wk.	https://www.clinicaltrials.gov/show/NCT01641939	412	Overall survival	NCT01641939	30 countries worldwide
Phase 3 Study of Nimotuzumab and Irinotecan as Second Line With Advanced or Recurrent Gastric and Gastroesophageal Junction Cancer (EGFR + IHC)	Irinotecan 150 mg/m^2 *iv* once every 2 wk until progression or unacceptable toxicity develops, with or without nimotuzumab 400 mg *iv* once-wk until progression or unacceptable toxicity develops.	https://clinicaltrials.gov/ct2/show/NCT01813253	400	Overall Survival	NCT01813253	Japan, South Korea
RAINFALL - A Study of Ramucirumab (LY3009806) in Combination With Capecitabine and Cisplatin in Participants With Stomach Cancer	Cisplatin 80 mg/m^2 *iv* on day 1 of each 21-d cycle (for up to 6 cycles) and 1000 mg/m^2 capecitabine orally twice-daily on days 1-14 with or without ramucirumab 8 mg/kg *iv* on days 1 and 8	https://clinicaltrials.gov/ct2/show/NCT02314117?term=Ramucirumab+gastric&rank=5	616	Progression-free survival	NCT02314117	20 countries worldwide
AIO-STO-0111 - A Randomized, Double Blind Study Evaluating Paclitaxel With and Without RAD001 in Patients With Gastric Carcinoma After Prior Chemotherapy	Paclitaxel 80 mg/m^2 on days 1, 8 and 15 of every 28-d cycle with or without everolimous 10 mg (2 × 5 mg tablets) per day on days 1-28	https://clinicaltrials.gov/ct2/show/NCT01248403	480	Overall survival	NCT01248403	Germany
BRIGHTER - A Study of BBI608 Plus Weekly Paclitaxel to Treat Gastric and Gastro-Esophageal Junction Cancer	Paclitaxel 80 mg/m^2 *iv* infusion on days 1, 8 and 15 of every 4-wk cycle with or without BBI608 480 mg orally twice-daily	https://clinicaltrials.gov/ct2/show/NCT02178956?term=BBI608+GASTRIC&rank=1	680	Overall survival	NCT02178956	United States

remained alive, and the median OS was 11.4 mo[63]. The incidence of side effects was low, and only 3 patients presented toxicities grade ⩾ 3. Further trials with different checkpoint inhibitors in GC are in preparation.

This trial is one example whereby identifying molecular subtypes of GC may help to better understand this heterogeneous cancer, leading to the development of novel therapeutic strategies. The discovery of key driver genes in these subgroups (such as TP53 in microsatellite stable tumors and ARID1A in EBV-positive tumors) reveals further potential molecular biomarkers, and the development of other targeted therapeutic strategies is ongoing. For example, JAK2 amplification was seen in 6% of EBV-positive tumors, leading to the activation of the JAK/STAT and PI3K/Akt/mTOR pathways, opening new perspectives for the design of clinical trials with JAK2 inhibitors.

CONCLUSION

The treatment of advanced GC remains a major challenge, and many questions remain unresolved. Although significant progress has been made in recent years by routinely treating patients with second- and further lines of chemotherapy, as well as integrating HER2-targeting drugs and ramucirumab in the routine care of patients with advanced GC, many phase Ⅲ trials (*e.g.,* those with EGFR inhibitors or everolimus) have had negative results, and others (*e.g.,* RILOMET) had to be closed prematurely due to unexpected toxicity. Among the unresolved issues is whether some subgroups of patients benefit more than others from certain chemotherapy regimens (*e.g.,* doublet *vs* triplet regimens).

Furthermore, the optimal duration of combination chemotherapy remains unclear: should we continue until progression, or just continue with maintenance therapy? Moreover, valid biomarkers other than HER2 are required to select patients for clinical trials in molecularly-defined subtypes of GC. The results of the KEYNOTE 12 trial have provided a first signal of the efficacy of immunotherapy in advanced GC. However, further trials, and especially longer follow-up, are necessary to validate the efficacy of immunotherapy.

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