Current Status and Future of Chemotherapy and Biochemotherapy in Gastroesophageal Cancers

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ABSTRACT

A number of advances recently have been made in the chemotherapeutic treatment of gastroesophageal cancer. Perioperative combination chemotherapy based on cisplatin and 5-fluorouracil (5-FU) improves the prognosis of patients with stage II and stage III disease. Preoperative initiation of chemotherapy seems to be essential for achieving this result, according to studies performed in the West. On the other hand, Japanese investigators demonstrated that postoperative administration of oral fluoropyrimidine prodrugs can substantially improve the prognosis of patients with curatively resected gastric cancer. The addition of docetaxel to cisplatin and 5-FU has significantly improved response rate, time to progression, and overall survival in patients treated for advanced gastric cancer, as well as prolonging time to definitive worsening of global health status and Karnofsky performance status. Due to increased hematologic toxicity with this regimen, particularly neutropenic infections, careful patient selection and optimal supportive care, including prophylactic granulocyte colony-stimulating factor, are required. Alternative schedules are being investigated that could improve the tolerability of docetaxel plus platinum/fluoropyrimidine combination regimens. Further improvements in outcome may be achieved when even more active chemotherapy combinations including docetaxel are systematically implemented into the preoperative treatment of locally advanced gastroesophageal cancers. Initial results with biologic targeted agents in this setting are promising. Pathways currently under investigation include the epidermal growth factor receptors Her-1 and Her-2, vascular endothelial growth factor, and the epithelial cell adhesion molecule EpCAM. It is hoped that targeting these pathways will further increase the efficacy of biochemotherapy of gastroesophageal cancer. Evaluating early response to biochemotherapy using metabolic imaging is a novel approach that may allow for tailoring systemic therapy to individual tumor biology. A deeper understanding of the relevant pathognomonic molecular patterns and signatures in individual tumors may facilitate faster drug development and permit more accurate selection of active therapies in the future.

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Until recently, the value of systemic chemotherapy in the treatment of gastroesophageal cancer has been questioned. Studies comparing chemotherapy with best supportive care in metastatic disease, however, have demonstrated increased overall survival and improved quality of life for patients who receive chemotherapy.[1–3] At the same time, randomized studies suggest that perioperative chemotherapy or chemoradiotherapy can improve survival in patients with locally advanced gastric cancer[4–7] and esophageal cancer.[8] These reports have spurred interest in systemic biochemotherapy for gastroesophageal cancer and the development of new regimens for these indications.

Indeed, new chemotherapy regimens are available, and some are clearly more active than older regimens, but at the expense of an increase in the rate and severity of adverse effects. Accordingly, optimization of chemotherapy schedules, supportive care, and patient selection has become an important issue in daily clinical practice. Further, the move to develop even more active treatment regimens by adding biologically targeted drugs has gained momentum. Initial results from

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phase II studies have been promising. This article reviews the current status of biochemotherapy in gastroesophageal cancer and outlines potential future developments in this field.

MONOTHERAPY FOR GASTROESOPHAGEAL CANCERS

Due to methodologic flaws in numerous studies, the true activity of many cytotoxic drugs used as monotherapy in metastatic gastric cancer remains unclear. Single-agent 5-fluorouracil (5-FU), doxorubicin, epirubicin, cisplatin, etoposide, and mitomycin C have achieved pooled responses in 15% to 20% of patients with chemonaïve tumors and were therefore considered active drugs.[9] 5-FU is still considered the cornerstone of chemotherapy for gastroesophageal cancer. It was traditionally given as an intravenous bolus on 5 consecutive days or once every week. The antiproliferative activity of 5-FU occurs during the S-phase of the cell cycle, and the drug has a plasma half-life of only 10 to 20 minutes. Therefore, continuous infusion may be superior to bolus infusion in antitumor activity. Infusion schedules for 5-FU have varied considerably. For example, it has been administered at a dose of 1,000 mg/m^2/day on 5 consecutive days (usually in combination with cisplatin every 3 to 4 weeks), as a weekly high-dose infusion (at up to 3,000 mg/m^2 over 24 hours), or as a low-dose, protracted infusion (300 mg/m^2/day as a continuous infusion administered until progression of disease or the occurrence of limiting side effects. In 1988, Moynihan et al observed responses in 31% of patients with advanced gastric cancer treated with protracted continuous infusion 5-FU.[10] To date, however, the optimal dose and schedule for 5-FU remain elusive.

In an effort to increase antitumor activity, biomodulators have been combined with 5-FU, with folinic acid emerging as the most likely candidate. Promising response rates with 5-FU/folinic acid were observed in nonrandomized phase II trials in patients with gastric cancer.[11,12] Recently, a randomized phase II trial initiated by the European Organisation for Research and Treatment of Cancer (EORTC) revealed a response rate of 6% for high-dose weekly 5-FU compared to 25% for high-dose weekly 5-FU/folinic acid.[13] In addition, time to tumor progression and overall survival time were higher with folinic acid. However, patient numbers were too small in the arms of this study (33 and 48 patients) to permit definitive conclusions regarding efficacy. Thus, the question whether folinic acid should be part of 5-FU–based chemotherapy for gastroesophageal cancer remains unanswered.

Table 1. Activity of newer cytotoxic drugs as monotherapy in gastric cancer.

Compound	Patients (n)	Complete/Partial Response (95% Confidence Interval) (%)
S-1	28	48 (35–73)[15,16]
Capecitabine	44	34 (20–50)[18]
Pemetrexed	38	21 (8–32)[24]
Irinotecan	15	33 (9–39)[20]
Paclitaxel	44	18 (6–30)[21,22]
Docetaxel	119	20 (13–33)[23]

In 1995, Jäger et al reported a remarkably high response rate of 42%, along with an acceptable toxicity profile, with weekly administration of 5-FU/folinic acid plus interferon alpha.[14] The value of interferon in the treatment of gastric cancer, however, has yet to be confirmed in a phase III study.

Orally administered prodrugs of 5-FU have been investigated as single-agent treatment. Despite the increased intratumoral concentrations of 5-FU that can be achieved with these agents, no increased gastrointestinal toxicity has been observed. The most studied drug in this category is tegafur, with much of the data coming from Asian countries. UFT (tegafur combined with uracil) and S-1 (tegafur plus gimeracil and oteracil) have been in use for the treatment of metastatic gastric cancer for many years in Japan. Single-agent S-1 has shown considerable activity, with response rates up to 48% in phase II studies.[15,16] Experience with these agents outside of Japan is limited; however, initial results with S-1 in combination with cisplatin, are encouraging.[17] Capecitabine has also shown activity as monotherapy in advanced gastric cancer.[18] Based on data from randomized studies, capecitabine has been approved in combination with platinum compounds for the treatment of advanced gastric cancer in Europe and the United States.

Cisplatin is one of the most active drugs in the treatment of gastroesophageal cancer. Response rates of up to 25% have been reported in chemonaïve patients.[19] Complete remissions and overall response rates up to 20% were observed when cisplatin was given in combination with anthracyclines in pretreated patients. Whereas carboplatin is only marginally active in gastric cancers, oxaliplatin in combination with fluoropyrimidines has shown activity comparable to that of cisplatin in multiple phase II and two phase III studies.

Among newer classes of cytotoxic drugs that have been investigated in gastroesophageal cancer, topoisomerase-I inhibitors, particularly irinotecan,[20] the taxanes paclitaxel and docetaxel,[21–23] and the multitargeting antifolate pemetrexed[24] have proven activity (Table 1). Both irinotecan and the two available taxanes led to remissions in up to 20% in patients who had previously been treated with platinum/fluoropyrimidine-based first-line combination regimens.[25,26] Monotherapy with the vinca alkaloid vinorelbine has shown activity in advanced esophageal squamous-cell cancer,[27] but it proved only marginally active in gastroesophageal adenocarcinoma.[28]

In summary, a number of older and newer cytotoxic drugs are active in gastroesophageal cancer. The availability of newer compounds has considerably expanded treatment options. But complete remissions are rarely achieved with monotherapy alone, and response durations are relatively short (median 2 to 6 months). Until recently, monotherapy has been considered the standard of care in Japan,[29] whereas many oncologists in the West favor combination regimens on the rationale of a suggested correlation between tumor response to first-line chemotherapy and prognosis in advanced gastric cancer.[30]

COMBINATION CHEMOTHERAPY FOR GASTROESOPHAGEAL CANCERS

Until recently, combination regimens of older drugs such as 5-FU/doxorubicin/methotrexate/folinic acid (FAMTX),[31] etoposide/doxorubicin/cisplatin (EAP),[32] etoposide/folinic acid/5-FU (ELF),[32] cisplatin/5-FU (CF),[34,35] and epirubicin/cisplatin/5-FU (ECF)[36] were considered standard of care

for the treatment of advanced gastric cancer. Reported remission rates and survival times with these regimens differ significantly, mainly due to variable patient selection and criteria of response.

In general, the high response rates reported in phase II trials of combination treatments are not reproduced in randomized phase III studies.[37–40] From a global perspective, none of the regimens developed between the years 1990 and 2000 was considered sufficiently efficacious to be accepted as a standard treatment. In the United Kingdom, ECF was adopted as a standard of care, especially after it had shown efficacy similar to that of mitomycin C/cisplatin/5-FU (MCF) but with milder toxicity.[41] In Europe and the United States, two-drug combinations based on cisplatin and 5-FU (sometimes with folinic acid) have been widely used.

The TAX 325 study, reported in 2005, compared docetaxel plus CF (DCF) vs. CF alone.[41] This was the first study to clearly reveal the superiority of a three-drug vs. two-drug combination in overall response rate (37% vs. 25%, $P = .01$), time to tumor progression (median 5.6 vs. 3.7 months; hazard ratio [HR] 1.47, $P = .0004$), and overall survival (median 9.2 vs. 8.6 months; HR 1.29, $P = .0201$). The proportion of patients surviving more than 2 years was also significantly increased in the DCF group (18.4% vs. 8.8%). Hematologic toxicity, particularly febrile neutropenia (29% vs. 12%) and gastrointestinal side effects were more pronounced with DCF. On the other hand, times to definite worsening of Karnofsky performance status and global health status score were significantly longer with DCF.[43,44] This indicates that intensifying chemotherapy by adding docetaxel not only prolonged survival but also led to a clinical benefit in terms of performance status and quality of life. Due to the relatively high rates of hematologic and other toxicities observed with the original DCF regimen, prophylactic use of granulocyte colony-stimulating factor (G-CSF) is recommended. Moreover, proper patient selection should include critical appraisal of performance status and comorbidities.

Table 2. The original DCF (docetaxel, cisplatin, 5-FU) regimen and its modifications.

Regimen	Patients (n)	Complete/Partial Response (%)	Febrile Neutropenia (%)
DCF, every 3 weeks (Van Cutsem, 2006[41]) Docetaxel 75 mg/m² d1 Cisplatin 75 mg/m² d1 5-FU 1000 mg/m² d1-5	221	37	29
GASTRO-TAX, every 7 weeks (Lorenzen, 2007[44]) Docetaxel 40 mg/m² d1,15,29 Cisplatin 40 mg/m² d1,15,29 Folinic acid 200 mg/m² d1,8,15,21,29,36 5-FU 2000 mg/m² d1,8,15,21,29,36	60	47	5
ATTAX, every 3 weeks (Tebbutt, 2007[45]) Docetaxel 30 mg/m² d1,8 Cisplatin 60 mg/m² d1 5-FU 200 mg/m²/d continuously	50	49	4
D-FOX, every 2 weeks (Ajani, 2007[46]) Docetaxel 50 mg/m² d1 Oxaliplatin 85 mg/m² d1 5-FU 2200 mg/m² d1 (48h)	36	43	0
FLOT, every 2 weeks (Al-Batran, 2008[47]) Docetaxel 50 mg/m² d1 Oxaliplatin 85 mg/m² d1 Folinic acid 200 mg/m² d1 5-FU 2600 mg/m² d1 (24h)	59	53	2

Abbreviations: d = day; h = hours.

Alternative scheduling of DCF-based combination regimens has been investigated. Phase II studies suggest that hematologic toxicity may be lowered with alternative scheduling (weekly or biweekly instead of thrice-weekly drug administration) without compromising antitumor activity (Table 2).[42,45–48] However, data from randomized controlled trials comparing the original DCF regimen with alternative schedules are not available. Therefore, it remains to be seen whether variations in the original DCF regimen lead to at least comparable clinical efficacy.

Other alternatives to DCF are currently being investigated, including the substitution of oxaliplatin for cisplatin and capecitabine for infusional 5-FU. Irinotecan in combination with 5-FU has shown promising activity in phase II trials,[49–51] but no improvements in progression-free survival or overall survival were achieved when irinotecan was substituted for cisplatin in combination with infusional 5-FU in a randomized phase III study.[52] Other studies were undertaken in an attempt to demonstrate noninferiority of capecitabine compared to infusional 5-FU[53,54] and of oxaliplatin compared to cisplatin.[53,55] Among other newer combinations, S-1 has been studied in combination with cisplatin in the SPIRITS (S-1 Plus cisplatin vs. S-1 In RCT In the Treatment for Stomach cancer) trial in a Japanese population.[56] The combination of was exceptionally active (54% response according to RECIST [Response Evaluation Criteria in Solid Tumors] criteria) and efficacious (progression free survival 6.0 months; overall survival 13.0 months). Data validating these results in a non-Asian population from the international phase III FLAGS (First-Line Advanced Gastric Cancer Study) trial are eagerly awaited.

The results of recent randomized controlled trials of combination chemotherapy regimens involving third-generation cytotoxic drugs are shown in Table 3.[42,52–55] Table 4 shows some of the most frequently used combination chemotherapy regimens that have been studied in phase

III trials.[39,42,52–56] Choice of the recommended treatment regimen still depends on geographic, institutional, and personal preferences at present. It is hoped that this situation will change when more sophisticated clinical and biological parameters are defined that allow for treatment selection on an individual basis.

However, consensus seems to have been reached on some issues. Platinum/fluoropyrimidine combinations now form the backbone of chemotherapy for advanced gastric cancer. This would be the combination of cisplatin and S-1 in Japan and cisplatin and capecitabine or infusional 5-FU in most non-Japanese countries, with the addition of epirubicin in the UK. Although not yet approved for the treatment of gastric cancer, there is strong evidence that oxaliplatin can be substituted for cisplatin with maintained efficacy and a slight decrease in grade 3 and 4 adverse events (except neuropathy). Therefore, oncologists have started to use oxaliplatin instead of cisplatin at least when intolerance to cisplatin (renal insufficiency, gastrointestinal side effects, volume overload due to cardiac insufficiency) is prevalent or expected. DCF currently is the only treatment regimen approved for superiority in response, time to progression, and overall survival compared with a standard platinum-fluoropyrimidine regimen. However, due to the increased toxicity associated with the original DCF regimen, selection of patients with no major comorbidities, use of prophylactic G-CSF to prevent neutropenic infections, and/or use of alternative schedules (eg, Table 2) are recommended.

Table 3. Combination chemotherapy with third-generation cytotoxic drugs in advanced gastric cancer.

Regimen	Patients (n)	Complete/partial response	Median survival (months)	Reference
DCF	221	37%	9.2[a]	Van Cutsem, 2006[42]
CF	224	25%	8.6	
IFL	170	32%	9.0[b]	Dank, 2008[52]
CF	163	36%	8.7	
XP	139	41%	10.5[c]	Kang, 2006[54]
CF	137	29%	9.3	
EOX	234	48%	11.2[d]	Cunningham, 2008[53]
ECF	246	41%	9.9	
			[Time to progression]	Al-Batran, 2008[55]
FLO	112	34%	5.7[e]	
FLP	106	25%	3.8	

[a]$P = .02$, [b]$P = .53$, [c]$P = .08$, [d]$P = .02$, [e]$P = .08$.
Abbreviations: DCF = docetaxel, cisplatin, 5-FU; CF = cisplatin, 5-FU; IFL = irinotecan, 5-FU, folinic acid; XP = capecitabine, cisplatin; EOX = epirubicin, oxaliplatin, capecitabine; ECF = epirubicin, cisplatin, 5-FU; FLO = 5-FU, folinic acid, oxaliplatin; FLP = 5-FU, folinic acid, cisplatin.

PERIOPERATIVE CHEMOTHERAPY FOR GASTROESOPHAGEAL CANCER

The value of adjuvant chemotherapy in gastroesophageal cancer has been debated for years. Recent results from two randomized European trials, however, have demonstrated a significant survival advantage with perioperative chemotherapy in patients presenting with locally advanced gastroesophageal adenocarcinoma deemed resectable (clinical stages II and III according to Union International Contre le Cancer [UICC] criteria).[6,7] Perioperative treatment consisted of 8 to 9 weeks of preoperative platinum/5-FU–based chemotherapy and another 9 to 12 weeks of the same chemotherapy for those who were able to tolerate postoperative treatment.[6,7] The results of these two studies are shown in Table 5.[6,7]

Since overall survival is significantly increased with perioperative treatment, neoadjuvant chemotherapy with epirubicin/cisplatin/5-FU or cisplatin/5-FU has become a standard of care for the treatment of stage II and III gastroesophageal cancers in many European centers. In theory, docetaxel-containing treatment regimens could be even more efficacious in the preoperative setting due to the proven higher response rate of DCF vs. CF in the metastatic setting.[42] Moreover, time to tumor response appears to be shorter with DCF compared to ECF.[57] Although systematic data on the use of docetaxel-containing triple-drug combinations in the neoadjuvant setting are scant at present,[45] more such data should be available in the relatively near future.

Recently, in the largest randomized adjuvant trial ever performed in gastric cancer, Japanese investigators demonstrated that S-1 (80 mg/m² day 1 to 28, repeated day 43) given for 1 year after curative resection (including D2 lymphadenectomy) significantly improves overall survival.[58] Of note, more than 90% of the patients in this study had node-positive disease. A similar survival advantage with adjuvant chemotherapy was demonstrated in a smaller study (N = 190) of surgery alone vs. postoperative UFT (360 mg/m²/day orally for 16 months) in node-positive gastric cancer patients.[60] Based on these results, it can be concluded that a new standard of care has emerged for node-positive, R0 D2 resected patients in Japan.

Clearly, the oral 5-FU prodrugs should be studied in the adjuvant setting outside Japan. To date, the value of adjuvant chemotherapy has yet to be demonstrated in non-Japanese patients.[61] European studies have more often than not focused on intensive combination chemotherapy regimens, usually associated with considerable toxicities. These studies failed to show a survival benefit. Nevertheless, there appeared to be a modest clinically significant benefit for patients with node-positive disease.[61,62] Interestingly, a recent study showed no benefit at all if cisplatin and epirubicin were added to adjuvant 5-FU/folinic acid in patients with serosa-negative, node-positive disease.[63] Of note, only 9% of patients were able to complete cisplatin-based combination chemotherapy as planned, reaffirming that reasonably tolerable regimens are preferable in the adjuvant setting. To date, no data support the use of more toxic (eg, cisplatin-based) combination chemotherapy regimens compared to 5-FU alone.

Even after complete R0 resection of gastric cancer, the risk of locoregional relapse is reported to be in the range of 20% to 25%.[64] In the Intergroup 0116 (INT

Table 4. Currently used chemotherapy regimens for gastroesophageal cancer (studied in phase III trials).

Drugs	Dose (mg/m²), Route, Schedule
Three-Drug Combinations	
ECF (Webb, 1997[39])	
Epirubicin	50 IV (30 min), d1
Cisplatin	60 IV (60 min), d1
5-FU	200 IV (continuous infusion), d1-21
Repeated	d22
ECX (Cunningham, 2008[53])	
Epirubicin	50 IV (30 min), d1
Cisplatin	60 IV (60 min), d1
Capecitabine	1250 orally, d1-21
Repeated	d22
EOX (Cunningham, 2008[53])	
Epirubicin	50 IV (30 min), d1
Oxaliplatin	130 IV (120 min), d1
Capecitabine	1250 orally, d1-21
Repeated	d22
DCF (Van Cutsem, 2006[42])	
Docetaxel	75 IV (60 min), d1
Cisplatin	75 IV (60 min), d1
5-FU	750 IV (24 h), d1-5
Prophylactic use of G-CSF recommended	
Repeated	d22
Two-Drug Combinations	
Cisplatin-Capecitabine (Kang, 2006[54])	
Cisplatin	80 IV (60 min), d1
Capecitabine	2000 orally, d1-14
Repeated	d22
Cisplatin-S1 (Japan) (Koizumi, 2008[56])	
Cisplatin	60 IV (60 min), d8
S-1	40-60 orally twice daily, d1-21
Repeated	d22
FLO (Al-Batran, 2008[55])	
Oxaliplatin	85 IV (120 min), d1
Folinic acid	200 IV (120 min), d1
5-FU	2600 IV (48 h), d1
Repeated	d22
IFL (Dank, 2008[52])	
Irinotecan	80 IV (90 min), d1,8,15,22,29,36
Folinic acid	200 IV (120 min), d1,8,15,22,29,36
5-FU	2000 IV (24 h), d1,8,15,22,29,36
Repeated	d50

Abbreviations: d = day; h = hours; IV = intravenous; min = minutes.

0116) trial, adjuvant chemoradiotherapy was shown to decrease the rate of local recurrence and increase overall survival.[65] The chemotherapy regimen used concomitantly and sequentially with adjuvant radiotherapy in INT 0116 consisted of 5-FU/folinic acid. This postoperative treatment regimen has become a standard of care at many North American institutions. The current Cancer and Leukemia Group B 80101 adjuvant chemoradiotherapy trial was designed to assess whether ECF in combination with radiotherapy could improve overall survival compared to 5-FU/folinic acid and radiation. Adjuvant radiotherapy in combination with cisplatin and 5-FU with or without paclitaxel has been studied in the phase II setting.[66]

For reasons of feasibility and tumor downsizing, it might be more attractive to use chemoradiotherapy prior to surgery. This approach was studied in four consecutive phase II trials,[67–70] with the results indicating that cisplatin and paclitaxel can be used without compromising patient safety. It appeared that more active preoperative chemoradiotherapy led to more complete pathologic responses and that histopathologic response predicts outcome. It was also shown that preoperative chemoradiotherapy can be safely administered in a multicenter setting. The next step should be to compare neoadjuvant chemoradiotherapy to any other standard of care (either adjuvant chemoradiotherapy or perioperative chemotherapy without radiation) in a randomized controlled trial.

NEW BIOLOGIC APPROACHES TO TREATING GASTRO-ESOPHAGEAL CANCER

While biotherapy or combined biochemotherapy has become a reality in accepted

Table 5. Perioperative chemotherapy in locally advanced gastroesophageal cancer—phase III studies.

Study	Patients (n)	Staging	Chemotherapy (x No. of Cycles)	RO Resection(%)	Hazard Ratio (95% Confidence Interval)		5-Year Survival (%)
					Progression-Free Survival	Overall Survival	
Cunningham, 2006[6]	250	CT, endoscopy	ECFx3 preop., x3 postop.	69	0.66 (0.53–0.81)	0.75 (0.60–0.93)	36
	253		none	66			23
Boige, 2007[7]	113	CT, barium swallow, endoscopy	CFx2 preop., x4 postop.	87	0.65 (0.48–0.89)	0.69 (0.50–0.95)	38
	111		none	74			24

Abbreviations: CT = computed tomography; CF = cisplatin, 5-FU; ECF = epirubicin, cisplatin, 5-FU; postop. = postoperative; preop. = preoperative.

treatment for many tumors, the systemic treatment of gastroesophageal cancer still relies on chemotherapy alone. However, potential treatment targets have been identified, and initial data on targeted agents have begun to emerge from phase I and II trials. At present, the most promising strategies appear to be inhibition of growth factor receptor-dependent signaling pathways and interruption of proangiogenic stimuli. Immune therapy strategies may also be of interest in the future.

Epidermal Growth Factor Receptor (Her-1)

The epidermal growth factor receptor (EGFR) has been shown to be heterogeneously expressed in individual gastroesophageal tumors. Of 89 carcinomas examined in one report,[71] staining of neoplastic cells was weak in 17 (19.1%, score 1), moderate in 16 (18.0%, score 2), and strong in nine cases (10.1%, score 3). Heterogeneity was frequently manifested as findings of no reactivity up to 3+ reactivity in different areas within an individual tumor. EGFR reactivity score correlated with distant metastases and clinical stage, and EGFR score 0/1 was significantly associated with an increase in patient survival when compared to score 2/3. In a review of 38 resected esophageal adenocarcinomas, higher EGFR expression on immunohistochemistry (IHC) was observed in poorly vs. well differentiated tumors (57% vs. 13%).[72] Of 52 patients enrolled in a recent phase II trial, EGFR was detectable by IHC in 60%.[73]

Cetuximab, a monoclonal chimeric IgG1 antibody directed against the extracellular domain of EGFR, has been studied in two phase II trials. In an Italian trial, the combination of cetuximab with irinotecan and 5-FU plus folinic acid (FOLFIRI) yielded a 44% overall response rate (95% confidence interval [CI] 27.5% to 60.9%).[74] The median time to progression was 8 months [95% CI 7 to 9 months]. At a median follow-up of 11 months, 55.3% of patients were alive, with a median expected survival time of 16 months (95% CI 9 to 23 months). In a recent trial conducted by the German Arbeitsgemeinschaft Internische Onkologie (AIO), cetuximab in combination with weekly oxaliplatin and 5-FU plus folinic acid (FUFOX) also yielded a very promising response rate of 65.2% (95% CI 49.8% to 78.6%) in 46 evaluable patients.[73] Response appeared to be independent of the EGFR receptor status determined by IHC. The time to tumor progression was 7.6 months and the overall survival was 9.5 months. These two studies suggest that there may be increased efficacy when an anti-EGFR antibody is combined with chemotherapy. Based on these findings, two randomized trials led by the AIO will soon be initiated. Cetuximab in combination with cisplatin and capecitabine will be investigated in the palliative treatment setting in a phase III study. Panitumumab, the other currently available anti-EGFR monoclonal antibody, will be tested in combination with epirubicin, cisplatin, and capecitabine in the perioperative treatment of stage II and III gastric cancer.

Inhibitors of the intracellular kinase domain of EGFR have yielded less promising results. In the Southwest Oncology Group (SWOG) 0127 study patients with advanced gastric cancer and cancer of the gastroesophageal junction received first-line erlotinib.[75] The treatment was moderately active in junctional cancers but inactive in gastric cancers. No mutations were found in exons 18, 19, and 21 of the EGFR and there was no gross amplification of the EGFR gene. In a phase II study, gefitinib had modest activity in second-line treatment of advanced esophageal cancer,[76] with outcome being significantly better in female patients and in patients demonstrating high EGFR expression or squamous cell histology. Gefitinib monotherapy also showed some activity in adenocarcinoma of the esophagus in another phase II study, yielding a 37% disease stabilization rate (partial responses and stable disease).[77] In summary, esophagogastric junction adenocarcinomas and esophageal cancers, particularly squamous cell cancers of the esophagus, seem to be more sensitive to treatment with EGFR tyrosine kinase inhibitors. A specific molecular pattern of tumors that have a clearly increased sensitivity to these drugs has not yet been established. However, mutations of EGFR were identified recently in esophageal cancers and cases of Barrett's esophagus; these mutations consisted of the recurrent missense L858R and in-frame deletion delE746-A750, previously characterized as activating EGFR mutations in non-small cell lung cancer.[78] In view of this finding, further investigation of gefitinib, erlotinib, or other small molecule tyrosine kinase inhibitors is warranted in esophageal tumors with activating mutations of the EGFR gene.

ErbB/Her-2

Her-2 is another member of the EGFR family. In a recent analysis of 1527 gastric tumor samples, 341 (22.3%) were Her-2-positive and 186 Her-2-negative.[79] IHC and fluorescence in situ hybridization (FISH) were concordant in 87% of samples, with differences largely being due to FISH-positive cases that were IHC 0/1+. Her-2-positivity differed significantly by histological subtype: 34% in intestinal, 6% in diffuse, and 20% in mixed types. Her-2-positivity also varied according to the site of the tumor, with rates of 32% (23/72) in gastroesophageal junction tumors and 18% (149/817) in gastric tumors. The Her-2-positivity rate was similar in specimens obtained by biopsy (242/1027; 24%) and surgery (95/477; 20%). These findings generally confirm findings of previous studies in a smaller number of samples. In these earlier investigations, it was also shown that overexpression of Her-2 is associated with amplification of the topoisomerase II alpha gene.[80,81]

Anecdotal reports suggest a sensitivity of Her-2-overexpressing gastric cancer to treatment with trastuzumab.[82,83] Trastuzumab currently is being investigated in advanced gastroesophageal cancers overexpressing Her-2 in a randomized controlled phase III study in combination with cisplatin and capecitabine (TOGA trial). Lapatinib, a small molecule inhibitor directed against the intracellular tyrosine kinase domain of Her-2 and Her-1, also seems to be active in some gastric cancers according to the preliminary results of the SWOG 0413 phase II trial.[84] The activity of lapatinib alone and in combination with capecitabine in Her-2-overexpressing gastric cancer defined by IHC and/or FISH is soon to be investigated in a randomized phase II trial steered by the German AIO. The NCT00486954 study will investigate the addition of lapatinib to paclitaxel in first-line treatment of advanced Her-2-amplified gastric cancers. The EORTC is also planning to investigate lapatinib plus

chemotherapy in Her-2- and/or EGFR-amplified advanced gastric cancers.

Insulin-Like Growth Factor-I Receptor

In a recent Japanese study, insulin-like growth factor-I receptor (IGF-IR) was expressed in 60% of esophageal cancer samples.[85] Its expression was associated with invasion depth, metastasis, advanced tumor stage, and recurrence. Similar results were obtained by another Japanese group, who also found elevated IGF and IGF binding protein 3 (IGFBP-3) serum levels in patients with esophageal cancer.[86] Overexpression of IGF and elevated serum levels were associated with more advanced stages and poor prognosis. These findings suggest a role for IGF-IR in the progression of esophageal cancer in vivo.

Suppression of IGFBP-3 by small interfering RNA resulted in augmented cell proliferation in vitro, suggesting that IGFBP-3 may inhibit tumor cell proliferation as a negative feedback mechanism.[87] In another in vitro experiment it was shown that IGF-I prevented the apoptosis of CE81T/VGH cells induced by such chemotherapeutic drugs as cisplatin, 5FU, and irinotecan. Thus, interruption of IGF-IR function may provide a way to retard tumor growth and increase the sensitivity of esophageal carcinoma to chemotherapy. On the basis of these findings, the German AIO has planned a randomized phase II study assessing the addition of CP-751,871, a monoclonal antibody directed against IGF-IR, to cisplatin/5-FU in esophageal squamous cell cancer.

Vascular Endothelial Growth Factor

Vascular endothelial growth factor (VEGF) is one of the most important pro-angiogenic stimuli. VEGF is overexpressed in gastroesophageal cancers, and overexpression is correlated with advanced stage, higher recurrence risk, increased tumor burden, and poor survival.[88–92]

Bevacizumab, a humanized monoclonal antibody that binds to all isoforms of VEGF, was recently studied in two phase II trials in gastroesophageal cancer.[93,94] In a study in first-line treatment of advanced disease, bevacizumab was combined with cisplatin and irinotecan, a regimen that has previously been investigated at Memorial Sloan Kettering Cancer Center.[95] The combination yielded an impressive response rate of 65% (including unconfirmed responses), median time to tumor progression of 8.3 months, and median overall survival of 12.3 months. Notably, 6% of patients had gastrointestinal perforations and 25% of patients developed venous thromboembolism, the latter of which was incidentally detected as asymptomatic pulmonary embolism in 66% of cases.[96] Therefore, there is some concern about the safety of bevacizumab during treatment of advanced gastric cancer. Potential contributors to the high observed thrombosis rate in addition to potential effects of bevacizumab include the hypercoaguable state of gastric cancer, irinotecan-induced thrombosis, and improved imaging techniques that can identify a higher number of asymptomatic thrombotic events. In a phase II study of bevacizumab and docetaxel in second-line treatment of gastroesophageal cancer, no gastrointestinal perforation or venous thromboembolism has been reported thus far.[94] However, arterial thromboembolic events occurred in 10% of patients and gastrointestinal bleeding occurred in 15%. Mature efficacy data from this second study have not yet been reported. Based on the promising efficacy data from the phase II study reported by Shah et al,[93] further studies adding bevacizumab to chemotherapy are justified. The UK Medical Research Council is investigating the addition of bevacizumab to perioperative chemotherapy with epirubicin, platinum, and capecitabine in stage II and III adenocarcinoma of the stomach and gastroesophageal junction. Phase II trials are examining bevacizumab in combination with docetaxel, cisplatin, and 5-FU in advanced disease. The NCT00548548 trial has been designed to study the addition of bevacizumab to cisplatin and capecitabine in advanced nonresectable gastric cancer. These trials will help clarify the safety and efficacy of bevacizumab in the treatment of gastric cancer.

Preclinical findings suggest a potential role for VEGF receptor tyrosine kinase inhibitors such as AZD2171 and ZD6474 in gastric cancer.[97,98] Preliminary results from a phase II trial suggest clinical activity of sunitinib, a potent VEGF receptor tyrosine kinase inhibitor, as second-line treatment in gastric cancer.[99] VEGF-Trap is a potent antiangiogenic soluble recombinant decoy protein constructed from VEGF receptor-1 and VEGF receptor-2 binding domains fused to a human immunoglobulin G1 constant region peptide.[100] Its biological affinity for VEGF is reported to be significantly higher than that of bevacizumab.[101] In rodent models, VEGF-Trap was shown to possess potent antiangiogenic efficacy,[102] and the agent currently is being assessed in phase I studies in patients with advanced stage solid malignancies, including gastroesophageal adenocarcinoma.

Gastrin 17

G17DT (Gastrimmune) is an antigastrin-17 immunogen that induces antibodies that block gastrin-stimulated tumor growth. The efficacy of both passive and active immunization with G17DT has been established in a number of tumor systems, with additive effects demonstrated in combination chemotherapy in pancreatic, colon, and gastric tumor models.[103] In a phase II trial of G17DT in combination with cisplatin and 5-FU in gastric and gastroesophageal junction cancer, the overall response rate was 30% among 79 patients.[104] Median overall survival was 9 months, and successful vaccination was associated with longer median survival. A phase III trial of G17DT in gastric cancer is warranted.

Epithelial Cell Adhesion Molecule

Epithelial cell adhesion molecule (EpCAM) is a transmembrane glycoprotein that is frequently overexpressed in a variety of carcinomas, including gastroesophageal cancer.[105–107] Catumaxomab, a monoclonal antibody directed against EpCAM and the T-cell surface antigen CD3, has yielded promising results in the intraabdominal treatment of peritoneal carcinomatosis and ascites due to gastric cancer.[108,109] Intraperitoneal administration of the antibody also provided relief of malignant ascites in patients with advanced ovarian cancer.[110] Catumaxomab is being studied in the intraoperative and adjuvant treatment of gastric cancer.

DISCUSSION

Gastroesophageal cancers continue to be

highly aggressive tumors causing death in a majority of affected patients. If the cure rate for patients with localized disease is to be improved, perioperative and multimodality treatments need to be refined and made available to all patients. Greater efforts are needed in defining routine multidisciplinary approaches to localized gastric cancer and in exploring gastric cancer biology.

Early assessment of response to biochemotherapy using metabolic and functional imaging techniques seems to be a most promising approach and may contribute to the ability to tailor treatment to individual tumor biology.[111–117] However, there are considerable limitations to positron emission tomography (PET) in gastric cancer. Nearly 45% of tumors are not fluordeoxyglucose (FDG)-avid,[112] and the fundus may exhibit physiologic (false-positive) FDG uptake that complicates interpretation in some 10% of cases. It is possible that other PET tracers (evaluating proliferation, apoptosis, or oxygenation) may prove useful in this setting.

Improvements in our knowledge of gastric cancer biology are likely to allow us to individualize therapy and follow-up, with the characterization of molecular prognostic and predictive factors representing a major step forward. However, this task is likely to be difficult given the heterogeneity of molecular changes and pathways involved in gastroesophageal cancer. Bild et al[117] have suggested that DNA microarray data can allow subtyping of cancers by identifying the type of activated pathways. This approach is of considerable appeal, since constructing pathway-based signatures may allow us to classify and eventually treat cancers irrespective of their site of origin.[119,120]

The development of new chemotherapeutic and biologically targeted drugs and regimens will hopefully make biochemotherapy of gastroesophageal cancers more efficacious. It is important that at the same time we are developing novel regimens, we are expending effort to identify molecular markers that allow us to tailor treatment according to individual tumor biology, since it is the advances in this regard that will ultimately allow us to have the greatest impact in improving treatment outcome.

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