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Biologics in Combination with Chemotherapy for Gastric Cancer: Is This the Answer?

N. Charalampakis[1,*], **E. Elimova**[1,*], **Y. Shimodaira**[1], **H. Shiozaki**[1], **R. Wadhwa**[1], and **J.A. Ajani**[1]

[1]Department of Gastrointestinal Medical Oncology, University of Texas M. D. Anderson Cancer Center 1515 Holcombe Blvd, (FC10.3022), Houston, TX 77030, USA.

Abstract

Gastric cancer (GC) continues to be a significant problem worldwide and is the third leading cause of cancer death. Armamentarium to treat GC whether it is potentially curable or metastatic (incurable) has changed little over the last decades with only two new agents being approved (trastuzumab and ramucirumab). Many relatively healthy patients after second line therapy have limited and generally ineffective options. The recent TCGA analysis has uncovered 4 genotypes of GC, however, it is not sufficient to change our treatment strategies and more work needs to be done. The popular front line regimen containing a platinum compound and a fluoropyrimidine is widely used for drug development and has worked well globally. Thus, this combination appears suitable for adding a biologic agent. The search for new classes of cytotoxics has almost stopped but it is clear that cytotoxic therapy continues to contribute and it is here to stay. Biologic agents that modulate the immune system of the host appear promising along with many other biologics that can potentially inhibit signaling pathways that are often employed by GC cells. We will briefly describe the efforts that have targeted EGFR, mTOR, angiogenesis, and MET pathways.

Keywords

gastric cancer; biologic therapy; chemotherapy; treatment

1. Introduction

Gastric cancer (GC) continues to be a significant problem worldwide and is the third leading cause of cancer death [1]. Armamentarium to treat GC whether it is potentially curable or metastatic (incurable) has changed little over the last decades with only two new agents being approved (trastuzumab and ramucirumab). Many relatively healthy patients after second line therapy have limited and generally ineffective options. The recent TCGA

All correspondence to: Jaffer A. Ajani, MD, Department of Gastrointestinal Medical Oncology, University of Texas M. D. Anderson Cancer Center, 1515 Holcombe Blvd, (FC10.3022), Houston, TX 77030, jajani@mdanderson.org; Phone: 713-792-2828; Fax: 793-745-1163.

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analysis has uncovered 4 genotypes of GC [2]. The Cancer Genome Atlas (TCGA) Research Network has classified gastric cancer into four subtypes based on the molecular characterization of 295 primary adenocarcinomas but it is not clear if these genotypes will ultimately guide patient therapy. However, they clearly converged on four major genomic subtypes of GC with distinct features and classes of molecular alterations:

1. Tumors containing EBV, along with recurrent mutations in the PIK3CA gene pathway, extreme DNA hypermethylation, amplification of JAK2 and extra copies of PD-L1 and PD-L2 genes, which are suppressors of immune response. This group makes up about 10% of the cancers, with nearly 80% harboring a protein-changing alteration in PIK3CA.
2. Tumors showing microsatellite instability, in which malfunctioning DNA repair mechanisms cause a high rate of mutations, including mutations of genes encoding targetable oncogenic signaling proteins. About 20% of tumors fall into this subtype.
3. The largest category (50%) of tumors, making up about half of the cancer specimens, is termed “chromosomally unstable.” These contain a jumble of extra or missing pieces of genes and chromosomes (aneuploidy) and have a striking number of genomic amplifications of key receptor tyrosine kinases. This subtype of tumor is frequently found in the junction between the stomach and the esophagus, a type of gastric cancer that has been dramatically increasing in the United States.
4. The fourth group was termed “genomically stable” since they lacked the molecular features of the other three types. These tumors, making up 20% of the specimens are largely those of a specific class of gastric cancer enriched for the diffuse-type histologic variant, with approximately 30% of these tumors having genomic alterations in the RHOA signaling pathway.

However, it is not sufficient to change our treatment strategies and more work needs to be done. The popular front line regimen containing a platinum compound and a fluoropyrimidine is widely used for drug development and has worked well globally. Thus, this combination appears suitable for adding a biologic agent. The search for new classes of cytotoxics has almost stopped but it is clear that cytotoxic therapy continues to contribute and it is here to stay. Biologic agents that modulate the immune system of the host appear promising along with many other biologics that can potentially inhibit signaling pathways that are often employed by GC cells. We will briefly describe the efforts that have targeted EGFR, angiogenesis and MET pathways.

2. EGFR Targeted Therapy

Epidermal growth factor receptor (EGFR) gene is often amplified and its protein is overexpressed in upper gastrointestinal cancers. Overexpression is prognostic. With the advent of monoclonal antibodies (mAbs) and tyrosine kinase inhibitors (TKIs) against EGFR, many randomized clinical trials in patients with advanced or localized gastroesophageal cancers (squamous cell carcinoma and adenocarcinoma) have been conducted, however, the results have been uniformly disappointing.

The most recent UK COG report on patients with Siewert type I/II advanced gastroesophageal cancers (adenocarcinoma or squamous cell carcinoma) in the second line setting [3] randomized 449 patients to receive gefitinib, an anti-EGFR TKI or placebo. The primary endpoint was overall survival (OS). Secondary endpoints were progression free survival (PFS) and quality of life outcomes. However, the median OS was 3.73 months for patients who received gefitinib and 3.63 months for those who received a placebo (HR=0.9,95% CI 0.74–1.09; p=0.29). There was a minor prolongation of PFS by 0.4 months for patients who received gefitinib compared to those who received placebo (HR=0.80, 95% CI 0.66–0.96; p=0.02) (Table 1). Some recent data suggests that there may be a benefit in EGFR amplified patients however this needs further validation. [4]

Equally disappointing results were reported from two EGFR targeting trials (EXPAND and REAL-3), of patients with metastatic gastric or gastroesophageal cancer. [5, 6] The EXPAND trial randomized 904 patients to receive capecitabine and cisplatin, with or without cetuximab, a chimeric anti-EGFR mAb. This study did not achieve its primary endpoint, with the median PFS for capecitabine-cisplatin plus cetuximab being 4.4 months compared to 5.6 months for capecitabine-cisplatin alone (HR 1.09, 95% CI 0.92–1.29; p=0.32) [5]. The REAL-3 study was terminated prematurely because a statistically significantly lower OS was noted in patients who received epirubicin/oxaliplatin/capecitabine (EOC) and panitumumab, a fully human anti-EGFR mAb [6]. Median OS of patients allocated to EOC was 11.3 months (95% CI 9.6–13.0) compared with 8.8 months (7.7–9.8) in 278 patients allocated to modified EOC and panitumumab (HR 1.37, 95% CI 1.07–1.76; p=0.013). A molecular exploratory analysis of tumors of patients in the REAL-3 trial did not identify any predictive biomarkers for panitumumab [7]. Table 2 presents the major phase 3 localized trials all of which were negative.

Squamous cell carcinomas (SCCs) seem to overexpress EGFR at a higher frequency (60–70%) and have fairly high rate of EGFR amplification (28%) [8]. These changes are associated with poor response to chemoradiotherapy and shorter OS [9]. However in the COG study, SCC patients formed a minority and there was a trend for improved OS for esophageal adenocarcinoma patients, highlighting the fact that overexpression of EGFR may not represent a therapeutic target. In GC, although EGFR amplification has been low, EGFR expression is similar to esophageal cancer and it is prognostic [10].

VEGF Targeted Therapy

Angiogenesis is recognized as a hallmark of several types of tumors, including gastric GC. Vascular endothelial growth factor (VEGF) is responsible for tumor-mediated angiogenesis, stimulating new blood vessel formation and higher levels of VEGF in tissues correlate with more advanced stage and poorer overall prognosis [11]. Thus, efforts to block this pathway, either by inhibiting VEGF or its receptor, have emerged as attractive strategies for GC treatment.

Bevacizumab, the humanized mAb to VEGF, was investigated in locally advanced or metastatic GC in the AVAGAST trial [12]. It was added to a combination of cisplatin and fluoropyrimidine. A total of 774 patients were randomized and the median OS was 12.1 months with bevacizumab plus fluoropyrimidine-cisplatin and 10.1 months with placebo

plus fluoropyrimidine-cisplatin (HR = 0.87; 95%CI: 0.73–1.03; *P* = 0.1002). A subsequent retrospective biomarker analysis of the AVAGAST trial showed that only Western patients with elevated baseline plasma VEGF-A levels and low baseline expression of neuropilin-1 seemed to have a statistically significant improvement of OS [13]. It is important to note that neither of these biomarkers has been prospectively validated. Unlike the ToGA trial, the AVAGAST trial did not use an enriched patient population, underscoring the importance of appropriate patient population selection in randomized controlled trials and the use of predictive biomarkers to direct care.

Ramucirumab is a fully human IgG1 mAb receptor antagonist designed to bind the extracellular domain of VEGFR-2, thereby blocking the binding of VEGF ligands and inhibiting receptor activation, thus inhibiting angiogenesis [14]. In the REGARD trial, 355 patients with advanced or metastatic GC that had progressed after first-line chemotherapy were randomized to receive ramucirumab or placebo [15]. This study demonstrated a marginal improvement in median OS, 5.2 months in patients in the ramucirumab group and 3.8 months in those in the placebo group (HR = 0.776, 95% CI: 0.603–0.998; *P* = 0.047) with a disease control rate improved from 23% to 49% and very low toxicity- 8% grade >=3 hypertension. In the recently published RAINBOW trial, ramucirumab was added to weekly paclitaxel as a second-line therapy in 665 patients with advanced or metastatic GC, demonstrating a significant improvement in both PFS and OS over paclitaxel alone which was more impressive [16]. A statistically significant prolongation of OS was demonstrated (HR = 0.81, 95% CI: 0.68–0.96, *P* = 0.017). Median OS was 9.6 and 7.4 months in the ramucirumab-plus-paclitaxel arm and placebo-plus-paclitaxel arm, respectively. This could imply that the use of ramucirumab mainly benefits patients when used in combination with paclitaxel and the combination has a modest safety profile.

Apatinib is a small-molecule multi-targeted TKI with activity against VEGFR-2 which was evaluated in a phase 3 trial in 271 patients with advanced GC (after 2nd line) [17]. The median survival is 6.5 months for apatinib and 4.7 months for placebo (HR = 0.71, 95% CI: 0.54–0.94, *P* = 0.015) and the median PFS 2.6 months for apatinib and 1.8 months for placebo (HR = 0.44, 95% CI: 0.33–0.61, *P* < 0.0001). Currently, apatinib is only approved in China.

3. Anti-HER2 Therapy

Trastuzumab has been a success in the first line metastatic GC TOGA trial which demonstrated a benefit in OS in HER2+ metastatic gastric and GEJ patients treated with this antibody in addition to cisplatin and fluoropyrimidine [18]. However in the second line setting targeted HER2 therapy with TKIs has been a failure.

Lapatinib, a HER1–2 TKI has been investigated in combination with capecitabine plus oxaliplatin in 545 HER2+ advanced or metastatic gastric and esophageal adenocarcinomas in the TRIO-013/LOGiC trial. Its addition to CapeOx did not improve efficacy (OS and PFS) among untreated HER2+ metastatic GC patients [19]. In the second line in a large 420 patient study (TyTAN Trial), randomized HER2+ patients to lapatinib plus paclitaxel *vs* paclitaxel alone [20]. Median OS was 11 months for the combination and 8.9 months for paclitaxel alone in the intent-to-treat (ITT) population (HR = 0.84; *P* = 0.2088). In a pre-

planned subgroup analysis, median OS in HER2 immunohistochemistry (IHC) 3+ subgroup was 14 months for the combination therapy and 7.6 months for paclitaxel alone (HR = 0.59; $P = 0.0176$). Interestingly, it has recently been demonstrated that although the study mandated IHC HER2 positivity, 35% of patients in TyTAN had tumors classified as IHC0/1+. Identification of specific biomarkers for various patient subpopulations with advanced GC may help define those patients who would receive the most benefit from treatment.

4. MET Targeted Therapy

Hepatocyte growth factor (HGF) and its receptor MET have been found to promote the proliferation, migration and survival of tumor cells and to play a role in GC. MET amplification and/or overexpression of its protein product has long been implicated in the pathogenesis of GC supporting its role as a poor prognostic factor [21]. Rilotumumab (AMG 102), a fully human anti-HGF mAb targeting the c-MET ligand, demonstrated prolonged PFS for patients whose tumors had high total c-MET expression in a phase 1b/2 study but was associated with higher rates of grade 3/4 neutropenia and venous thromboembolism [22]. Currently, two phase 3 studies were testing the efficacy of rilotumumab in combination with epirubicin, cisplatin and capecitabine (RILOMET-1) and rilotumumab with cisplatin and capecitabine (RILOMET-2) as a first line treatment of metastatic gastric and GEJ adenocarcinoma. However, the company recently terminated both its studies because they did not meet safety standards and the protocol-defined futility criteria would likely have been met at the planned interim analysis set for March 2015.

A recent phase 2 trial testing the efficacy of onartuzumab, an anti c-MET mAb versus placebo combined with mFOLFOX6 in patients with metastatic HER2-negative and MET-positive GC, failed to show a significant difference in PFS-the primary endpoint-between the onartuzumab and placebo arms in either the intent-to-treat population or the subgroup of patients with MET-positive tumors[23]. In contrast to the onartuzumab findings, the investigational oral MET TKI AMG 337 is generating excitement based on early-phase results in patients with gastrointestinal cancers. In a phase I analysis of single-agent AMG 337 in 90 patients with advanced solid tumors, 13 individuals were found to have MET-amplified gastroesophageal adenocarcinomas. Eight of 13 patients had partial to near-complete responses to the small-molecule inhibitor AMG-337[24]. On the basis of these results, a phase II study of AMG-337 in patients with MET-amplified gastroesophageal cancer or other MET-amplified solid tumors is currently recruiting participants.

5. Expert Opinion

Establishing valid biomarkers in the clinic and then targeting them for therapeutic advantage is challenging. Most of the time, such efforts have failed. The sheer complexity of the genome is staggering, and structural alterations do not necessarily translate into functional/protein aberrations. For advancing research in GC, the clinical trial machinery has been well established. Many pivotal trials are being conducted; therefore, we can anticipate some advances in the near future. Much work remains to be done. We must spend our resources to establish reliable preclinical models that will assure success in the clinic. We must also

delve deep in uncovering true drivers of GC in individual patients. One of the most challenging and exciting frontiers is the potential of host's immune system. We should harness the power of the immune system, either through vaccines, antibodies, cell therapy and/or programmed cell death inhibitors.

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Table 1

Major phase 3 trials involving biologics in combination with chemotherapy in the advanced/metastatic gastric cancer setting

Trial	No. of patients	Treatment arms	HR for OS/Death (P value)	Survival Comparison (in months)
First line				
Lordick et al [5] (EXPAND trial)	904	CX and cetuximab *vs* CX	1.004 (0.9547)	OS: 9.4 *vs* 10.7
Waddell et al [6] (REAL-3 trial)	553	EOC and panitumumab *vs* EOC	1.37 (0.013)	OS: 8.8 *vs* 11.3
Bang et al [18] (ToGA trial)	584	CX, CF and trastuzumab *vs* CX and CF*	0.74 (0.0046)	OS: 13.8 *vs* 11.1
Hecht et al [19] (TRIO-013/LOGIC trial)	545	CapeOx and lapatinib *vs* CapeOx and placebo	0.91 (0.35)	OS: 12.2 *vs* 10.5
Ohtsu et al [12] (AVAGAST trial)	774	Cisplatin, 5FU and bevacizumab *vs* cisplatin and 5FU	0.87 (0.1002)	OS: 12.1 *vs* 10.1 PFS: 6.7 *vs* 5.3
Second line				
Dutton et al [3] (UK COG trial)	449	Gefitinib *vs* placebo	0.9 (0.29)	OS: 3.73 *vs* 3.63
Fuchs et al [15] (REGARD trial)	355	BSC and ramucirumab *vs* BSC	0.776 (0.047)	OS: 5.2 *vs* 3.8
Wilke et al [16] (RAINBOW trial)	665	Paclitaxel and ramucirumab *vs* paclitaxel	0.81 (0.017)	OS: 9.6 *vs* 7.4
Satoh et al [20] (TyTAN trial)	420	Paclitaxel and lapatinib *vs* lapatinib	0.84 (0.2088)	OS: 11.0 *vs* 8.9
Third line				
Qin et al [17]	271	BSC and apatinib *vs* BSC	0.71 (0.015)	OS: 6.5 *vs* 4.7 PFS: 2.6 *vs* 1.8
Ohtsu et al [25] (GRANITE-1 trial)	656	BSC and everolimus *vs* BSC and placebo	0.90 (0.1244)	OS: 5.4 *vs* 4.3

*Hazard ratio reduced to 0.8 on follow-up analysis

HR: hazard ratio; OS: Overall survival; PFS: Progression free survival; CX: Cisplatin and Capecitabine; EOC: Epirubicin, Oxaliplatin and Capecitabine; BSC: Best supportive care; CF: Cisplatin and 5FU; Cape Ox: Capecitabine and Oxaliplatin.

Table 2

Major phase 3 trials involving biologics in combination with chemotherapy in the localized gastric cancer setting

Trial	No. of patients	Treatment arms	HR for OS/Death (P-value)	Survival comparison
Suntharalingam et al [26] (RTOG 0436 trial)	344	Cisplatin, paclitaxel and cetuximab plus radiation *vs* cisplatin and paclitaxel plus radiation	0.92 (0.70)	2-year OS rate: 44% *vs* 41.7%
Crosby et al [27] (SCOPE-1 trial)	258	Cisplatin, capecitabine and cetuximab plus radiation *vs* cisplatin and capecitabine plus radiation	1.53 (0.035)	22.1 months *vs* 25.4 months
Okines et al [28]	1,103	ECX and bevacizumab *vs* ECX	NR	NR

* HR: Hazard ratio; OS: Overall survival; ECX: Epirubicin, Cisplatin and Capecitabine.