Multimodal approach of advanced gastric cancer: based therapeutic algorithm

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Abstract. – Gastric cancer (GC) is the third leading cause of cancer death in both sexes worldwide, with the highest estimated mortality rates in Eastern Asia and the lowest in Northern America. However, the availability of modern treatment has improved the survival and the prognosis is often poor due to biological characteristics of the disease. In oncology, we are living in the "Era" of target treatment and, to know biological aspects, prognostic factors and predictive response informations to therapy in GC is mandatory to apply the best strategy of treatment.

The purpose of this review, according to the recently published English literature, is to summarize existing data on prognostic aspects and predictive factors to response to therapy in GC and to analyze also others therapeutic approaches (surgery and radiotherapy) in locally, locally advanced and advanced GC. Moreover, the multidisciplinary approach (chemotherapy, surgery and radiotherapy) can improve the prognosis of GC.

Key Words:
Gastric cancer, Radiotherapy, Surgery, Chemotherapy, Treatment, Prognostic factors.

Introduction

Gastric cancer (GC) is one of the most common cancers worldwide. More than 21000 patients have diagnosed annually in the United States (US), of whom 10990 are expected to die[1-6]. Epidemiological evidence suggests that GC was the first cause of cancer death until the 1980s when it was overtaken by lung cancer. The incidence of GC has declined in the past two decades, after the identification of several risk factors such as *H. pylori* and other dietary and environmental risks[7-10]. Despite this, several authors reported that the reduction of its incidence partially began before the discovery of *H. pylori*. The decline first took place in countries with low GC incidence such as the US, while the decline in countries with high incidence like Japan was slower[11]. In China, the decline in the incidence was lower than those reported in other countries; the epidemiological data reveal that despite an overall decrease in GC incidence, an increase in the oldest and the youngest group has been found with a fewer remarkable decline observed among women than in men. In the US, risk factors for non-cardia GC include male gender, non-white race, and older age. Moreover, between 1977 and 2006, it has been reported that the incidence rate of non-cardia GC in the US declined among all race and age groups. The only exception regards whites aged 29 to 39 years for whom the incidence of GC increased[12-14]. Noteworthy, since this may consider as a signal of the introduction of new environmental factors. One of the most important factors contributing to the marked reduction in the incidence rates of GC was the mass utilization of refrigerators. The storage of food reduced salt-based preservation of food, prevented bacterial and fungal contamination.

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Moreover, the refrigeration also allowed for fresh food and vegetables to be more readily available, which may be a valuable source of antioxidants, important for cancer prevention[15,16].

Prognostic Clinical Factors

Several factors can be considered important clinical predictors for response to treatment and survival rate[17].

The TNM stage is one of the most important prognostic tools for GC[18].

The prognosis of patients with GC is related to tumor size, nodal involvement, direct tumor extension beyond the gastric wall and tumor grade[19].

However, the early-stage disease accounts for only 10% to 20% of all cases diagnosed in the US. From 80% to 90% of patients show a metastatic disease in either regional or distant sites. The overall survival (OS) rate in these patients at 5 years ranges from almost no survival for patients with disseminated disease to almost 50% survival for patients with localized distal GCs confined to resectable regional disease. In the case of localized disease, the 5-year survival rate of patients with proximal GC is only 10% to 15%. Although the treatment of patients with disseminated GC may result in palliation of symptoms and some prolongation of survival, long remissions are uncommon. The complete resection is the most important prognostic factor. Recurrence following surgery is a major problem and is often the ultimate cause of death.

Residual tumor after gastric resection with curative intent is categorized by a system known as R classification and indicates the amount of residual disease after tumor resection: R0 indicates no gross or microscopic residual tumor, R1 indicates microscopic residual tumor, and R2 shows macroscopic residual disease[19].

The degree of penetration of the tumor through the gastric wall and the presence of lymph node involvement are the basis for all staging systems developed for this disease. The relationship between T stage and survival is well defined. Some authors from Japan, Europe, and the US have shown that advanced T stage has the major prognostic impact[20].

In the past, the N stage classification was based on the anatomical location of lymph nodes. Although the prognostic significance of such a classification may be relevant, it is very complicated for practice. In 1997, the AJCC/UICC N stage was changed and became based on the number of positive lymph nodes[21]. This new classification has fewer methodological problems, and it seems more reproducible provided that a minimum of 15 nodes are removed and analyzed. Apart from TNM classification and R0 resection, many other factors have been considered for prognostic purposes.

In some reports, the histological tumor type has no effect on prognosis with the exception of the rare small cell carcinoma of the stomach, which has an unfavorable prognosis[22]. Other histological prognostic factors were considered the Laurén classification (intestinal or diffuse type), or the Ming classification (expanding or infiltrating type)[23,24]. Based on Lauren's classification, we can differentiate GCs two major types of GC: intestinal or diffuse. The intestinal type consists of a differentiated cancer with a tendency to form glands. By contrast, the diffuse form exhibits low cell cohesion and tends to replace the gastric mucosa by signet-ring cells. About 16% of cases will be unclassifiable or of mixed type. Ming et al[25] proposed a classification favorable expanding type, and the poor prognosis infiltrating type.

Tumor configuration types as described by Borrmann has been shown to have prognostic significance in several large studies; according to Borrmann (Type I: polypoid fungating, Type II: ulcerative with distinct elevated borders, Type III: ulcerative with indistinct borders, Type IV: diffuse, indistinct borders). Type I and II represent localized types, Types III and IV infiltrative Types. The localization of the tumor is crucial, as it determines different surgical strategies.

Carcinoma of the proximal gastric third can frequently not be differentiated from the true carcinoma of the cardias. Also, these tumors must be distinguished from adenocarcinoma of the distal esophagus (called Barrett's carcinoma)

Studies in Asia have questioned the dictum that signet ring cell carcinoma (SRC) has a worse prognosis than other forms of GC[26]. SRC presented in younger patients and less often in men. SRC patients were more frequently black, Asian, American Indian/Alaska Native, or Hispanic. SRC was more likely to be stage T3-4 (45.8% *vs.* 33.3%), have lymph node spread (59.7% *vs.* 51.8%), and distant metastases (40.2% *vs.* 37.6%). SRC was more likely to be found in the lower (30.7% *vs.* 24.2%) and middle stomach (30.6% *vs.* 20.7%). Median survival was not different between the two (AC, 14.0 months *vs.* SRC, 13.0 months; $p = 0.073$). Multivariable analyses demonstrated SRC was not associated with mortality (hazard ratio [HR], 1.05; 95% CI,

0.96 to 1.11; $p = 0.150$). Mortality was associated with age (HR, 1.01; 95% CI, 1.01 to 1.02; $p = 0.001$), black race (HR, 1.10; 95% CI, 1.01 to 1.20; $p = 0.026$), and tumor grade. Variables associated with lower mortality risk included Asian race (HR, 0.83; 95% CI, 0.77 to 0.91; $p = 0.001$) and surgery (HR, 0.37; 95% CI, 0.34 to 0.39; $p = 0.001$). In the US, SRC significantly differs from AC in the extent of disease at presentation. However, when adjusted for stage, SRC does not portend a worse prognosis.

The adverse prognostic factor of tumor size is controversial. Tumor site has been shown to be an independent prognostic factor in gastric carcinoma, with proximal carcinomas having a poorer prognosis than distal cancers[27].

Lymphatic, venous, or perineural invasion have been shown to be adverse prognostic factors[28]. Several studies[29-32] have reported a positive surgical resection margin associated with a significant decrease in OS. The ratio of lymph nodes metastases (number of metastatic lymph nodes to the total number of dissected lymph nodes) appears to be an important prognostic factor and the best classification factor for lymph node metastasis[33]. Different survival rates have been reported in patients having undergone surgical intervention for the treatment of gastric carcinoma in Japan and Western countries. However, when using a similar staging classification and similar prognostic characteristics, the prognosis for GC in Japan and Germany may be the same[34]. Tumor volume, measured from serial tissue sections of gastric carcinoma by using a computer graphics analysis, seems to be of prognostic significance.

Maehara et al[35], by a multivariate analysis revealed that the 10 factors of: (A) depth of invasion, (B) lymph node metastasis, (C) lymph node dissection, (D) tumor size, (E) liver metastasis, (F) peritoneal dissemination, 8G) lymphatic invasion, (H) vascular invasion, (I) lesion in the whole stomach, and (J) lesion in the middle stomach were independent factors for determining the prognosis.

Although most reports have suggested a dismal prognosis for young patients with GC, one study has suggested that young patients (≤ 39 years) do not have a worse prognosis than older patients[36]. Women appeared to have a better prognosis than men in one study[37], but this was not confirmed in other reports[38].

According to some investigations, older patients have been reported to have a poorer prognosis than do to younger patients, because they have more advanced disease stage at the time of diagnosis and a lower rate of curative resection[39]. Also, other causes such cardiovascular disease, diabetes mellitus, other gerontological medical problems; alterations in the immune system, malnutrition have been suggested to reflect the increased operative mortality and shortened long-term survival in older patients.

Surgical Treatment: Gastrectomy and Lymphadenectomy

The worldwide surgical practices may vary between surgeons, countries and continents. Current topics of debate in GC surgery are: (1) The influence of volume of hospitals and surgeons on the outcome after gastrectomy; (2) The technique of surgery: open or minimally invasive gastrectomy; (3) Reconstruction of the alimentary tract using a jejunal pouch. (4) The extent of lymph node dissection and need for omental resection and/or pancreatic splenectomy; and (5) The type of (neo-)adjuvant treatment in patients with GC. Advanced GC can be defined as a non-early/non-metastatic GC infiltrating deeper than sub mucosal layer with or without nodal involvement (T2-4b/N0-3b/M0, 7th AJCC/UICCTNM)[40].

Brenkman et al[41] in a survey revealed that minimally invasive distal gastrectomy was preferred by 65% of surgeons in the treatment of early gastric cancer. The Asian respondents performed minimally invasive distal gastrectomy for early GC in 82% of the cases. In South America, minimally invasive and open distal gastrectomy were equally performed[42]. Minimally invasive distal gastrectomy for advanced GC was performed by only 9% of respondents. These results were comparable in all continents. For total gastrectomy, minimally invasive total techniques were favored by 49% for early gastric cancer and by 6% for advanced GC. However, in Asia, the majority (64%) of respondents performed minimally invasive total gastrectomy for early GC, whereas other continents preferred the open procedure. For total gastrectomy for advanced cancer, there was no difference between continents.

According to the most recent consensus conference of the Italian Society of Surgery (SIC) and the Italian Research Group for Gastric Cancer (GIRCG), when performing a gastrectomy, the proximal margin should be assessed in fresh specimens according to the AJCC T stage. In detail, the gastrectomy is adequate when the margin is > 2 cm in T1 and > 3 cm in T2-4 for intestinal-

type cancer with non-infiltrative appearance. In all the other cases, and when the T and the histotype were not clarified before surgery, the margin should be larger than 5 cm. In all the cases in which it is possible to obtain a proximal margin free from the tumor as specified above, subtotal gastrectomy is preferable to total gastrectomy[43].

The lymph node stations surrounding the stomach have been precisely defined by the Japanese Gastric Cancer Association (JGCA), formerly known as the Japanese Research Society for Gastric Cancer[44]. Previously, the JGCA divided these stations into four levels (N1 through N4) based on analysis of lymphatic flow and the likelihood of GC to metastasize to each station, and these designations change based on the primary location of the tumor (i.e., upper third, middle third, and lower third). The anatomic definitions of the lymph node stations were not modified during further revisions of the classification system but the N designation of the stations as a component of D1 or D2 resection has changed as guidelines have been revised. The JGCA recently abandoned their N designation of nodal stations in order to more closely adopt and avoid confusion with International Union Against Cancer (UICC)/American Joint Committee on Cancer (AJCC) staging. Staging of tumors near the oesophagogastric junction remain an area of discrepancy between the JGCA and UICC/AJCC staging systems. Nodal stations for a D1 and D2 are now defined by the operation performed rather than the location of the tumor. D1 lymphadenectomy along with proximal gastrectomy and pylorus-preserving gastrectomy are only recommended for T1N0 disease.

There are significant differences in the extent of lymphadenectomy performed in the different institution and different countries. D2 lymphadenectomy is the standard lymphadenectomy performed in Japan and South Korea for all resectable tumors except for T1 tumors. Less extensive lymphadenectomies are usually performed in countries with a lower incidence, such as the United States. There is no disagreement that a D1 lymphadenectomy is the minimum lymphadenectomy for gastric adenocarcinoma, yet this minimum standard may not be met for the majority of patients in the United States. Less extensive lymphadenectomies also likely result in increased loco-regional recurrence. In terms of overall survival, the effects of more extensive lymphadenectomy are difficult to discern. Comparing D1 versus D2 lymphadenectomy, the renowned Dutch trial demonstrated that morbidity and mortality were significantly higher in the D2 dissection group (25% *vs*. 43%; $p = 0.001$, and 4% *vs*. 10%; $p = 0.004$, respectively) and, after 11 years, no overall difference in survival was observed (30% *vs*. 35%; $p = 0.53$)[45].

The 15-year follow-up update of the trial confirmed that any statistically significant difference exists between D1 and D2 dissection in terms of OS, while GC-related death rate, local recurrence rate, and regional recurrence rate were significantly lower after D2 dissection[46].

Laparoscopic surgery has been shown to provide important advantages in comparison with open procedures in the treatment of several malignant diseases, such as less perioperative blood loss and faster patient recovery. It also maintains similar results regarding the tumor resection margins and the oncological long-term survival.

However, recent data suggest that the popularity of laparoscopic surgery for GC is slowly increasing[47]. According to the above-mentioned Italian consensus on GC, given all the parameters of correct surgical oncology, a radical gastrectomy can be performed for early GCs with a laparoscopic or a robotic approach. Conversely, the use of the laparoscopic approach in advanced malignancy not protruding to the serosa (cT2, cT3) is still under evaluation, while no data are available up-to-now to consider safe the laparoscopic approach to tumors protruding to the serosa[48]. Chen et al[47] recently reported a meta-analysis of the long-term outcomes of laparoscopic (LG) versus open gastrectomy (OG) for GC. The inclusion criteria of the analysis were as follows: (1) randomized or nonrandomized comparative studies; (2) the patients included were diagnosed with GC; (3) early or locally advanced candidates were acceptable; (4) there were no limitations for race, age, or gender; (5) the staging system was based on the individual reports; (6) the patients in the LG and OG groups were compared; (7) the laparoscopic procedures mainly included Laparoscopic Assisted Gastrectomy (LAG), and additionally totally laparoscopic gastrectomy (TLG) and hand-assisted laparoscopic gastrectomy (HALG) were also considered; (8) any extent of lymphadenectomy from D1 to D2. was acceptable; (9) in the LG and OG groups, the range of follow-up length should cover 60 months; (10) all the potentially eligible studies should report at least one of the primary outcome measures, including the 5-year OS, tumor recurrence, and gastric cancer–related death rates; and

(11) the numbers of events could be extracted from the original reports. The authors reported that the 5-year OS, the recurrence rate and the GC–related death rate are comparable between LG and OG for early and advanced GCs[49]. An international expert panel mainly made up of US and Canadians physicians was organized to define appropriate and necessary processes of surgical care for GC[50]. The results are reported in a manuscript, by Brar et al[50], stating that laparoscopic distal gastrectomy is appropriate for distal GC patients with T1-2 N0 disease only; moreover, for patients with proximal GC, laparoscopic total gastrectomy was considered appropriate for patients with T1 N0 disease and indeterminate for patients with T2 N0 disease. A large Chinese study reported that postoperative morbidity and mortality after Laparoscopic Assisted Gastrectomy (LAG) and D2 dissection for advanced GC are 10.1% and 0.1%, respectively[51]. Age > 65 years and having two or more comorbidities ($p = 0.024$ and $p = 0.009$, respectively) resulted to be significant predictors of the development of postoperative complications at the multivariate analysis. Moreover, those two factors were also significant predictors of moderate and severe complications ($p = 0.016$ and $p = 0.001$, respectively).

In addition to the confusing debate in the literature on the role of the laparoscopic approach, novel studies are expanding the field of robotic surgery for gastric cancer. Recently, an international multi-institutional database has been established to evaluate the role of robotic, laparoscopic and open approaches in gastric cancer, in terms of surgical, clinical and oncological features[52]. In a paper edited in 2013 Coratti et al[53] reported that Robotic Assisted Gastrectomy (RAG) represents a valid alternative to conventional open or laparoscopic resection for early stage gastric carcinoma. In particular, they claimed advantages of RAG over LG in terms of (1) lymph node dissection, (2) intracorporeal reconstruction, (3) decreased blood loss, (4) shorter learning curve and reproducibility.

Radiotherapy

Even after a complete resection with D2 dissection with the best surgical technique, about 10% of patients died with locoregional relapse without any other documented site of failure[45]. Therefore, it is important to retain the interest in treating patients with radiotherapy in the postoperative, the preoperative and the intra-operative setting.

Clinical controlled trials of radiotherapy as a single adjuvant in the post-surgical setting have shown conflicting results[54-57]. Although locoregional failure was substantially reduced in all studies, no OS benefit was seen.

Surgical resection of GC has produced suboptimal survival despite multiple randomized trials that used postoperative chemotherapy or more aggressive surgical procedures. Intergroup 0116 performed a randomized phase III trial of postoperative radiochemotherapy in those at moderate risk of locoregional failure (LRF) following surgery. INT-0116 demonstrates strong, persistent benefit from adjuvant radiochemotherapy. Toxicities appear acceptable, given the magnitude of RFS and OS improvement. LRF reduction may account for the majority of overall relapse reduction. Adjuvant radiochemotherapy remains a rational standard therapy for curatively resected gastric cancer with primaries T3 or greater and/or positive nodes[58].

In a meta-analysis of postoperative radiochemotherapy[59], 5-year OS is significantly higher with radiochemotherapy as compared to surgery alone (odds ratio [OR] 0.45, 95% confidence interval [CI] 0.32–0.64). In all studies, adding chemotherapy to radiotherapy enhances radiation response and increases the benefit of radiations. Despite a higher frequency of severe and life-threatening toxicities in the radiochemotherapy group, fewer patients need to be treated by radiochemotherapy to benefit from a long-term treatment than the patients need to be treated by radiochemotherapy after surgery.

The authors in The Adjuvant Chemoradiotherapy in Stomach Tumors (ARTIST) trial tested whether the addition of radiotherapy to adjuvant chemotherapy improved disease-free survival (DFS) in patients with D2-resected GC.

Between November 2004 and April 2008, 458 patients with GC who received gastrectomy with D2 lymph node dissection were randomly assigned to either six cycles of adjuvant chemotherapy with capecitabine and cisplatin (XP) or to two cycles of XP followed by chemo radiotherapy and then two additional cycles of XP (XPRT). This final update contains the first publication of OS, together with updated DFS and subset analyses[60].

With 7 years of follow-up, DFS remained similar between treatment arms (hazard ratio [HR], 0.740; 95% CI, 0.520 to 1.050; $p = 0.0922$). OS also was similar (HR, 1.130; 95% CI, 0.775 to 1.647; $p = 0.5272$). The effect of the addition of

radiotherapy on DFS and OS differed by Lauren classification (interaction $p = 0.04$ for DFS; interaction $p = 0.03$ for OS) and lymph node ratio (interaction $p < 0.01$ for DFS; interaction $p < 0.01$ for OS). Subgroup analyses also showed that chemo radiotherapy significantly improved DFS in patients with node-positive disease and with intestinal-type GC. There was a similar trend for DFS and OS by stage of disease.

In D2-resected GC, both adjuvant chemotherapy and chemo radiotherapy are tolerated and equally beneficial in preventing relapse. Because results suggest a significant DFS effect of chemo radiotherapy in subsets of patients, the ARTIST 2 trial evaluating adjuvant chemotherapy and chemo radiotherapy in patients with node-positive, D2-resected GC is under way.

Finally, two recent randomized trials studied combined radiotherapy and chemotherapy, preoperatively. The POET trial compared, preoperatively, chemotherapy and radiochemotherapy, showed an increased gain for patients treated with radiochemotherapy, median survival 33.1 months *vs*. 21.1, respectively[61].

Similarly, the CROSS trial[62] showed a median OS of 49,9 months in patients treated with radiochemotherapy *vs*. 24 months with surgery alone; furthermore, in both arms postoperative complications and in-hospital death rate were comparable.

The use of intra operative radiotherapy (IORT) as a component in the management of gastric cancer was evaluated for local control and toxicity. A clinical trial by Chen and Song demonstrated that IORT (25-40 Gy) without other radiotherapy increased 5-year survival of patients with stage III by 35%[63].

A small randomized trial[64] found a similar result; it reported substantially improved 5-year survival rates for stages II-IV with adjuvant IORT. Differently, Sidebar et al[65] showed that IORT (20Gy) improved local control but no survival benefit.

Finally, a recent meta-analysis[66] showed a statistically significant locoregional control benefit with the addition of IORT in patients with GC. Moreover, the available data revealed that adjuvant IORT might provide promising results on the survival rate for the subgroup of patients with stage III disease.

Medical Oncological Approach

Despite the recent progress in the development of new therapeutic strategies and early diagnosis, the prognosis of GC continues to be poor, with < 20% of patients surviving at 5 years[67-69]. The median survival for these patients is around 10 months, and less than 10% survive at 5 years. Furthermore, even after curative resection, about 50%-60% of patients relapse locally or with distant metastases.

Multiple agents are active in the treatment of GC, including fluoropyrimidines (5-FU, capecitabine), anthracyclines, platinum agents, taxanes, irinotecan, and some targeted therapies such as trastuzumab for HER-2 overexpressing GCs. Combination regimens are associated with higher response rates (RR), and according to one meta-analysis, are also associated with increased survival when compared with single-agent chemotherapies[70]. Usually, the trials addressing the efficacy of targeted therapies, for example, EGFR and vascular endothelial growth factor (VEGF) were done in un-selected (not bio-marker enriched) populations and have not-surprisingly yielded disappointing results[71-73].

Trastuzumab, a monoclonal antibody against human epidermal growth factor receptor 2 (HER2; also known as ERBB2), was investigated in combination with chemotherapy for first-line treatment of HER2-positive advanced gastric or gastro-oesophageal junction cancer in ToGA trial.

ToGA (Trastuzumab for Gastric Cancer) was an open-label, international, phase 3, randomized controlled trial undertaken in 122 centers in 24 countries. Patients with gastric or gastro-oesophageal junction cancer were eligible for inclusion if their tumors showed an overexpression of HER2 protein by immunohistochemistry or gene amplification by fluorescence in-situ hybridization. Participants were randomly assigned in a 1:1 ratio to receive a chemotherapy regimen consisting of capecitabine plus cisplatin or fluorouracil plus cisplatin given every 3 weeks for six cycles or chemotherapy in combination with intravenous trastuzumab. The allocation was by block randomization stratified by Eastern Cooperative Oncology Group performance status, chemotherapy regimen, extent of disease, primary cancer site, and measurability of disease, implemented with a central interactive voice recognition system. The primary endpoint was OS in all randomized patients who received study medication at least once[74].

The 594 patients were randomly assigned to study treatment (trastuzumab plus chemotherapy, n=298; chemotherapy alone, n=296), of whom 584 were included in the primary analysis

(n=294; n=290). Median follow-up was 18.6 months in the trastuzumab plus chemotherapy group and 17.1 months in the chemotherapy alone group. Median overall survival was 13.8 months (95% CI 12-16) in those assigned to trastuzumab plus chemotherapy compared with 11.1 months (10-13) in those assigned to chemotherapy alone (hazard ratio 0.74; 95% CI 0.60-0.91; $p = 0.0046$). The most common adverse events in both groups were nausea (trastuzumab plus chemotherapy, 197 [67%] *vs*. chemotherapy alone, 184 [63%]), vomiting (147 [50%] *vs*. 134 [46%]), and neutropoenia (157 [53%] *vs*. 165 [57%]). Rates of overall grade 3 or 4 adverse events (201 [68%] *vs*. 198 [68%]) and adverse cardiac events (17 [6%] *vs*. 18 [6%]) did not differ between groups. In conclusion, Trastuzumab in combination with chemotherapy can be considered as a standard option for patients with HER2-positive advanced gastric or gastro-oesophageal junction cancer.

Pertuzumab is a new moAb that binds to the extracellular ligand binding domain of HER2 and blocks its dimerization with other HER-family receptor. When used together, the combination of pertuzumab plus trastuzumab provides a more comprehensive blockade of HER signalling than either agent alone. Therefore, the JACOB phase III study was designed to evaluate the effectiveness of pertuzumab in addition to trastuzumab plus chemotherapy (cisplatin plus capecitabine or 5-FU) in chemo-naïve patients with HER2-overexpressing advanced gastric or GEJ cancer. Trastuzumab emtansine (T-DM1) is a newly developed HER2-targeted antibody–drug conjugate that links trastuzumab to a highly potent maytansine-derived anti-microtubule drug (DM1). After binding the trastuzumab moiety to HER2 receptors on the tumor surface, T-DM1 is internalized by endocytosis and degraded in lysosomes, resulting in the release of DM1-containing cytotoxic catabolites. A phase II-III trial has investigated the effectiveness of T-DM1 compared with taxanes (docetaxel or paclitaxel) in patients with metastatic HER2-positive GC who develop progression of disease following first-line chemotherapy. Unfortunately, in both of these cases, the results are negative. In fact, preliminary data from these studies show no activity of anti- HER 2 drugs in the treatment of gastric cancer beyond the first line[75].

Moreover, the angiogenesis is an important aspect of tumor-genesis, and preliminary clinical studies suggested a clinical benefit in the addition of bevacizumab, a monoclonal antibody against VEGF-A, in combination with CT in GC[76,77]. Despite the failure of bevacizumab to improve OS in the phase III AVAGAST trial, a careful analysis of subsets allows note that there is a western population may derive some benefit[78,79]. When subset analyses were performed in the AVAGAST trial, it appeared that those with type 3 (distal non-diffuse) GC and those from European/American populations derived more benefit from bevacizumab than other GC subtypes or patients from Asian/Pacific populations. The VEGFR-2 (vascular endothelial growth factor receptor-2) antagonist ramucirumab, as reported in the REGARD trial, demonstrated modest activity in patients with advanced gastric or gastroesophageal junction adenocarcinoma who had disease progression after first-line platinum-containing or fluoropyrimidine-containing CT[80].

The median OS was 5.2 months (IQR 2.3–9.9) in patients in the ramucirumab group and 3.8 months (IQR 1.7–7.1) in those in the placebo group (HR = 0.776, 95% CI 0.603–0.998; $p = 0.047$). The subsequently reported RAINBOW trial investigated paclitaxel ± ramucirumab in patients with metastatic GEJ or gastric adenocarcinoma who had disease progression on or within 4 months after first-line platinum and fluoropyrimidine-based combination therapy[81].

The primary endpoint was OS. Median OS was 9.63 months for ramucirumab+paclitaxel compared to 7.36 months for paclitaxel alone (HR=0.807, 95% CI 0.678–0.962, $p = 0.017$). Based on these results the combination of ramucirumab + paclitaxel is expected to become a standard of care treatment regimen in the second-line setting for metastatic upper GI tumors. The success of ramucirumab in the second line setting has prompted its clinical investigation in the first line setting. When ramucirumab was combined with FOLFOX in the first-line setting, it did not improve median progression-free survival (PFS) (6.4 *vs*. 6.7 months, HR = 0.98, 95% CI 0.69–1.37, $p = 0.89$) or OS (11.7 *vs*. 11.5 months, HR = 1.08, 95% CI 0.73–1.58) in patients with advanced gastric/GE junction tumors[82]. Clinical trials investigating alternative combinations of CT with ramucirumab in the first-line setting are ongoing.

Before the success of ramucirumab, tyrosine kinase inhibitors had been explored as antiangiogenic agents in the treatment of esophagogastric cancers, but the results are have been disappointing.

Sorafenib, a multitarget TKI of BRAF, VEGF, and PDGFR, was tested in Phase II trial in combination with oxaliplatin in patients who had progressed on first-line cisplatin/fluoropyrimidine CT[83]. In this trial, the primary endpoint of efficacy was unmet.

Sunitinib was studied in a phase II trial in patients with advanced gastric or GE junction tumors, who had progressed to CT[84]. The clinical benefit rate was 7.7% with 32.1% of patients exhibiting disease stability. The addition of docetaxel to sunitinib resulted in a higher objective RR (41.1% *vs*. 14.3%, $p = 0.02$) although this study did not meet its primary endpoint of prolonging time-to-progression[85].

The US Food and Drug Administration (FDA) has been recently improved the use of Ramucirumab in combination with Paclitaxel for advanced gastric or gastroesophageal junction adenocarcinoma.

Another important pathway in gastric cancerogenesis involves mesenchymal-epithelial transition factor (MET) [86,87].

Overexpression or amplification of the MET factor has been observed in GC and been correlated with unfavorable clinical outcomes[88,89].

Compared to the proportion of genes identified by immunohistochemical (IHC) detection of overexpression, the rate of detection of activating mutations or amplifications of MET gene is higher, defining a small group of cancers with aggressive clinical behaviour regardless of disease stage[90].

AMG 337 is a highly selective, orally available MET inhibitor that showed promising preclinical activity. In a multicenter, Phase I, open-label trial, 80 patients with MET-amplified cancers and good performance status (PS) received increasing doses of AMG 337 monotherapy, defining 300 mg/day as the maximum tolerated dose[91]. In the small subset of 13 heavily pretreated patients with MET-amplified gastrooesophageal cancers exposed to AMG 337, the investigators observed a notable 62% rate of response. Interestingly, the response was fast and usually detectable within 4 weeks from treatment start, which may be a remarkable advantage for symptomatic patients. The experimental treatment had a favorable profile of tolerability. The most common side effects were headache (45%), nausea (32%), vomiting (21%), fatigue (14%), and peripheral oedema (12%); headache (9%) and fatigue (4.5%) were the most frequent severe adverse events. Another MET inhibitor is Onartuzumab; it is a recombinant, fully humanized, monoclonal anti-MET antibody. Results of the randomized Phase II trial testing upfront FOLFOX6 with onartuzumab at the dose of 10 mg/kg or FOLFOX6 plus placebo were presented[92]. One hundred and twenty-three patients with advanced gastroesophageal cancer were enrolled from 25 centers; key eligibility criteria included no previous treatments for metastatic disease, Eastern Cooperative Oncology Group (ECOG) PS status of 0 or 1, and retention of organ function. MET-positive patients were well balanced in the two arms: 28% in the experimental arm *vs*. 33% in the control arm. At data cut-off, 96 out of 121 randomized patients had PFS events, 74% of those exposed to FOLFOX and onartuzumab and 82% of those receiving FOLFOX and placebo. The primary end point, PFS, in the intention-to-treat population, was not met (6.77 months in the onartuzumab arm, 6.97 months in the placebo arm; hazard ratio [HR]: 1.08, 95% confidence interval [CI]: 0.71–1.63). Also, the pre-planned analyses in the MET-positive population generated similarly disappointing results: median PFS was 5.95 months for those exposed to FOLFOX6 and onartuzumab *vs*. 6.8 months for those treated with FOLFOX6 and placebo (HR: 1.38). No differences were found despite the use of different definitions for MET positivity. The addition of onartuzumab was not beneficial, and produced more adverse events.

Phase III trial testing onartuzumab was prematurely interrupted because of failure of the drug in lung cancers, and another randomized study testing rilotumumab in the advanced disease setting failed to meet the primary trial end point[93,94].

New Strategies

Targeting the immune checkpoints in solid malignancies is becoming a major methodological approach. Lymphocytes T may recognize and eliminate cancer antigens, while immune checkpoints such as cytotoxic T-lymphocyte-associated antigen (CTLA)-4 and programmed cell death (PD-1) receptor and its ligands (PD-L1, PD-L2) can suppress the activity of T-lymphocytes.

Therefore, enhancing antitumor immunity by blocking PD-1 is now an attractive reality.

Pembrolizumab, a highly selective IgG4k, humanized monoclonal antibody against PD-1, has recently received approval from the FDA for the treatment of advanced melanoma after the failure of ipilimumab administration or BRAF V600E-

Table I. Targeted drugs and trials for GCs.

Agents	Target	Most significant trials	Results	Ref
Trastuzumab	HER2	584 patients HER2+ who receive fluoropyrimidine plus cisplatin with or without trastuzumab	OS increased of 2.7/mo ($p = 0.0046$) PFS increased of 1.2/mo ($p = 0.002$)	Bang YJ, 2010[74]
Bevacizumab	VEGF-A	AVAGAST phase III	No improvements in OS were recorded	Shah MA, 2012[77]
Ramucirumab	VEGFR-2	Randomized placebo *vs*. ramucirumab (REGARD) in patients (pts) who had disease progression after first-line CT	OS 5.2/mo *vs*. 3.8/mo (placebo group) ($p = 0.047$)	Fuchs CS, 2014[80]
		Randomized Paclitaxel ± Ramucirumab (RAINBOW) in pts with metastatic GCs who failed first-line CT	OS 9.6/mo *vs*. 7.4/mo (paclitaxel alone) $p = 0.017$	Wilke H, 2014[81]
Sunitinib	VEGFR, PDGFR, c-KIT, FLT3	Phase II trial in pts with advanced GC Junction who had progression after CT	Clinical benefit rate 7.7% OS 6.8/mo RR 41.1% in addition of docetaxel ($p = 0.02$)	Bang YJ, 2011[84], Yi JH, 2012[85]
Sorafenib	VEGFR, PDGFR, KIT, B-RAF	Phase II (GEMCAD) in pts who had progression after Cisplatin/5-FU	OS 6.5/mo PFS 3/mo Failure of primary endpoint	Martin-Richard M, 2013[83]
AMG 337	c-MET	Phase I trial in 80 pts MET+	RR 62%	Forner A, 2012[91]
Onartuzumab	c-MET	Phase II FOLFOX6 plus onartuzumab or placebo in 123 pts MET+	PFS was failed (6.8/mo *vs*. 7.0/mo)	Thorgeirsson SS[92]
Pembrolizumab (MK-3475)	IgG4k anti-PD-1	KEYNOTE-012 cohort of 39 pts with PD-1+ advanced GC	RR 30.8%	Muro K, 2015[99]

mutant melanoma in progression following BRAF inhibitor administration[95]. Because the high expression of PD-L1 on tumor gastric cells and macrophages can suppress immune surveillance and permit neoplastic growth, the molecule has become an interesting target even in GC[96,97]. Preliminary data of the KEYNOTE-012 gastric cohort study, in which pembrolizumab (MK-3475) was given at 10 mg/kg every 2 weeks to 39 patients with PD-L1-positive advance GC, were recently presented[98]. The trial enrolled heavily pretreated Asian (19) or non-Asian (20) patients, wherein 67% received ≥ 2 treatment lines. Overall RR was 30.8% (95% CI: 17.0–46.6) and 41% of patients experienced a decrease in tumor burden. The aim of the abstract presented at the 2015 Gastrointestinal Cancers Symposium was to analyze the relationship between PD-L1 expression and clinical outcome in patients with advanced disease treated with pembrolizumab[97]. Muro et al[99] found a significant association between PD-L1 expression level and objective RR (one-sided $p = 0.10$). Median OS was not reached, but the 6-month OS rate was surprisingly high (69%). Though described as easily manageable by the authors, the toxicity profile appears a bit challenging, with five severe adverse events (peripheral sensory neuropathy, fatigue, decreased appetite, hypoxia, and pneumonitis) and one drug-related death (hypoxia). Because the immune-related response may not be fully captured by conventional response criteria, it would be interesting to assess the response with immune-related response criteria to further confirm the activity of pembrolizumab[100]. On the basis of the KEYNOTE results, a Phase III randomized trial that compares pembrolizumab to paclitaxel in patients with recurrent or metastatic gastric or gastroesophageal junction adenocarcinoma who progressed after first-line treatment have been planned.

Conclusions

Gastric cancer has long represented one of the most difficult gastrointestinal malignancies to treat. Encouragingly, recent progress with targeted therapies and multidisciplinary appraoches[101]

offers hope for patients with advanced GC, and expands the therapeutic armamentarium considerably against this formidable disease. Moreover, the use of the pharmacogenomic tests could improve the results concerning the response rates and the toxicity[102-106].

Conflict of Interest

Any of the Authors has financial or personal relationships with other people or organizations that could potentially and inappropriately influence (bias) this work and conclusions.

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