Gastric Cancer: An Update

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Gastric cancer is an aggressive malignancy, which, if metastatic or unresectable, is incurable. However, with metastatic or unresectable disease, patients receive a palliative benefit from chemotherapy. Although the understanding of the biology of this disease is increasing, the development of biologically targeted therapies for gastric cancer has been limited. Cytotoxic therapy remains the standard approach, and although there is agreement on the active agents and active combination chemotherapy regimens, consensus on the standard or reference regimen is lacking. This article reviews the pathophysiology of this disease, placing it in the context of its epidemiology, and the current advances in the treatment of this disease.

Introduction

Gastric cancer is an aggressive neoplasm that is associated with an extremely poor prognosis. Median survival for metastatic or unresectable disease is approximately 8 to 10 months. On a global basis, cancer of the stomach is the third most prevalent malignancy, with approximately 947,000 new cases in 2000, and the second leading cancer cause of death (734,000 deaths annually). Almost two thirds of cases occur in developing countries [1]. The incidence of stomach cancer is highest in Japan, Central and South America, and eastern Asia and much lower in North America and parts of Africa. In the United States in 2005, approximately 22,400 cases of gastric cancer were diagnosed, and 12,100 patients died from this disease [2]. A distinct racial disparity has been observed with this disease that is not well understood. Gastric cancer is notable for a race-specific propensity for the site of the disease within the stomach, the stage at diagnosis, and for survival following diagnosis [3,4•]. Specifically, in one large cohort study from southern California, Asian patients were more likely to have localized disease (eg, lymph node negative, odds ratio ([OR]=1.61; 95% CI, 1.23–2.10), less likely to have tumors of the gastroesophageal junction and proximal stomach (OR=0.22; 95% CI, 0.15–0.31), and less likely to be older than 50 years (OR=0.58, 95% CI, 0.43–0.77) [3]. Perhaps most notable was the marked racial variance in 5-year survival rates in this cohort study: 5-year survival for patients of Asian ethnicity was 20.9%, whereas for white patients, 5-year survival was 10.2%. The University of Texas M.D. Anderson gastric cancer registry demonstrated a similarly high survival rate in Asian patients (5-year survival of 26%) but also showed that blacks had the worst prognosis (5-year survival of 9%) and that Hispanics and white patients had an intermediate prognosis (5-year survival of 13% and 11%, respectively). In this study, the significantly worse survival of black patients was independent of stage, tumor location, or histologic subtype [4•]. These epidemiology, prevalence, and mortality statistics suggest that cancers of the stomach are of significant clinical relevance to the practicing oncologist and that many of the underpinnings of the disease pathophysiology are not well understood.

In the current era of molecularly targeted therapies, notable limited advances have been made in the development of therapies targeted specifically for gastric cancer. This is undoubtedly related to the limited, but evolving understanding of the pathogenesis of this disease, as described. As another example, virtually all stomach cancers are adenocarcinomas that can be pathologically distinguished according to the Lauren [5] classification as an intestinal or diffuse pathologic subtype. Intestinal gastric cancers are generally well differentiated, with a glandular appearance, and tend to expand through the stomach wall, whereas diffuse gastric cancers are non-cohesive cells that infiltrate through the stomach wall. Intestinal gastric cancers predominate in high-incidence areas, and this histology is responsible for much of the ethnic variation around the globe [6]. Despite these significant differences in the epidemiology of these two major types of gastric adenocarcinoma, the disease is generally treated uniformly with chemotherapy, independent of the histologic and biologic phenotype. It is no wonder we have made so little progress in the treatment of this disease with chemotherapy over the past 15 years. In this review I have highlighted some of the recent devel-

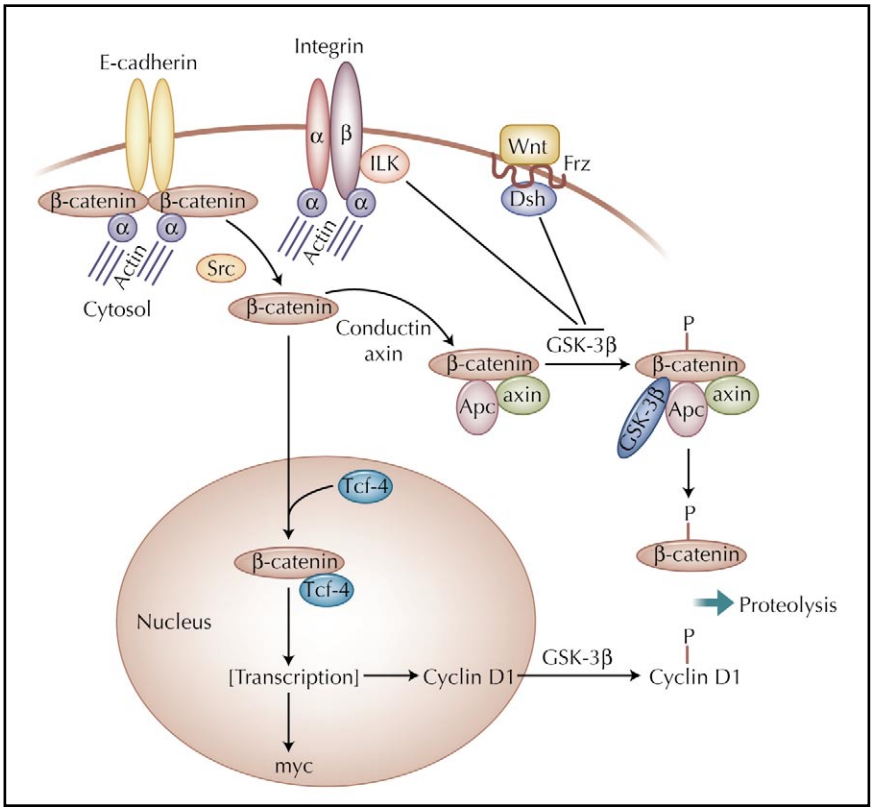

Figure 1. The E-Cadherin/β-catenin/Wnt signaling pathway is depicted. In the "canonical" pathway, activation is primarily mediated via the binding of soluble Wnt ligand(s) to Frizzled (Frz), a serpentine receptor, and the low density lipoprotein receptor-related (LRP) co-receptors, LRP5 and LRP6. This transduces an activating signal to Disheveled (Dsh). Upon activation, Dsh is released from its complex with the cytosolic end of the Frz receptor and acts as an inhibitor of proteolytic degradation of β-catenin. Targeting of β-catenin for proteolysis is accomplished by axin-mediated phosphorylation (in association with a large complex that includes glycogen synthase kinase 3β [GSK-3β], adenomatous polyposis coli [*APC*], type 2 protein serine/threonine phosphatase [PP2A]) of serine, and threonine residues on a region of β-catenin that is encoded by exon 3 of the β-catenin gene. Cytoplasmic levels of β-catenin are also regulated by cell-cell and/or cell-substrate interactions via E-cadherin and integrin cell surface receptors respectively.

opments in understanding of the pathogenesis of this disease and have updated the modern chemotherapy treatment options for metastatic gastric cancer.

Emerging Biology of Gastric Cancer

E-cadherin and the Wnt pathway: implications in the development of diffuse and intestinal gastric cancer

The Wnt signaling pathway is a central regulatory mechanism of gene expression that is present in vertebrates and invertebrates and is highly conserved in both. It has an essential role in embryonic development but also functions in differentiated cells in a variety of processes, including cell cycle regulation. Central to the Wnt signaling pathway is the regulation of β-catenin, which has multiple cellular functions, from cell surface signaling involving E-cadherin to nuclear translocation and transcription (Fig. 1). Mutations in the genes encoding Wnt components are associated with various cancers, including those of the gastrointestinal tract, and in particular, gastric cancer. Diffuse gastric cancer is associated with loss of E-cadherin function in approximately 50% of cases [7•]. Germline mutations in E-cadherin (CDH1) are associated with loss of E-cadherin function and are associated with the familial form of diffuse gastric cancer, hereditary diffuse gastric cancer [8•]. Because E-cadherins are components of adherins junctions, this observation is consistent with the loose cell-cell attachment characteristic of the histology of diffuse-type gastric tumors.

In contrast to diffuse gastric cancer, intestinal gastric cancer is known as the "epidemic-type" of gastric cancer because the high-risk areas of gastric cancer around the globe result from the high incidence of the intestinal histopathologic phenotype of gastric cancer in those areas. There is generally a defined pathologic carcinogenesis of intestinal-type stomach cancers beginning with mutlifocal atrophic gastritis followed by intestinal metaplasia, dysplasia, and then carcinoma [9]. The Wnt signaling pathway is also implicated in the development of intestinal gastric cancer. Although decreased E-cadherin expression is associated with diffuse gastric cancer, increased cytosolic expression of β-catenin and its nuclear translocation appear to be associated with the development of intestinal gastric cancer [10]. Specifically, *APC* gene mutations and mutations in the third exon of β-catenin lead to decreased phosphorylation of β-catenin and reduced proteolytic degradation of this protein. This results in cytosolic accumulation of β-catenin, nuclear translocation, and malignant transformation [10,11]. Somatic mutations in *APC* genes in gastric tumors have also been reported and are thought to occur in approximately 30% of intestinal-type gastric cancers [12]. Patients with a germline mutation of the *APC* tumor suppressor gene have a 10-fold increased risk of developing gastric cancer compared with healthy individuals [13].

The understanding of the biology of gastric cancer remains in its infancy. Recently, using the mouse equivalent of *Helicobacter pylori*–induced gastric cancer, some of the most clear and convincing evidence implicating

bone marrow–derived stem cells as the malignant cell in gastric cancer was published [14••]. These findings have significant implications in the understanding of the development of the disease and potentially its treatment as well. Clearly, the genetic determinants of the development of the disease are just now beginning to be better understood. With the explosion of new biologically directed therapies for the treatment of a variety of solid tumors in the past decade, the future of the treatment of this disease clearly lies in our better understanding of its pathogenesis. We are still struggling to define a standard cytotoxic combination for the treatment of this disease. An increased understanding of when, how, and to whom to administer targeted therapies with standard cytotoxic agents will undoubtedly have the greatest impact on future treatment of this disease.

Chemotherapy: Old and New

Palliative benefit of chemotherapy and evolution of combination therapy

Conventional chemotherapy for metastatic gastric cancer remains palliative, with few patients ever demonstrating long-term survival. Historically, most tumors develop rapid drug resistance and evidence of disease progression within a few months of initiation of therapy. However, palliative chemotherapy has a proven survival advantage over best supportive care for gastric cancer. Four randomized trials have shown that patients assigned to receive best supportive care alone, even when allowed to receive chemotherapy at a later date, did significantly worse than those assigned to receive immediate chemotherapy (reviewed by Shah and Schwartz [15••]).

The chemotherapeutic agents historically considered active in this disease include 5-fluorouracil, cisplatin, anthracyclines (doxorubicin and epirubicin), mitomycin C, and etoposide (reviewed previously [15••,16]). Single-agent activity response ranges from 10% to 20%, though the data are pooled from clinical trials performed in the 1960s and 1970s and may be an overestimation of the true single-agent activity as assessed by objective radiographic measurement. Several combination regimens have been developed with the aims of improving overall response rates and duration of response.

Recently, several random-assignment studies have reported common combination chemotherapy regimens for gastric cancer. These studies failed to demonstrate a clear superior regimen and are summarized in Table 1. A three-arm random-assignment trial comparing ELF (folinic acid, 5-fluorouracil and etoposide), CF (cisplatin and 5-fluorouracil), and FAMTX (5-fluorouracil, doxorubicin, and high-dose methotrexate) was reported by Vanhoefer et al. [17] in 2000. Overall response rates were notably low compared with previously reported phase II studies, ranging from 9% to 20% in the three arms, and survival was equally dismal at less than 7.2 months for each of the arms. These authors concluded that none of the regimens tested should be regarded as a standard treatment for metastatic or unresectable gastric cancer [17]. Another recently reported three-arm random-assignment trial compared CF, UFTM (uracil, tegafur, and mitomycin), and single-agent 5-fluorouracil [18]. The CF regimen was associated with a modest, significant increase in progression-free survival and response rate over 5-fluorouracil (3.9 months and response rate [RR] of 34% vs 1.9 months and 11%, respectively) [18]. However, despite these improvements, overall survival was not improved by CF, with median and 1-year survival of 7.3 months and 29%, respectively, compared with 7.1 months and 28% with 5-fluorouracil alone. Approximately 50% of patients who were assigned to 5-fluorouracil alone received cisplatin-based therapy on progression in this study (Ohtsu, Personal communication). The UFTM arm was inferior, with a 6-month median survival and a 16% 1-year survival arm and was closed early [18]. These authors concluded that single-agent 5-fluorouracil should remain the reference standard regimen for advanced-phase gastric cancer studies [18]. A similar conclusion was drawn by the authors of another random-assignment study comparing EEP (etoposide, epirubicin, and cisplatin) and FEP (5-fluorouracil, epirubicin, and cisplatin) [19].

Modern Combination Chemotherapy Regimens

The case for ECF: epirubicin, cisplatin, and 5-fluorouracil low-dose continuous infusion

The ECF regimen has recently been examined in two large random-assignment studies (Table 2). First, ECF was compared with FAMTX [20] and an update of the results was recently reported by Waters et al. [21]. This study randomly assigned 274 patients (137 in each group) to receive ECF or FAMTX. ECF was associated with a better response rate (46% vs 21%, $P=0.0002$) and an improvement in median survival (8.7 months vs. 6.1 months, $P=0.0005$) when compared with FAMTX. The investigators then proceeded to examine ECF versus MCF (mitomycin, cisplatin, and infusional 5-fluorouracil) in the largest random-assignment study of chemotherapy in metastatic or unresectable esophagogastric cancer published to date [22]. This study randomly assigned 574 eligible patients with esophageal ($n=188$), gastroesophageal junction ($n=125$), or gastric cancers ($n=221$) to receive either ECF ($n=289$) or MCF ($n=285$). Response to therapy was equivalent (42.4% for ECF vs 44.1% for MCF), as was survival (median survival 9.4 months for ECF vs 8.7 months for MCF). Although ECF appeared to have greater toxicity, global quality of life scores were maintained in the ECF arm but fell in the MCF arm, suggesting that ECF was subjectively perhaps a more tolerable regimen [22]. Notably, 5-fluorouracil administration in the MCF arm was 50% higher (300 mg/m^2/d) than in the ECF arm (5-fluorouracil, 200 mg/m^2/d), resulting in an

Table 1. Recent phase III clinical trials for gastric cancer using "older" combination regimens

Study	Disease	Treatment regimen	Patients, *n*	Response rate, (95% CI, %)*	1-Year survival, (95% CI, %)	Median survival, *mo*	*P*-value
Tebbutt et al. 2002 [56]	Esophagus + gastric	PVI	123	16.1 (9.5–22.7)	22.5 (15.2–30)	6.3	NS
		PVI + MMC	127	19.1 (12–26.0)	18.4 (12–25.9)	5.3	
Ohtsu et al. 2003 [18]	Gastric	5-FU	105	11.4 (6–19.1)	28	7.1	NS
		5-FU + cisplatin	105	34.3 (25.3–44.2)	28	7.3	
		UFTM	70	8.6 (3–18)	16	6	
Icli et al. 1998 [19]	Gastric	EEP	64	20.3 (12–59)	16†	6	NS
		FEP	67	15.3 (9–59)	11†	5	
Vanhoefer et al. 2000 [17]	Gastric	ELF	132	9 (3.5–17.5)	28	7.2	NS
		CF	134	20 (11–30)	32	7.2	
		FAMTX	133	12 (6–20.5)	33	6.7	

*Relative risk in evaluable patients.
†One-year survival estimated by Kaplan-Meier curves.
CF—cisplatin, 5-fluorouracil; EEP—etoposide, epirubicin, cisplatin; ELF—folinic acid, 5-fluorouracil, etoposide. FEP—bolus 5-fluorouracil, epirubicin, cisplatin; 5-FU—5-fluorouracil; MMC—mitomycin; PVI—continuous-infusion 5-fluorouracil (300 mg/m^2/d). UFTM—uracil, tegafur, mitomycin.
(*Adapted from* Shah and Schwartz[15••].)

Table 2. Recent important studies for gastric cancer using modern regimens

Study	Disease	Treatment regimen	Patients, *n*	Response rate, 95% CI, %*	1-Year survival, 95% CI, %	Median survival, *mo*	*P*-value
The case for ECF							
Ross et al. 2002 [22]	Esophagus + gastric	ECF MCF	289 285	42.4 (37– 48) 44.1 (38–50)	40.2 (34– 46) 37.7 (27–38)	9.4 8.7	NS
Webb et al. 1997 [20,21]	Esophagus + gastric	ECF FAMTX	121 116	46 (37–55) 21 (13–28)	37 (28–45) 22 (15–29)	8.7 6.1	*P*<0.01
The case for DCF							
Ajani et al. 2003 [57]; Moiseyenko et al. 2005 [25••]	Gastric + GEJ	DCF CF	221 224	36.7 (30.3–43.4) 25.4 (19.9–31.7)	40.2 31.6	9.2 (8.38–10.58) 8.6 (7.16–9.46)	*P*=0.02
The case for irinotecan-based therapies (only Dank et al. [31•] is a phase III study)							
Pooled results [27,58,59]	Esophagus + gastric	Irinotecan + cisplatin	105	48–58			
Pozzo et al. 2004 [29]	Gastric + GEJ (random-assignment phase II)	Irinotecan + cisplatin Irinotecan/5-FU infusion/ FA	56 59	32.1 (20.3–46)† 42.4 (29.6–55.9)†	25.3 44.9	6.9 (5.55–8.67)‡ 10.7 (8.02-14.62)‡	*P*=0.002
Dank et al. 2005 [31•]	Gastric +GEJ	Irinotecan/5-FU infusion/FA CF	170 165	31.8 25.8		9.0 (8.3–10.2) 8.7 (7.8–9.8)	*P*=0.53

*Relative risk in evaluated patients.
†Per protocol population.
‡Full analysis population.
A—Adriamycin; CF—cisplatin, 5-fluorouracil; DCF—docetaxel, cisplatin, 5-fluorouracil; ECF—epirubicin, cisplatin, 5-fluorouracil (continuous infusion); FA—folinic acid; FAMTX—5-fluorouracil, doxorubicin, high-dose methotrexate; 5-FU—5-fluorouracil; GEJ—gastroesophageal junction. MCF—mitomycin, cisplatin, 5-fluorouracil; MTX—high-dose methotrexate; NS—not significant.

imbalance between total 5-fluorouracil administered between the two arms (net 42% higher with MCF, $P<0.00001$). Although this study confirmed the activity of ECF in esophagogastric tumors, it also raises a question about the role of epirubicin in a cisplatin plus 5-fluorouracil combination. The study also confirmed that the prognosis of patients with esophagogastric tumors not amenable to resection remains dismal (with median survival remaining less than 10 months).

The case for DCF: docetaxel, cisplatin, and 5-day 5-fluorouracil infusion

Taxanes and taxane-containing combinations have considerable activity in the treatment of gastric cancer. Although paclitaxel and docetaxel have similar single-agent response rates in the first-line setting, occasional complete responses (CR) were reported with docetaxel. Both drugs have been examined in combination chemotherapy regimens with cisplatin, with associated improvements in response rates (ranging from 37% to 56%) and CRs [23,24].

Based on the single-agent and early combination activity observed with docetaxel-based therapy in upper gastrointestinal malignancies, docetaxel was examined in combination with cisplatin and 5-fluorouracil (DCF) and compared with the "standard" chemotherapy regimen of CF in a large random-assignment phase III study (Table 2) [25••]. The results reported at the 41st Annual Meeting of the American Society of Clinical Oncology (ASCO) demonstrate a significant improvement in time to progression (primary endpoint) with the docetaxel-containing combination (5.6 vs 3.7 months, $P=0.0004$) as well as improvement in median and overall survival (median survival of 9.2 vs 8.6 months, $P=0.02$) with the addition of docetaxel to cisplatin and 5-fluorouracil when compared with CF alone. However, both DCF and CF were associated with significant toxicity. Specifically, in the DCF arm, 84% of patients developed grade 3 and 4 neutropenia, 30% developed febrile neutropenia or a neutropenic infection, and 81% developed a non-hematologic grade 3 or 4 adverse event, including stomatitis, lethargy, nausea, and vomiting. In the CF arm, although a similarly high rate of grade 3 and 4 non-hematologic toxicity occurred (75.4%), the incidence of hematologic toxicity was substantially less. Specifically, 57% of patients in the CF arm developed grade 3 or 4 neutropenia, and 13.5% of patients developed febrile neutropenia or neutropenia with infection. At this time, the question remains whether the toxicity attributable to the addition of docetaxel to CF will outweigh the modest observed improvement in survival. However, it is clear that docetaxel is an active chemotherapy agent in the treatment of this disease and that its addition to cisplatin and 5-fluorouracil may confer a clinically important survival advantage.

The case for irinotecan/5-fluorouracil–based therapy

The combination of irinotecan and cisplatin has been examined in several phase II studies in gastric and gastroesophageal junction tumors [26–28]. Altogether, the combination was found to be active, achieving response rates in the range of 42% to 58%, with several patients achieving a CR. Moreover, the regimen was well tolerated, with its primary dose-limiting toxicity being myelosuppression. However, despite this encouraging activity, the time to progression in these studies was approximately 5 months (range, 4.2–5.8 months), with median survival of approximately 9 months in patients with metastatic disease [26,27]. This combination was also examined as part of a phase II random-assignment study, with patients in the other investigational arm given irinotecan and infusional 5-fluorouracil [29]. Notably, the previous studies of the irinotecan and cisplatin combination used a weekly schedule. For example, Ajani et al. [26] and Saltz et al. [30] administered irinotecan, 50 to 65 mg/m^2 (depending on the extent of previous myelosuppressive therapy) and cisplatin, 30 mg/m^2 weekly for 4 weeks in a row followed by a 2-week break. This regimen was adopted and modified with significant improvement in hematologic and non-hematologic toxicity by Ilson et al. [28] by going to a 3-week cycle, administering weekly irinotecan and cisplatin on day 1 and 8 every 21 days. However, Pozzo et al. [29] administered irinotecan, 200 mg/m^2, and cisplatin, 60 mg/m^2, every 3 weeks. On this schedule, a considerable amount of toxicity was observed and the efficacy was considered inferior to irinotecan and 5-fluorouracil infusion administered in week l. The results of this phase II study indicate that irinotecan and 5-fluorouracil constitute a superior regimen in terms of safety and efficacy compared with irinotecan and cisplatin, at least when given every 3 weeks. These findings led to a multicenter random-assignment phase III study of irinotecan and 24-hour 5-fluorouracil infusion given weekly versus standard cisplatin and 5-fluorouracil 5-day infusion (CF) [31•]. This 337-patient study demonstrated no improvement in survival with irinotecan and infusional 5-fluorouracil (IF; hazard ratio 1.08; 95% CI, 0.86–1.35); however, this arm appeared to have a reduction in grade 3 and 4 toxicity.

Another random-assignment phase II study, performed by Bouche et al. [32], demonstrated similar results of approximately equal efficacy of cisplatin and 5-fluorouracil versus irinotecan and 5-fluorouracil. Based on these data, it is unlikely that irinotecan will receive registration approval for the treatment of gastric cancer. However, alternatively, it is clear that irinotecan does have clinical activity in this disease.

Other Cytotoxic Drugs

Oxaliplatin (Eloxatin; Sanofi Synthelabo, Paris, France) is a third-generation platinum compound with activity in combination regimens in a variety of malignancies that is now being examined in phase II and III studies for upper gastrointestinal malignancies [33–35]. Reported activity of FOLFOX6 (oxaliplatin, leucovorin, and 5-fluorouracil

push followed by 46- to 48-hour 5-fluorouracil infusion) in the first-line setting is encouraging (ranging from 44.9% to 53%), with occasional CRs observed [34,35]. However, in the study reported by Louvet et al. [34], toxicity was concerning, with 38% of patients developing grade 3 and 4 neutropenia, 21% developing grade 3 and 4 neuropathy, and 13% withdrawing from the study for toxicity [34]. FOLFOX6 also appears to have activity in the salvage setting with a response rate of 26% in a primarily cisplatin-refractory patient population [33].

Given the activity of 5-fluorouracil in upper gastrointestinal malignancies, oral fluoropyrimidines have been examined as well. Capecitabine is being substituted for infusional 5-fluorouracil and has reasonable single-agent activity, with a response rate of 35% in a phase II clinical trial from Korea [36]. Also reported are phase II studies of capecitabine in combination with oxaliplatin [37] or cisplatin [38]. These reports demonstrate reasonable response rates of 28% to 35% and reasonable activity, suggesting that it may be possible to substitute capecitabine for 5-fluorouracil in combination chemotherapy. This regimen will be formally tested as part of the REAL-2 study, a four-arm study comparing the substitution of capecitabine for infusional 5-fluorouracil, and the substitution of oxaliplatin for cisplatin [39], with results anticipated at ASCO 2006. S-1 is a fluoropyrimidine derivative more commonly used in Japan, with response rates to single first-line therapy of approximately 44% [40,41]. However, in a study from the European Organization for Research and Treatment of Cancer, gastrointestinal toxicity was substantial, requiring a dose reduction, and the response rate appeared to be lower at 26% [42]. Ajani et al. [43] recently reported their experience combining S-1 with cisplatin in a phase I study in advanced gastric cancer. One of the main conclusions of this study was that the maximal tolerated dose of S-1 with cisplatin in patients with gastric cancer from Western countries (or United States specifically) is 50 mg/m^2/d in divided doses, whereas in patients from Japan, it is 80 mg/m^2/d. A random-assignment phase III study comparing cisplatin and S-1 versus cisplatin and 5-fluorouracil infusion is underway.

Targeted Treatments In Development

An obvious new targeted drug to be investigated in upper gastrointestinal malignancies is bevacizumab, a recombinant humanized monoclonal antibody to vascular endothelial growth factor (VEGF). When combined with irinotecan-based chemotherapy for colorectal cancer, this bevacizumab/chemotherapy combination demonstrated significant antitumor activity over chemotherapy alone [44•]. All measures of efficacy, including response rate, response duration, progression-free survival, and median survival were improved with the addition of bevacizumab. With regard to gastric carcinoma, VEGF expression or serum concentration has been positively correlated with vascular involvement and lymph node, liver, and peritoneal metastases [45,46]. Bevacizumab is currently being evaluated in combination with irinotecan and cisplatin in gastric and gastroesophageal junction cancers [47]. Although, on the initial analysis, the combination appears to be quite active with a response rate of 61% (95% CI, 38%–80%), concerns about toxicity, including thromboembolic events [48] and perforation, were notable. These results are preliminary because the response rate is based on 24 evaluable patients and the toxicity rate is based on 38 evaluable patients. The final results of this phase II study are anticipated at ASCO 2006.

The epidermal growth factor pathway has also been implicated in the pathogenesis of upper gastrointestinal malignancies [49–52]. The epidermal growth factor receptor (EGFR) inhibitor (Erb-B1) gefitinib (ZD1839) was examined as salvage therapy in 75 patients with gastric and gastroesophageal tumors [53]. Minimal antitumor activity was observed with one patient achieving a partial response and 12 with disease stabilization. Notably, in 32 patients who underwent serial biopsies, the phosphorylation status of the EGFR was significantly reduced with gefitinib, but the inhibition of proliferation (in an ex vivo assay) was more dependent on levels of phosphorylated Akt [54], suggesting that resistance to EGFR inhibitors may be mediated downstream through the PI3-Akt pathway.

Evaluation of inhibitors of the EGFR pathway, as single agents and in combination with cytotoxic agents, continues in upper gastrointestinal malignancies. Erbitux and matuzamab are antibodies directed at the EGFR that are under development in gastric cancer. The Cancer and Leukemia Group B is pursuing a random-assignment phase II study of FOLFOX, irinotecan/cisplatin, and ECF, all with erbitux in a pick-the-winner phase II design. Matuzumab is another monoclonal antibody to the EGFR that has been evaluated in a phase I clinical trial [55]. This study defined the recommended phase II dose of this drug and also demonstrated inhibition of downstream targets of the EGFR, suggesting biologic efficacy. Matuzumab will also be examined in advanced studies in upper gastrointestinal malignancies.

Conclusions

Gastric cancer is a common disease worldwide with a high mortality rate. Palliative chemotherapy is considered for the majority of patients with this disease, with benefits in quality of life and in survival. Many cytotoxic drugs are considered active in the treatment of this disease, with several combination chemotherapy regimens having been examined. There is little consensus on a standard chemotherapy regimen because the most active combinations also are associated with the most atrocious toxicity. For registration purposes, cisplatin and 5-day 5-fluorouracil infusion is considered an acceptable standard, even though this combination is rarely if ever used outside

the context of a clinical trial. The fact that there is no accepted standard regimen makes drug development with targeted drugs in this disease even more challenging, with regard to which reference regimen to use to randomize the targeted agent. As we begin to understand the biology of gastric cancer better, we will have opportunities to examine more targeted therapies in this disease. Indeed, novel targeted agents in combination with chemotherapy will define the next era of drug therapy for advanced and metastatic gastric cancer.

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