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TOPIC HIGHLIGHT

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Medical management of gastric cancer: A 2014 update

Elena Elimova, Hironori Shiozaki, Roopma Wadhwa, Kazuki Sudo, Qiongrong Chen, Jeannelyn S Estrella, Mariela A Blum, Brian Badgwell, Prajnan Das, Shumei Song, Jaffer A Ajani

Elena Elimova, Hironori Shiozaki, Roopma Wadhwa, Kazuki Sudo, Qiongrong Chen, Mariela A Blum, Shumei Song, Jaffer A Ajani, Department of Gastrointestinal Medical Oncology, University of Texas, Anderson Cancer Center, Houston, TX 77030, United States
Jeannelyn S Estrella, Pathology, University of Texas, Anderson Cancer Center, Houston, TX 77030, United States
Brian Badgwell, Surgical Oncology, University of Texas, Anderson Cancer Center, Houston, TX 77030, United States
Prajnan Das, Radiation Oncology, University of Texas, Anderson Cancer Center, Houston, TX 77030, United States
Author contributions: Elimova E and Ajani JA both contributed to writing the original paper; Shiozaki H, Wadhwa R, Sudo K, Chen Q, Estrella JS, Blum MA, Badgwell B, Das P and Song S contributed by editing the text and adding information pertaining to their field of expertise.
Correspondence to: Jaffer A Ajani, MD, Department of Gastrointestinal Medical Oncology, University of Texas, Anderson Cancer Center, 1515 Holcombe Blvd, (FC10.3022), Houston, TX 77030, United States. jajani@mdanderson.org
Telephone: +1-713-7922330 Fax: +1-713-7944535
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Abstract

Gastric cancer represents a serious health problem on a global scale. It is the second leading cause of cancer-related death worldwide. Novel therapeutic targets are desperately needed because the meager improvement in the cure rate of about 10% realized by adjunctive treatments to surgery is unacceptable as > 50% patients with localized gastric cancer succumb to their disease. Either postoperative chemoradiotherapy (United States), pre-and post-operative chemotherapy (Europe), and adjuvant chemotherapy after a D2 resection (Asia) can all be regarded as standards of care in the localized gastric cancer management. In metastatic disease the addition of trastuzumab to chemotherapy is standard of care in Her2 positive disease. In the HER2 negative population, the treatments remain limited. In the first line setting, the standard of care is a combination of fluoropyrimidine and platinum containing chemotherapy, with or without epirubicin or docetaxel. The results of targeted therapy trials have by and large been disappointing, but none of these trials looked at an appropriately enriched population. Finally there is a meager overall survival benefit in treating patients with metastatic disease in the second line setting, with either irinotecan, docetaxel or ramucirumab however none of these drugs have been compared head to head in a well-powered randomized controlled trial.

Key words: Chemotherapy; Gastric cancer; Chemoradiation; Metastatic; Localized

Core tip: The standard of care for the management of localized gastric cancer continues to vary depending on where in the world this treatment takes place. In metastatic gastric cancer the outcomes remain poor. The first line treatment consists of trastuzumab in addition to chemotherapy in Her2 positive disease or fluoropyrimidine and platinum (with or without docetaxel or epirubicin) in Her2 negative disease. What is now clear is that second line chemotherapy, with either irinotecan, docetaxel or ramucirumab does improve overall survival.

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INTRODUCTION

Gastric cancer represents a serious health problem on

a global scale. It is the second leading cause of cancer-related death worldwide[1]. Eastern Asia, Eastern Europe, and South America are major endemic areas with a high incidence of gastric cancer. In the United States, gastric cancer is relatively uncommon, with 21600 new cases and 10990 cancer deaths occurring in 2013[2]. Between 2002 and 2008 the 5-year relative survival rate was only 27% according to the SEER database[3]. More than 90% of the tumors are adenocarcinomas, the focus of this review.

It is important to note, that despite these worrying statistics, the incidence of gastric cancer globally has been decreasing since World War Ⅱ[4]. The factors that have led to this decline include improved living standards[4-7], and early detection strategies that have reduced death rates in countries such as Japan[8].

The only curative option in the treatment of gastric cancer is surgery and for metastatic disease patients, conventional chemotherapy has shown only a modest benefit in metastatic disease with an average survival of approximately ten months.

This Review will primarily focus on the medical treatments for localized and metastatic stage gastric cancer and the challenges we face with the development and use of targeted molecular therapies.

RISK FACTORS FOR GASTRIC CANCER

Factors associated with an increased risk of gastric cancer include nutrition, such as high salt and nitrate intake, a diet low in vitamins A and C, the consumption of large amounts of smoked or cured foods, lack of refrigerated foods and poor quality drinking water[9]. Occupational exposure to rubber and coal also increase the risk. Other risk factors which have been implicated include: cigarette smoking, *Helicobacter pylori* (*H. pylori*) infection, Ebstein-Barr virus, radiation exposure, and prior gastric surgery for benign ulcer disease[10]. More recently, a number of authors have demonstrated that polymorphisms in inflammatory genes can be associated with gastric cancer risk[11-13]. Genetic risk factors include type A blood group, pernicious anemia, family history of gastric cancer, hereditary non-polyposis colon cancer, and Li-Fraumeni syndrome[10]. In a limited number of patients (1%-3%), its diagnosis is associated with inherited syndromes. E-cadherin mutations occur in approximately 25% of families with an autosomal-dominant hereditary form of diffuse gastric cancer[14]. Genetic counseling is recommended, and prophylactic gastrectomy should be considered in young, asymptomatic individuals with germline truncating CDH1 (E-cadherin 1) mutations with a family history of highly penetrant hereditary diffuse gastric cancer[15].

PREVENTION

Results from a number of studies have demonstrated an increased likelihood of *H. pylori* infection in patients with gastric cancer, particularly cancer of the distal stomach[16,17]. Although gastric cancer does not occur in most patients infected with *H. pylori*, the increased risk in patients who are infected has raised the issue of whether *H. pylori* eradication might decrease the risk of gastric cancer. Although the role of *H. pylori* in gastric cancer pathogenesis is well defined, no definitive evidence shows that mass eradication could reduce the incidence of gastric cancer[18]. A large Chinese study of 1630 patients showed no benefit in the prevention of gastric cancer with the eradication of *H. pylori*[19]. However, in a subgroup of patients with no precancerous lesions on presentation, no patient developed gastric cancer during a follow-up of 7.5 years after *H. pylori* eradication treatment compared with those who received placebo (0 *vs* 6; $P = 0.02$)[19]. In contrast, in another large study short-term treatment with amoxicillin and omeprazole statistically significantly reduced gastric cancer incidence by 39% during the period extending 14.7 years after *H. pylori* treatment[20]. A meta-analysis suggested that eradication could reduce the risk of gastric cancer, however this meta-analysis was criticized for methodological issues[21]. At the present time the treatment of this infection should be confined to patients with peptic ulcer disease, MALT, and post endoscopic resection for esophogogastric cancer and a role of broad prevention strategy has yet to be defined.

TREATMENT OF LOCALIZED DISEASE

Localized gastric cancer can be classified as clinical T1 disease or higher with or without involved regional lymph nodes. A minimum of 15 examined lymph nodes is recommended for adequate staging. Clinical staging has improved with the availability of diagnostic modalities such as endoscopic ultrasound, computed tomography (CT), combined PET-CT, magnetic resonance imaging, and laparoscopic staging (For details on staging please refer to[22]).

The adjunctive therapy used for the treatment of localized gastric cancer in addition to surgery depends on geographic location in the world. In North America and Europe, results from the INT-0116[23] (the adjuvant chemoradiation approach) and Medical Research Council Adjuvant Infusional Chemotherapy (MAGIC) (the neoadjuvant and adjuvant chemotherapy approach) trials have established the standard of care[24]. In Asia, on the other hand adjuvant chemotherapy following a D2 resection is considered the gold standard[25,26].

Perioperative chemotherapy

This approach is based on the assumption that neo-adjuvant systemic therapy, can lead to tumor down-staging, leading to an improved R0 resection rate. This is particularly significant in Western patients in whom the tumors are usually bulky at diagnosis[27]. The question of the benefit of neo-adjuvant chemotherapy was addressed as a part of the MAGIC trial, which has established Level 1 evidence for this approach (Table 1)[24].

The MAGIC trial enrolled 503 patients with gastric,

Table 1 Major phase Ⅲ trials for gastric cancer in the localized setting

Ref.	*n*	Treatment arms	HR for overall survival or death (*P* value)	Survival comparison
Macdonald *et al*[23]	556	Surgery and chemoradiotherapy[1] *vs* surgery	1.35 (0.005)	Overall survival: 36 mo *vs* 27 mo
Cunningham *et al*[24]	503	ECF, surgery, ECF vs surgery	0.75 (0.009)	5-yr overall survival: 36.3% *vs* 23%
Fuchs *et al*[62]	546	5-FU, chemoradiotherapy, 5-FU *vs* ECF, chemoradiotherapy, ECF	1.03 (0.800)	Overall survival: 37 mo *vs* 38 mo
Lee *et al*[31]	458	Surgery and XP *vs* surgery, XP, XRT, XP	HR for DFS 0.6865 (0.0471)	3-yr DFS: 74.2% *vs* 78.2%
Sakuramoto *et al*[25]	1059	Surgery *vs* surgery and S-1	0.68 (0.003) 5 yr data in JCO 0.669	3-yr overall survival: 70.1% *vs* 80.1% 3-yr RFS: 72.2% *vs* 59.6%
Bang *et al*[26]	1035	XELOX and surgery *vs* surgery	0.56 (< 0.0001)	3-yr DFS: 74% *vs* 59%
Ychou *et al*[28]	224	Perioperative chemotherapy *vs* surgery	0.69 (0.02)	5-yr overall survival: 38% *vs* 24%
Tsuburaya *et al*[63]	1495	Surgery and UFT *vs* surgery and S-1 *vs* surgery, paclitaxel and UFT *vs* surgery, paclitaxel and S-1	NR	NR
ARTIST II[64]	1000	Surgery and S1Ox *vs* surgery, S1Ox, XRT and S1Ox	NR	NR
Okines *et al*[65]	1100	ECX and bevacizumab *vs* ECX	NR	NR
Leong *et al*[33]	752	Preoperative chemotherapy *vs* preoperative chemoradiotherapy	NR	NR

[1]Forty-five Gy radiotherapy plus 5-FU. Ongoing trial; Hazard ratio reduced to 0.8 on follow-up analysis. 5-FU: 5-Fluorouracil; ASC: Active symptom control; BSC: Best supportive care; CapeOx: Capecitabine and oxaliplatin; CF: Cisplatin and 5-FU; CX: Cisplatin and capecitabine; DFS: Diseas-free survival; ECF: Epirubicin, cisplatin and 5-FU; ECX: Epirubicin, cisplatin and capecitabine; EOC: Epirubicin, oxaliplatin and capecitabine; HR: Hazard ratio; mEOC–P: EOC plus panitumumab; PFS: Progression-free survival; RFS: Relapse-free survival; UFT: Tegafur and uracil; XELOX: Capecitabine and oxaliplatin; XP: Capecitabine and cisplatin; S1Ox: S1 and oxaliplatin; XRT: Chemoradiation.

gastroesophageal junction, and esophageal carcinoma[24]. These patients were randomized to receive three cycles of perioperative chemotherapy, consisting of epirubicin, cisplatin and 5-fluorouracil (5-FU) (ECF) followed by surgery, followed by three more cycles of ECF or to surgery followed by observation. In this trial, post-operative chemotherapy proved hard to deliver with only 34% of patients receiving this treatment and only 68% of patients underwent a curative resection. Despite this, both progression free survival (PFS) and overall survival (OS) were improved in the group receiving ECF (HR for PFS hazard ratio for progression, 0.66; 95%CI: 0.53-0.81; $P < 0.001$, and HR for OS = 0.75; 95%CI: 0.60-0.93; $P = 0.009$). Five-year survival rates were 36.3% (95%CI: 29.5%-43.0%) among patients in the perioperative-chemotherapy group and 23.0% (95%CI: 16.6%-29.4%) among those in the surgery group[24]. Taken together this suggests that that majority of the benefit may in fact come from the preoperative portion of the chemotherapy.

A second, French study supports the results of the MAGIC trial. This is the FNCLCC and FFCD multicenter phase Ⅲ trial that was terminated prematurely for poor accrual and is therefore not adequately powered[28]. Overall, 224 patients with resectable adenocarcinoma of the lower esophagus, gastroesophageal junction (GEJ), or stomach (only 25%) were randomly assigned to either perioperative chemotherapy (with Cisplatin and 5-FU) and surgery followed by three to four cycles of cisplatin and 5-FU or surgery alone. Only approximately 50% of patients received any post-operative chemotherapy. Despite these issues the chemotherapy and surgery group had a significantly higher OS (HR for death = 0.69; 95%CI: 0.50-0.95; $P = 0.02$) and DFS (HR for recurrence or death = 0.65; 95%CI: 0.48-0.89; $P = 0.003$). Five-year survival rates were 38% (95%CI: 29%-47%) in the chemotherapy and surgery group compared to 24% (95%CI: 17%-33%) in the surgery group. These results are quite similar to those of the MAGIC trial and bring into question the usefulness of the addition of epirubicin to cisplatin and 5-FU.

In contrast, a study by the European Organization for Research and Treatment of Cancer (EORTC) did not demonstrate a benefit from the addition of perioperative chemotherapy[29]. This trial showed a significantly increased R0 resection rate but failed to demonstrate a survival benefit for the addition of chemotherapy, however it was not sufficiently powered to demonstrate a difference given its premature termination due to poor accrual. An ongoing Japanese Clinical Oncology Group (JCOG0501) trial is attempting to answer the question of whether perioperative chemotherapy with cisplatin and S-1 adds anything to their standard of care which is surgery followed by adjuvant S-1 chemotherapy. The results of this trial are awaited; however, they are unlikely to be generalizable to the North American population because of different tumor biology.

POSTOPERATIVE CHEMORADIOTHERAPY

The appeal of adjuvant chemoradiation therapy comes from Level 1 evidence of its benefit from the Intergroup 0116 trial that showed a significant improvement in OS in the group of patients treated with adjuvant chemoradiotherapy (Table 1)[23,30]. In this trial 559 patients with stage Ⅰ B to Ⅳ disease were randomized to chemoradiation following surgery or surgery alone. The chemoradiation group received chemotherapy consisting of 5-FU and leucovorin starting on day 1 and was followed by chemo-

radiotherapy beginning 28 d after the start of the initial cycle of chemotherapy. Chemoradiotherapy consisted of 4500 cGy of radiation at 180 cGy per day, five days per week for five weeks, with fluorouracil (400 mg/m^2 per day) and leucovorin (20 mg/m^2 per day) on the first four and the last three days of radiotherapy. One month after the completion of radiotherapy, two five-day cycles of fluorouracil (425 mg/m^2 per day) plus leucovorin (20 mg/m^2 per day) were given one month apart. The three-year survival rates were 50% in the chemoradiation group and 41% in the surgery-only group. The hazard ratio for death in the surgery-only group, as compared with the chemoradiation group, was 1.35 (95%CI: 1.09-1.66; P = 0.005). The hazard ratio for relapse in the surgery-only group, as compared with the chemoradiation group, was 1.52 (95%CI: 1.23-1.86; $P < 0.001$)[23]. Recently updated results of this study continue to demonstrate a benefit both in terms of OS and recurrence free survival (RFS)[30]. The major issue of this study was that the majority of patients did not receive an adequate lymph node dissection. Although a D1 resection was mandated per protocol, more than 50% of patients underwent a D0 resection, and only 10% of patients underwent a D2 resection. It is therefore questioned whether the survival difference occurred because of inadequate surgery rather than a true benefit of chemoradiation.

The Adjuvant Chemoradiation Therapy in Stomach Cancer (ARTIST) trial[31] compared adjuvant chemoradiotherapy with adjuvant chemotherapy after an R0 resection with D2 dissection in 458 patients. However, the 3-year DFS rate, as the primary end point was not statistically different between the two groups. In the subgroup analysis, patients with node-positive cancer in the adjuvant chemoradiotherapy group had a significantly better 3-year DFS rate than those in the adjuvant chemotherapy group. This result suggests that the adjuvant chemoradiotherapy might have been beneficial compared with adjuvant chemotherapy among the node-positive populations, a theory currently being tested in the ARTIST Ⅱ Trial. This trial differs from The Macdonald trial in that all patients received a D2 resection and the chemotherapy administered to all patients consisted of S1 and oxaliplatin (and not 5-FU). This brings into question the usefulness of chemoradiation after a D2 resection.

Finally the results of two trials, the TOPGEAR trial and the CRITICS trial, exploring the role of chemoradiotherapy are still awaited[32,33].

Adjuvant chemotherapy

The benefits of adjuvant chemotherapy after a D2 resection were initially demonstrated in Japan and the chemotherapy used was S1 (an oral fluoropyrimidine)[25]. The Adjuvant Chemotherapy Trial of S-1 for Gastric Cancer (ACTS-GC) trial randomized 1059 patients to 1 year of S-1 or observation. The primary analysis of follow-up data showed that the 3-year OS rate was 80.1% in the S-1 group and 70.1% in the surgery-only group. The hazard ratio for death in the S-1 group, as compared with the surgery-only group, was 0.68 (95%CI: 0.52-0.87; P = 0.003). This analysis was updated after five years of follow-up and demonstrated consistent results[34]. The OS rate at 5 years was 71.7% in the S-1 group and 61.1% in the surgery-only group (HR = 0.669; 95%CI: 0.540-0.828). The RFS rate at 5 years was 65.4% in the S-1 group and 53.1% in the surgery-alone group (HR = 0.653; 95%CI: 0.537-0.793).

A second Asian study, the Capecitabine and Oxaliplatin Adjuvant Study in Stomach Cancer (CLASSIC trial) randomized 1035 patients who had undergone D2 gastrectomy to capecitabine plus oxaliplatin for 6 mo or observation[26]. The study demonstrated a benefit of capecitabine and oxaliplatin treated patients for the primary end point of disease-free survival (at 3 years; HR = 0.56, 95%CI: 0.44-0.72; $P < 0.0001$) at the pre-specified interim analysis. After this analysis, the trial was stopped after a recommendation by the data monitoring committee. The mature OS data are awaited, however 3-year OS was 83% (95%CI: 79-87) in the chemotherapy group and 78% (74-83) in the surgery only group (HR = 0.72, 95%CI: 0.52-1.00; P = 0.0493). It is likely that an OS benefit will be found with longer follow-up.

A meta-analysis based on single patient-data from 3,838 patients and 17 randomized controlled trials showed a 7% improvement in OS (HR = 0.82; 95%CI: 0.76-0.90; $P < 0.001$) for fluorouracil-based postoperative chemotherapy when compared with surgery alone[35]. This meta-analysis was criticized because it combined studies from different time periods with differing eligibility criteria and therapeutic approaches, making it difficult to make a firm conclusion.

Based on the previously mentioned trials and meta-analysis, postoperative chemoradiotherapy (United States), pre-and post-operative chemotherapy (Europe), and adjuvant chemotherapy after a D2 resection (Asia) can all be regarded as standards of care in the localized gastric cancer management.

TREATMENT OF METASTATIC DISEASE

The medical treatment of metastatic gastric cancer is primarily palliative and confers a modest effect on OS. Multiple agents are active in the treatment of gastric cancer, including fluoropyrimidines (5-FU, capecitabine, and S1), anthracyclines, platinum agents, taxanes, irinotecan, and some targeted therapies such as trastuzumab for HER-2 overexpressing gastric cancers). Combination regimens are associated with higher response rates, and according to one meta-analysis, are also associated with increased survival when compared with single-agent chemotherapies[36]. By and large the trials addressing the value of targeted therapies, for example epidermal growth factor receptor (EGFR) and vascular endothelial growth factor (VEGF) were done in un-selected (not bio-marker enriched) populations and have not-surprisingly yielded

Table 2 Major phase Ⅲ trials for gastric cancer in the advanced setting

Trial	*n*	Treatment arms	HR for overall survival (*P* value)	Survival comparison
Advanced gastric cancer - first-line				
Bang *et al*[39]	584	CX, CF and trastuzumab *vs* CX and CF[1]	0.74 (0.0046)	Overall survival: 13.8 mo *vs* 11.1 mo
Ohtsu *et al*[42]	774	Cisplatin and 5-FU *vs* cisplatin, 5-FU and bevacizumab	0.87 (0.1002)	Overall survival: 10.1 mo *vs* 12.1 mo PFS: 5.3 mo *vs* 6.7 mo
Lordick *et al*[44]	904	CX *vs* CX and cetuximab	1.004 (0.9547)	Overall survival: 10.7 mo *vs* 9.4 mo
Waddell *et al*[45]	553	EOC *vs* mEOC–P	1.37 (0.013)	Overall survival: 11.3 mo *vs* 8.8 mo
Van Cutsem *et al*[37]	445	DCF *vs* CF	TTP 1.47 (< 0.001) OS 1.29 (0.02)	Time to progression: 5.6 mo *vs* 3.7 mo, 9.2 mo *vs* 8.6 mo
Koizumi *et al*[40]	305	S-1 and cisplatin *vs* S-1	0.77 (0.04)	Overall survival: 13.0 mo *vs* 11.0 mo
Ajani *et al*[66]	1053	Cisplatin and S-1 *vs* cisplatin and 5-FU	0.92 (0.20)	Overall survival: 8.6 mo *vs* 7.9 mo
Hecht *et al*[67]	545	CapeOx and lapatinib *vs* CapeOx and placebo	0.91 (0.35)	Overall survival: 12.2 mo *vs* 10.5 mo
Advanced gastric cancer - second-line				
Ohtsu *et al*[51]	656	BSC and placebo *vs* BSC and everolimus	0.90 (0.1244)	Overall survival: 4.3 mo *vs* 5.4 mo
Fuchs *et al*[47]	355	BSC and ramucirumab *vs* BSC	0.776 (0.047)	Overall survival: 5.2 mo *vs* 3.8 mo
Bang *et al*[52]	261	Lapatinib and paclitaxel *vs* paclitaxel	0.84 (0.2088)	Overall survival: 11.0 mo *vs* 8.9 mo
Kang *et al*[50]	202	BSC *vs* docetaxel or irinotecan	0.657 (0.007)	Overall survival: 3.8 mo *vs* 5.3 mo
Thuss-Patience *et al*[48]	40	Irinotecan and BSC *vs* BSC	0.48 (0.012)	Overall survival: 4.0 mo *vs* 2.4 mo
Cook *et al*[49]	168	Docetaxel and ASC *vs* ASC	0.67 (0.01)	Overall survival: 5.2 mo *vs* 3.6 mo

[1]Hazard ratio reduced to 0.8 on follow-up analysis. 5-FU: 5-Fluorouracil; ASC: Active symptom control; BSC: Best supportive care; CapeOx: Capecitabine and oxaliplatin; CF: Cisplatin and 5-FU; CX: Cisplatin and capecitabine; DFS: Diseas-free survival; ECF: Epirubicin, cisplatin and 5-FU; ECX: Epirubicin, cisplatin and capecitabine; EOC: Epirubicin, oxaliplatin and capecitabine; HR: Hazard ratio; mEOC–P: EOC plus panitumumab; PFS: Progression-free survival; RFS: Relapse-free survival; UFT: Tegafur and uracil; XELOX: Capecitabine and oxaliplatin; XP: Capecitabine and cisplatin; XRT: XP and radiotherapy.

disappointing results.

First line therapy

Only a minor amount of level 1 evidence exists for the treatment of gastric cancer in the first line setting. In fact, only docetaxel[37], cisplatin/oxaliplatin[38], and trastuzumab[39] use is supported by high level evidence (Table 2).

A phase Ⅲ trial involving 445 patients with metastatic cancer randomized patients to receive, cisplatin and 5-FU or Cisplatin, 5-FU and docetaxel. They found that the addition of docetaxel was superior in terms of response rate (37% *vs* 25%; $P = 0.01$), time-to-tumor progression (5.6 mo *vs* 3.7 mo; $P < 0.001$), and OS (9.2 mo *vs* 8.6 mo; $P = 0.02$)[37]. One could question the clinical significance of a less than one month absolute improvement in OS particularly in the context of significant toxicities, most notably, a high rate of febrile neutropenia (30%). Importantly, this regimen should not be used in patients who have a reduced performance status.

Another randomized phase Ⅲ trial including 1002 patients, tried to improve on the regimen of ECF, by substituting oral capecitabine (X) for infusional 5-FU, and by using the non-nephrotoxic oxaliplatin (O), rather than cisplatin. The combination of epirubicin/oxaliplatin/capecitabine (EOX) was found to be less toxic and at least as effective as ECF. The median survival times for ECF (control), ECX, EOF, and EOX arms were 9.9 mo, 9.9 mo, 9.3 mo, and 11.2 mo, respectively. The one year survival rates were 37.7%, 40.8%, 40.4% and 46.8%, respectively. In the secondary analysis, OS was longer with EOX than with ECF, with a hazard ratio for death of 0.80 in the EOX group (95%CI: 0.66-0.97; $P = 0.02$). Progression-free survival and response rates did not differ significantly among the regimens[38].

The third randomized phase Ⅲ trial enrolled 305 patients in Japan, to either S-1 alone or S1 and cisplatin. Median OS was significantly longer in patients assigned to S-1 plus cisplatin (13 mo) than in those assigned to S-1 alone [11 mo (HR for death = 0.77; 95%CI: 0.61-0.98; $P = 0.04$)]. Progression-free survival was significantly longer in patients assigned to S-1 plus cisplatin than in those assigned to S-1 alone (median progression- free survival 6 mo *vs* 4 mo; $P < 0.0001$)[40]. This trial provided evidence for the superiority of the addition of cisplatin when compared to a fluoropyrimidine alone, and established the use of a fluoropyrimidine in addition to a platinum as a reasonable treatment option.

Trastuzumab was the first targeted agent with documented clinical activity in the advanced gastric and gastroesophageal setting cancer setting. This treatment is useful in the HER2 enriched population, however approximately 20% of gastric cancers and 30% of gastroesopageal cancers overexpress HER2 so that a relatively small proportion of patients benefits from the treatment. The trastuzumab in Gastric Cancer (ToGA) trial randomized 584 patients whose tumors overexpressed HER2 by immunohistochemistry (IHC) or fluorescence in situ hybridization (FISH) to receive a fluoropyrimidine (5-FU or capecitabine) plus cisplatin with or without trastuzumab. The chemotherapy was administered every 3 wk for six cycles and trastuzumab was administered every 3 wk until disease progression[39]. They found that the addition of trastuzumab to chemotherapy increased OS from 11.1 mo to 13.8 mo (HR = 0.74, 95%CI: 0.60-0.91;

$P = 0.0046$). The secondary endpoints of PFS (6.7 mo *vs* 5.5 mo; $P = 0.0002$) and response rate (47.3% *vs* 34.5%; $P = 0.0017$) were also improved. On extended follow-up the HR of OS for the addition of trastuzumab has decreased to 0.80[41], indicating that although real the response to trastuzumab may be short lived. The difference in median OS was reduced from 2.7 mo to merely 1.4 mo, representing an approximate 50% decrease in the effect of trastuzumab, which suggests that only a few patients benefit. Based on this trial the combination of trastuzumab to chemotherapy has become the standard of care in patients whose tumors overexpress HER2.

In contrast to the encouraging results with trastuzumab in HER2 overexpressing cancers, bevacizumab failed to demonstrate an OS benefit when it was added to a combination of cisplatin and fluoropyrimidine in patients with advanced gastric and gastroesophageal junction adenocarcinoma[42]. A total of 774 patients were randomized and the median OS was 12.1 mo with bevacizumab plus fluoropyrimidine-cisplatin and 10.1 mo with placebo plus fluoropyrimidine-cisplatin (HR = 0.87; 95%CI: 0.73-1.03; $P = 0.1002$). Both median progression-free survival (6.7 mo *vs* 5.3 mo; HR = 0.80; 95%CI: 0.68-0.93; $P = 0.0037$) and overall response rate (46.0% *vs* 37.4%; $P = 0.0315$) were significantly improved with bevacizumab *vs* placebo[42]. In a pre-planned subgroup analysis, they were able to show that a benefit in terms of OS existed for "Pan-American" patients but not for European and Asian patients. This might point to differences in tumor biology, but is also dependent on other factors. A subsequent retrospective biomarker analysis of the AVAGAST trial showed that patients with high baseline plasma VEGF-A levels and with low baseline expression of neuropilin-1 seemed to have an improved OS. For both biomarkers, subgroup analyses demonstrated significance only in patients from non-Asian regions[43]. It is important to note that neither of these biomarkers has been 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.

Equally disappointing results were also reported from two EGFR targeting trials (EXPAND and REAL-3)[44,45]. The EXPAND trial randomized 904 patients to receive capecitabine and cisplatin, with or without cetuximab. This study did not achieve its primary endpoint, with the median PFS for 455 patients allocated capecitabine-cisplatin plus cetuximab being 4.4 mo compared to 5.6 mo for 449 patients who were allocated to receive capecitabine-cisplatin alone (HR = 1.09, 95%CI: 0.92-1.29; $P = 0.32$)[44]. The REAL-3 study was terminated prematurely because a statistically significantly lower OS was noted in patients treated with modified epirubicin/oxaliplatin/capecitabine (EOC) and panitumumab. The final analysis of this study, which randomized patients with advanced esophogogastric adenocarcinoma, was published in Lancet Oncology[45]. Median OS of patients allocated EOC was 11.3 mo (95%CI: 9.6-13.0) compared with 8.8 mo (7.7-9.8) in 278 patients allocated to modified EOC and panitumumab (HR = 1.37, 95%CI: 1.07-1.76; $P = 0.013$). There was a non-significant trend to worse outcome in patients treated with panitumumab, again highlighting the importance of patient selection in randomized controlled trials. A biomarker analysis of the REAL-3 trial did not identify any biomarkers whose presence predicted resistance to modified EOC and panitumumab, however only a few biomarkers were evaluated in this study[46].

In summary, the standard of care in the first line setting remains a combination of fluoropyrimidine and platinum containing chemotherapy, with the addition of trastuzumab in the HER-2 enriched population. The results of targeted therapy trials have by enlarge been disappointing, but none of these trials looked at an appropriately enriched population.

Second line therapy

The validity of the use of second line chemotherapy, and its benefit in gastric cancer has long been questioned, however three recently published trials all demonstrated an OS prolongation, albeit very modest, when three agents were compared to best supportive care (BSC) (Table 2)[47-49]. A small German phase Ⅲ study (AIO trial) compared the efficacy of irinotecan plus BSC to BSC alone in patients with advanced gastric and gastroesophageal junction adenocarcinoma[48]. Only 40 patients were randomized and the study was closed early due to poor accrual. The hazard ratio for death is 0.48 with a 95% confidence interval of 0.25-0.92 favoring the active treatment with irinotecan ($P = 0.023$). The median survival is 4.0 mo (95%CI: 3.6-7.5) in the irinotecan arm and 2.4 mo (95%CI: 1.7-4.9) in the BSC-arm[48]. There were no documented responses to irinotecan in this trial. The second trial, COUGAR-02, randomized 186 patients to docetaxel plus BSC *vs* BSC alone. Docetaxel significantly improved OS over BSC alone [median 5.2 mo (95%CI: 4.1-5.9 mo) for docetaxel; 3.6 mo (95%CI: 3.3-4.4 mo) for BSC, HR = 0.67 (95%CI: 0.49-0.92); $P = 0.01$][49]. The recently published REGARD trial, randomized 355 patients to receive ramucirumab or placebo[47]. This study demonstrated a marginal improvement in median OS, 5.2 mo in patients in the ramucirumab group and 3.8 mo in those in the placebo group (HR = 0.776, 95%CI: 0.603-0.998; $P = 0.047$). Interestingly, the average patient on study treated with ramucirumab received treatments for two weeks longer than the average patient on placebo.

Another study which demonstrated an OS of patients treated with chemotherapy (either docetaxel or irinotecan) *vs* best supportive care was published by Kang *et al*[50] Median OS was 5.3 mo among 133 patients in the chemotherapy arm and 3.8 mo among 69 patients in the best supportive care arm (HR = 0.657; 95%CI: 0.485-0.891; one-sided $P = 0.007$). There was no median OS difference between docetaxel and irinotecan (5.2 mo *vs* 6.5 mo; $P = 0.116$).

Two other large studies in the second and third

line setting were recently published with disappointing results[51,52]. The GRANITE-1 study randomized 656 patients to everolimus plus BSC *vs* placebo plus BSC. Unfortunately this study did not achieve its primary end point of OS [5.4 mo with everolimus and 4.3 mo with placebo (HR = 0.90; 95%CI: 0.75-1.08; $P = 0.124$)][51]. Notably, the estimated percentage of patients remaining progression free at 6 mo was higher with everolimus (12.0% *vs* 4.3%), as were the disease control rate (43.3% *vs* 22.0%) and the tumor shrinkage rate (37.8% *vs* 12.3%). These results suggest everolimus has activity in this heavily pretreated population. Identification of specific biomarkers for various patient subpopulations with advanced gastric cancer may help define those patients who would receive the most benefit from everolimus treatment[51]. Finally lapatinib, has been investigated in a large 420 patient study (TYTAN Trial), which randomized HER2 positive patients to lapatinib plus paclitaxel *vs* paclitaxel alone. Median OS was 11.0 mo for L + P and 8.9 mo for P 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 14.0 mo for the combination therapy and 7.6 mo for paclitaxel alone (HR = 0.59; $P = 0.0176$)[52]. Interestingly, it has recently been demonstrated that although the study mandated IHC HER 2 positivity, 35% of Patients in TYTAN had tumors classified as IHC0/1[52].

Two studies highlight the importance of identification and targeting of driver mutations, and their usefulness in the creation of appropriate biomarkers to direct care[53,54]. In a small study with crizotinib, two out of four patients with more than five MET copy number gains had a longer drug response duration than those with fewer gains[53]. Furthermore, in a phase Ⅱ study of rilotumumab (AMG 102), a fully human monoclonal antibody, the investigators were able to demonstrate that patients whose tumors had a high total c-MET expression had longer OS[54].

CONCLUSION

In summary, the treatment for gastric cancer remains quite complex with varying standards of care across the world. However outcomes in the western world remain poor, even in localized disease and better treatments are clearly needed.

Either postoperative chemoradiotherapy (United States), pre-and post-operative chemotherapy (Europe), and adjuvant chemotherapy after a D2 resection (Asia) can all be regarded as standards of care in the localized gastric cancer management.

In the metastatic gastric cancer setting the benefit of the addition of trastuzumab to standard chemotherapy, in HER2 positive patients has clearly been established as the standard of care[39]. In the HER2 negative population, the treatments remain limited. In the first line setting, the standard of care is a combination of fluoropyrimidine and platinum containing chemotherapy, with or without epirubicin (which is of questionable benefit). The results of targeted therapy trials have by enlarge been disappointing, but none of these trials looked at an appropriately enriched population.

In the second line setting three agents have now been shown to improve OS over BSC[47-49]. The benefits in terms of OS are modest at best, with an average absolute improvement of one to two months. Ramucirumab provided a modest benefit over placebo in the REGARD[47] trial, however, the combination of ramucirumab plus paclitaxel provided greater and more meaningful benefit compared to paclitaxel in the RAINBOW[55] trial. We recommend combination of ramucirumab and paclitaxel in the second line setting over other options when possible.

Overall, the results with targeted therapy in the metastatic setting have generally been disappointing, this is likely because they used unselected and un-enriched (by bio-markers) patient populations. Sequencing strategies will hopefully help us find new potentially useful targets, which must be present in a larger proportion of patients.

All patients with localized gastric cancer should undergo multidisciplinary evaluation by medical oncologists, radiation oncologists, radiologists and surgeons. To go one step further because localized gastric cancer is a complex disease and we are dealing with a potentially curable situation, high-volume physicians in centers which have the necessary infrastructure should only treat patients. Only patients with stage T1aN0 disease should be evaluated for endoscopic therapy. Patients with clinical stage greater than T1bN0 should be offered adjunctive therapy (either pre- or post-operative) to increase the chances of cure. Suitable patients with metastatic disease can be offered both first and second line therapy with a known survival advantage.

FUTURE DIRECTIONS

Several studies of single nucleotide polymorphisms (SNPs) and genome-wide association studies (GWAS) have revealed some plausible genes implicated in gastric cancer and the targeting of driver mutations/genetic alterations and this is likely the future of cancer treatment. These types of studies although interesting, have their limitations.

Rare germline mutations (< 0.001% of the general population) in *CDH1* have been implicated in familial cases of gastric cancer[15,56]. Intuitively, SNPs can facilitate gastric cancer such that one adverse allele contributes weakly, but multiple adverse alleles can considerably increase the risk[57]. However, these studies have had limited yield and none can be used clinically because SNP studies require customized approaches (with *a priori* assumptions that alterations in certain functional SNPs would increase susceptibility to gastric cancer). In spite of the correlations between certain SNPs and gastric cancer, prospective validation requiring large, population-based studies have been lacking as they are labor-intensive and resource-intensive.

GWAS have been used to scan the whole genome to

identify SNPs that are implicated in the disease[58]. Such studies have identified genes not previously known to be involved in gastric cancer-for example, *PLCE1* (encoding pancreas-enriched phospholipase C) has an oncogenic role in skin and intestinal cancers[59], but is now thought to have a role in gastric cancer. A Chinese research group documented that SNPs in *PSCA* (encoding prostate stem-cell antigen) was associated with diffuse gastric cancer[60,61].

The large volume of genomic information in the field of cancer medicine remains unutilized. Because cancer is a complex and heterogeneous disease the gap between genomic evidence and personalized medicine is wide. The primary problem we face is an incomplete database of genomic information important in cancer biology and a rudimentary understanding of how those genomic alterations translate into biologic consequences. We are unable to experimentally validate functionally relevant driver mutations and differentiate these from non-relevant bystanders because of the assay limitations, but also because genes act in specific contexts (*i.e.*, differing microenvironments and developmental states can influence the expression of a genetic factor of interest). Because of the sheer complexity of cancer it is likely that hundreds of distinct molecular entities contribute to the maintenance of cancer in the context of hundreds of other genetic and epigenetic events.

For the future it is important to galvanize the research community towards the single goal of understanding the functionality of genes and driver mutations in particular. To date our efforts have been largely uncoordinated and random, however we believe that this effort will be helped by the transdisciplinary team science approaches with multiple scientists interacting and working towards the same goal.

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