Esophageal Cancer Chemotherapy: Recent Advances

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ABSTRACT

Esophageal cancer, though relatively uncommon in the United States, is a major global health threat. Squamous cell carcinoma remains the most common histology worldwide, whereas adenocarcinoma of the esophagus is increasing at epidemic proportions in the United States and other Western countries. Both histologies carry a poor prognosis: 5-year mortality for esophageal cancer exceeds 85% to 90%. Locally advanced esophageal cancer treated with the standard approaches of surgery or radiotherapy is associated with poor prognosis, due to both a high incidence of local-regional treatment failure and early systemic dissemination of disease. The obvious need to address the early spread of esophageal carcinoma through systemic treatment has led to the study of combined-modality therapies incorporating chemotherapy. Concurrent chemotherapy and radiotherapy is now a standard of care in the nonsurgical management of locally advanced esophageal cancer. Preoperative chemotherapy and combined preoperative chemoradiotherapy are also standards of treatment based on recent clinical trials. With the increasing use of chemotherapy as part of operative management as well, systemic chemotherapy will ultimately be used to treat the majority of patients with esophageal cancer. This article reviews results of recent clinical trials in the use of single-agent chemotherapy, combination chemotherapy, targeted agents, and neoadjuvant chemotherapy in the treatment of esophageal cancer.

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Esophageal cancer, a highly virulent malignancy, will have taken nearly 14,000 lives in the United States in 2007.[1] Although the disease is relatively uncommon in the United States, it is a major global health threat. Particularly high incidences are observed in northern China, the Caspian littoral of Iran, the Transkei province of South Africa, and Brittany in France. Squamous cell carcinoma remains the most common histology worldwide, whereas adenocarcinoma of the esophagus is increasing at epidemic proportions in the United States and other Western countries. Despite differences in potential causative factors and geographic occurrence, both histologies carry a poor prognosis—5-year mortality exceeds 85% to 90%.

The prognosis for patients with locally advanced esophageal cancer treated with the standard approaches of surgery or radiotherapy is poor. Treatment failure is due to both a high incidence of local-regional failure and early systemic dissemination of disease. The obvious need to address the early spread of esophageal carcinoma through systemic treatment has led to the study of combined-modality therapies incorporating chemotherapy. Concurrent use of chemotherapy and radiotherapy is now a standard of care in the nonsurgical management of locally advanced esophageal cancer. Preoperative chemotherapy and combined preoperative chemoradiotherapy are also standards of treatment, based on the results of recent clinical trials.

Nearly 50% of patients with a diagnosis of esophageal cancer present with overt metastatic disease, and chemotherapy is the mainstay of palliation in this setting. With the increasing use of chemotherapy as an adjunct to surgical management, systemic chemotherapy will ultimately be used to treat the majority of patients with esophageal cancer. Data from recent clinical trials in the use of single-agent chemotherapy, combination chemotherapy, targeted agents, and neoadjuvant chemotherapy in the treatment of esophageal cancer are reviewed herein.

SINGLE-AGENT CHEMOTHERAPY

Early studies of single-agent chemotherapy evaluated only squamous cell carcinoma. Modest antitumor activity for a broad range of chemotherapy drugs is seen in esophageal carcinoma, but the duration of response to single-agent chemotherapy is generally brief and on the order of 4 to 6 months.

Older Single Agents

Older agents, including bleomycin, 5-fluorouracil (5-FU) given by bolus or continuous infusion, cisplatin, and mitomycin have single-agent response rates ranging from 10% to 20%. Carboplatin, by contrast, has shown a lower single-agent response rate in both squamous cell carcinoma[2-4] and adenocarcinoma,[5] though carboplatin-based

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combination regimens (discussed later) appear similar to cisplatin combinations.

Taxanes and Other New Agents

Oxaliplatin, a new platinum analog, has not been evaluated as a single agent in esophageal cancer, but 5-FU and capecitabine combinations with oxaliplatin have been evaluated in phase II and III trials. Oral 5-FU prodrugs, which may mimic a daily continuous-infusion 5-FU schedule, have also undergone single-agent evaluation in metastatic gastric and gastroesophageal junction cancer. Capecitabine has been evaluated in Japanese and Korean trials, with reported response rates of 26% to 34%.[6,7] The alkaloids vindesine and vinorelbine have reported response rates ranging from 15% to 20%.[8,9] Toxicity for vindesine included significant sensory neuropathy, and vinorelbine had significant hematologic toxicity, with grade 3 and 4 neutropenia seen in 59% of patients.

Paclitaxel, another active single agent in esophageal cancer, has also been studied in combination chemotherapy trials. Phase II trials have evaluated a 24-hour, every-3-week schedule, and a weekly, 1-hour schedule, with response rates ranging from 15% to 32% in combined adenocarcinoma and squamous cell carcinoma trials.[10,11] Similar response rates were seen for both histologies with either infusion schedule, though the weekly 1-hour schedule had substantially less grade 3 and 4 neutropenia (5%) compared to the every-24-hour schedule administered every 3 weeks (86%), which also employed prophylactic granulocyte colony-stimulating factor (G-CSF). Docetaxel has been evaluated in esophageal squamous cell and adenocarcinoma at doses of 70 to 100 mg/m^2 every 3 weeks.[12–14] Response rates ranged from 20% to 25%. Hematologic toxicity was significant in these trials, with relatively high rates of grade 3 and 4 neutropenia (up to 88% of patients) and neutropenic fever (32%–45%).

The topoisomerase I inhibitor etoposide has been studied in both adenocarcinoma and squamous cell carcinoma, with response rates ranging from 0% to 19%.[15-17] The topoisomerase II inhibitor irinotecan has been evaluated in two recent phase II trials in adenocarcinoma of the stomach and gastroesophageal junction, with a response rate of 15% observed.[18,19]

COMBINATION CHEMOTHERAPY

Cisplatin and 5-FU

The combination of cisplatin (60–100 mg/m^2) and 5-FU (750–1,000 mg/m^2) given by continuous infusion for 4 to 5 days has been studied extensively, primarily on the basis of the activity of this regimen in squamous cell carcinoma of the head and neck. Interest in the use of bleomycin-containing regimens, on the other hand, has been waning, because of the pulmonary toxicity observed in surgical and radiotherapy protocols. Toxicity observed for the combination of cisplatin and 5-FU, mainly mucositis and myelosuppression, has been substantial but tolerable. Kies and associates[20] reported the first use of 5-FU and cisplatin in local-regional squamous cell carcinoma of the esophagus, with 11 major responses observed in 26 patients treated preoperatively with three cycles (42%). The duration of response was indeterminate, because most of the patients underwent surgical resection or later received radiotherapy.

Subsequent reports noted similar response proportions, predominantly in patients with local-regional disease.[21-25] Of 238 pooled patients with squamous cell carcinoma, the majority of whom had local-regional disease and were treated preoperatively or prior to local radiotherapy, 116 (48.7%) showed a major response. Occasionally, pathologically confirmed complete responses were observed in patients treated preoperatively (14 patients, 7.0%).

In trials of patients with metastatic or unresectable disease, the response to cisplatin and 5-FU has been lower, ranging from 35% to 40%.[25,26] Efforts have been made to improve upon this regimen by adding other agents. In one study, mitomycin (6 mg/m^2) was added to the cisplatin/5-FU regimen in 33 mostly untreated patients with unresectable or metastatic squamous cell carcinoma and yielded a 61% major response rate.[27] Toxicity was reported as mild, yet 46% of patients required a treatment delay. The addition of doxorubicin[28] or doxorubicin and etoposide[29] to 5-FU and cisplatin in squamous cell carcinoma has shown no significant improvement over cisplatin and 5-FU alone. Similarly, in adenocarcinoma, the addition of etoposide[30] or leucovorin with etoposide[31] has shown no advantage.

Despite common use of 5-FU/cisplatin for the treatment of esophageal carcinoma in the oncology community, only one trial has directly addressed the issue of the comparative efficacy of single-agent cisplatin and the combination of 5-FU and cisplatin.[26] This phase II study in locally advanced or metastatic squamous cell carcinoma randomly assigned patients to receive either cisplatin (100 mg/m^2) plus continuous infusion 5-FU (1,000 mg/m^2/day, days 1–5) or cisplatin (100 mg/m^2) alone, with both regimens repeated every 3 weeks. The cisplatin/5-FU arm had a higher response rate (35%) and better median survival (33 weeks) than the cisplatin arm (19% and 28 weeks, respectively), but these findings were not statistically significant. Cisplatin/5-FU was also more toxic, with 16% treatment-related deaths for the combination vs. no such deaths for cisplatin alone.

Cisplatin in combination with UFT, an oral 5-FU prodrug combining tegafur with uracil (an inhibitor of the enzyme dihydropyrimidine dehydrogenase, which degrades 5-FU) has also been evaluated in esophageal cancer. A response rate of 46% was reported.[32]

Cisplatin/5-FU has been accepted as a treatment standard in squamous cell and adenocarcinoma of the esophagus. More recent phase III trials have treated adenocarcinoma of the gastroesophageal junction in the context of gastric cancer studies; recent studies have also included squamous cell and adenocarcinoma of the esophagus in these trials. One European trial called into question the adoption of infusional 5-FU and cisplatin as the treatment standard.[33] This trial in gastric and gastroesophageal junction cancer compared cisplatin combined with a 5-day infusion of 5-FU to the combination of 5-FU, doxorubicin, and methotrexate (FAMTX), or to the combination of etoposide, leucovorin, and 5-FU (ELF). All treatments in this trial, including cisplatin/5-FU, resulted in disappointing response rates of less than 10% to 20% and a median survival of less than 8 months.

Epirubicin/Cisplatin/5-FU

Recent phase III trials have compared the addition of a third agent to cisplatin/5-FU vs. cisplatin/5-FU alone, or have compared alternative non–cisplatin-containing regimens to cisplatin/5-FU. The Royal Marsden

group developed the ECF regimen, a combination of epirubicin 50 mg/m^2 and cisplatin 60 mg/m^2 every 3 weeks in combination with daily protracted continuous infusion 5-FU 200 mg/m^2/day, in gastric cancer. In a phase III trial in gastric and gastroesophageal junction adenocarcinoma, the ECF regimen was compared to a bolus regimen of FAMTX.[34] The ECF regimen resulted in a superior response rate (45% vs. 21%), failure-free survival (7.4 vs. 3.4 months), and median survival (8.9 vs. 5.7 months) in comparison to FAMTX. The ECF regimen had a tolerable toxicity profile, with less than 10% grade 3 or 4 diarrhea or stomatitis.

A more recent trial treating nearly 600 patients with advanced esophageal squamous cell and adenocarcinoma and gastric adenocarcinoma compared the ECF regimen to a similar regimen substituting mitomycin 7 mg/m^2 every 6 weeks for epirubicin.[35] This trial validated the previously reported response rate and median survival for the ECF regimen (42%, 9.4 months), but the response rate and median survival time observed for the mitomycin combination regimen (44%, 8.7 months) were identical to ECF. Given that there was no difference in efficacy for the epirubicin- vs. mitomycin-containing arms, this study raises the question of whether the addition of a third agent makes a difference in outcome when combined with cisplatin and protracted infusion 5-FU. These trials, however, validate use of a lower dose of cisplatin (60 mg/m^2) and confirm the better tolerance of a low-dose protracted infusion of 5-FU over 6 weeks as opposed to a higher-dose infusion administered over 4 to 5 days.

Another concern about the ECF trials is the large percentage of patients with locally unresectable, nonmetastatic disease, which accounted for 40% of persons treated on both ECF trials. The inclusion of patients with locally advanced disease may lead to inflation of both antitumor response rates and survival, and results from these trials may not be entirely comparable to studies treating only patients with distant metastatic disease.

Whether or not the addition of epirubicin adds to the activity of cisplatin/5-FU was recently addressed in a meta-analysis of chemotherapy trials in gastric cancer. Addition of an anthracycline as a third agent to cisplatin and 5-FU resulted in a 1-month improvement in median survival, compared to treatment with 5-FU and cisplatin alone.[36]

Paclitaxel/Cisplatin/5-FU

Paclitaxel, which had shown significant promise as a single agent, was added to the cisplatin/5-FU regimen in a phase II multicenter study.[37] Paclitaxel (175 mg/m^2/3 hr, day 1), cisplatin (20 mg/m^2, days 1–5), and continuous infusion 5-FU (750 mg/m^2, days 1–5) were given to patients with metastatic or recurrent esophageal cancer on a 28-day treatment cycle without G-CSF support. A 3-hour schedule of paclitaxel was selected on the basis of results of a prior phase I trial reported by Bhalla and associates,[38] who had used the regimen in an attempt to reduce myelosuppression and permit the delivery of full doses of 5-FU and cisplatin. A 48% response rate was reported in 60 patients, with similar response rates seen in patients with adenocarcinoma (46%) and patients with squamous cell carcinoma (50%). Toxicity was severe for the combination of paclitaxel, 5-FU, and cisplatin, and 48% of patients required dose attenuation. Half the patients were hospitalized for toxicity, yet there were no treatment-related deaths. Alternative schedules of cisplatin, 5-FU, and paclitaxel have also been evaluated.[39]

Two-drug combinations of paclitaxel and cisplatin have also been studied. When paclitaxel 200 mg/m^2 over 24 hours and cisplatin 75 mg/m^2 were combined with G-CSF support,[40] a response rate of 44% in 32 patients was observed. Gastrointestinal toxicity was less severe with the elimination of 5-FU from the regimen, but myelosuppression remained significant, with grade 4 neutropenia in 47% of patients and treatment-related deaths in 11%.

Two European groups evaluated a biweekly schedule of paclitaxel and cisplatin. Petrasch and coworkers[41] gave 3-hour paclitaxel (90 mg/m^2) with cisplatin (50 mg/m^2) every 14 days in a phase II trial to patients with unresectable or metastatic disease. Of 20 patients with either adenocarcinoma or squamous cell carcinoma, 40% had a major response, and the complete response rate was 15%. Grade 3/4 toxicity was limited to neutropenia (10%) and neurotoxicity (5%). Kok and associates[42] reported a phase I trial of cisplatin 60 mg/m^2 and escalating doses of 3-hour paclitaxel without G-CSF support in 31 patients with adenocarcinoma and 28 patients with squamous cell carcinoma. Paclitaxel was increased from 100 to 200 mg/m^2. Grade 3/4 granulocytopenia was the predominant toxicity, yet sensory neuropathy was dose-limiting, with a maximum tolerated paclitaxel dose of 180 mg/m^2. Of 58 evaluable patients, 30 (52%) had an objective response: 53% of those with adenocarcinoma and 50% of those with squamous cell carcinoma. No treatment-related deaths were reported in either trial.

Paclitaxel has undergone limited evaluation in combination with carboplatin in metastatic esophageal cancer. A phase I trial of weekly carboplatin dosed from an area under the concentration-time curve (AUC) of 2 to 5 combined with a 1-hour infusion of paclitaxel 100 mg/m^2 in 40 patients with advanced esophageal and gastroesophageal junction cancer, with an overall response rate of 54% observed.[43] The trial suggests comparable activity for the substitution of carboplatin for cisplatin in paclitaxel combination therapy.

Docetaxel/Cisplatin/5-FU

The addition of docetaxel as a third agent added to 5-FU/cisplatin in a phase III trial of gastroesophageal junction and gastric cancer was recently reported. 5-FU dosed at 1,000 mg/m^2 by continuous infusion over 5 days combined with cisplatin 100 mg/m^2 was compared to cisplatin 75 mg/m^2, 5-FU 750 mg/m^2 by continuous infusion over 5 days, and docetaxel 75 mg/m^2 (DCF) in 445 patients with metastatic gastric or gastroesophageal junction adenocarcinoma.[44] The DCF regimen resulted in a higher response rate and longer time to progression (36%, 5.6 months) compared to 5-FU and cisplatin (26%, 3.7 months), but only a marginal median survival improvement (0.6 months) was noted for the three-drug regimen. Toxicity was substantial in both treatment arms, including hematologic and gastrointestinal toxicity, with 82% of patients receiving the three-drug combination experiencing grade 3 or 4 neutropenia.

The potential superiority of DCF was underscored by a recent randomized phase

II trial comparing ECF to DCF in gastric and gastroesophageal junction cancer. The DCF regimen appeared to result in a superior response rate and time to tumor progression when compared to ECF, but toxicity — particularly rates of neutropenia and neutropenic fever — was substantial.[45]

Irinotecan Plus 5-FU

The combination of irinotecan and infusional 5-FU was compared head to head to conventional 5-FU and cisplatin in a recent phase III trial in gastric and gastroesophageal junction cancers[46] based on previous phase II data for the irinotecan combination.[47] Irinotecan 80 mg/m^2 in combination with 5-FU 2 g/m^2 over a 24-hour infusion and leucovorin 500 mg/m^2 administered weekly for 6 weeks on and 1 week off was compared to cisplatin 100 mg/m^2 and 5-FU 1,000 mg/m^2 continuous infusion for 5 days, administered every 4 weeks, in 333 patients. There was no difference in response rate (26% vs. 32%), time to progression (4.2 vs. 5.0 months), or median survival (8.7 vs. 9.0 months). However, the toxicity profile significantly favored the irinotecan/5-FU combination, with less neutropenia, neutropenic fever, stomatitis, and nausea. Only the rate of grade 3 or 4 diarrhea was greater in the irinotecan arm. This trial suggests that irinotecan/5-FU may represent a comparably active but potentially better tolerated alternative to 5-FU/cisplatin.

Oxaliplatin/Capecitabine vs. Cisplatin/5-FU

Oxaliplatin as a potential substitute for cisplatin has been explored in single-arm and randomized phase II trials in esophageal and gastric adenocarcinoma. Mauer and colleagues combined oxaliplatin 85 mg/m^2 on day 1, with boluses of 5-FU 400 mg/m^2 and leucovorin 500 mg/m^2 and a 22-hour continuous infusion of 5-FU administered on days 1 and 2, cycled every 2 weeks.[48] A response rate of 40% was observed in 34 patients with metastatic squamous cell or adenocarcinoma of the esophagus.

The Royal Marsden group recently completed a 1,000-patient phase III trial in esophageal squamous cell and adenocarcinoma and gastric cancer, evaluating the front-line use of oxaliplatin.[49] This trial compared conventional ECF with the substitution of capecitabine for infusional 5-FU, and oxaliplatin for cisplatin. The trial employed a 2×2 design, with the control arm ECF, and the experimental arms including capecitabine 625 mg/m^2 twice daily substituted for infusional 5-FU, oxaliplatin 130 mg/m^2 substituted for cisplatin, and a fourth arm with a substitution of both capecitabine and oxaliplatin. The primary end point was to demonstrate noninferiority for the capecitabine and oxaliplatin treatment arms.

An interim analysis of the trial results in the first 204 patients treated revealed comparable rates of 5-FU–related toxicities in all the treatment arms, and comparable response rates of 31% to 48% across treatment arms. A recent abstract presentation of the results from this trial indicated that substitution of either oxaliplatin for cisplatin, or capecitabine for infusional 5-FU was not inferior to conventional cisplatin or infusional 5-FU.[50] Further comparison of capecitabine vs. infusional 5-FU in combination with cisplatin in gastric cancer has also recently been reported in abstract form in a trial of patients with gastric cancer. The capecitabine arm also appeared to be noninferior to the infusional 5-FU arm.[51]

A recent German trial, reported in abstract form, employed a dose and schedule of 5-FU typically used in colorectal cancer regimens, using every-2-week administration of infusional 5-FU in combination with either oxaliplatin or cisplatin.[52] Toxicity of both regimens was very favorable, indicating a potential advantage for this schedule of 5-FU in combination with platinum agents.

The recent trials of infusional 5-FU combination chemotherapy indicate improved therapy tolerance and potentially enhanced antitumor activity, employing either a more protracted low-dose infusion of 5-FU, as in the ECF regimen, or weekly or every-2-week infusions of 5-FU, as in the irinotecan/5-FU or cisplatin/oxaliplatin regimens. The addition of a third agent, including epirubicin or docetaxel, to 5-FU and cisplatin may modestly increase response rates and survival, but docetaxel combination therapy results in substantial therapy-related toxicity. The use of relatively high and relatively toxic doses of cisplatin (75–100 mg/m^2) is also called into question, given data from the British phase III ECF trials suggesting better therapy tolerance for 60 mg/m^2 with no apparent compromise in efficacy. Capecitabine appears to be comparable to infusional 5-FU.

NON–CISPLATIN/ 5-FU–BASED REGIMENS

On the basis of promising results observed in lung, colon, and gastric cancer by Japanese investigators, Saltz and colleagues[53] developed a regimen of irinotecan 65 mg/m^2 and cisplatin 30 mg/m^2 given weekly for 4 weeks followed by a 2-week rest period. A phase II trial of this regimen was then initiated in patients with previously untreated metastatic esophageal cancer.[54] A 57% response rate in 35 evaluable patients was observed. Response rates for patients with adenocarcinoma (52%) and squamous cell carcinoma (66%) were similar. Toxicity was relatively mild, with tolerable myelosuppression and rare grade 3 diarrhea. On the basis of the favorable experience with the combination of weekly irinotecan and cisplatin, recent trials have evaluated the addition of paclitaxel, docetaxel, 5-FU, and capecitabine in phase I and II trials.[55-58] In a recent phase II trial, docetaxel 30 mg/m^2 was combined with irinotecan 50–65 mg/m^2 and cisplatin 25 mg/m^2 on a day 1 and day 8 schedule every 3 weeks.[58] A response rate of 58% was observed in 26 treated patients with esophageal and gastric cancer.

There are few combination chemotherapy regimens in esophageal cancer that do not incorporate cisplatin. An early trial of bleomycin in combination with doxorubicin showed relatively modest activity.[59] Braybrooke and associates[60] investigated the combination of mitomycin and oral etoposide in patients with advanced adenocarcinoma of the upper gastrointestinal tract. Of 28 evaluable patients, 15 had esophageal or gastroesophageal junction cancers. In this group, only two patients (13%) had a major response.

More recent non–cisplatin-containing combination trials have explored regimens including taxanes and irinotecan. Although these trials have indicated encouraging response rates in the phase II setting, substantial hematologic and gastrointestinal (diarrhea) toxicities of these regimens may not offer an advantage over the older cisplatin-containing regimens. A preliminary report of the combination of paclitaxel 225

mg/m^2 and irinotecan 100 mg/m^2 administered once every 3 weeks indicated a response rate of 27% in patients with adenocarcinoma of the gastroesophageal junction.[61]

Docetaxel has been evaluated in combination with irinotecan in four recent phase II trials. Two trials evaluated irinotecan doses of 100–160 mg/m^2 and docetaxel 50–60 mg/m^2 administered once every 3 weeks, and two other trials evaluated a day 1 and day 8 schedule of irinotecan 50–55 mg/m^2 and docetaxel 25–35 mg/m^2 cycled every 3 weeks. The every-3-week schedule, which treated predominantly patients with adenocarcinoma, resulted in response rates ranging from 26% to 30%.[62,63] The day 1 and day 8 schedule studies reported a response rate of 29% in 24 patients with previously untreated squamous cell or adenocarcinoma,[64] and only a 13% response rate in 24 patients with prior therapy for esophageal squamous or adenocarcinoma.[65] Hematologic toxicity, which exceeded 50% in patients treated on the every-3-week schedule, seemed to be less severe using the day 1 and day 8 schedule compared to the every-3-week schedule, and grade 3/4 diarrhea on both schedules ranged from 13% to 31%.

Docetaxel and vinorelbine were evaluated in a phase II trial in 20 patients with squamous cell carcinoma mainly with locally recurrent disease; a response rate of 60% was reported.[66] Docetaxel 75 mg/m^2 every 3 weeks plus capecitabine 1,000 mg/m^2 twice daily for 14 days was studied in a phase II trial in 24 patients with predominantly squamous cell carcinoma of the esophagus. A response rate of 46% was observed.[67] Toxicity was mainly hematologic, with 42% of patients experiencing grade 3 or 4 neutropenia.

In addition to the irinotecan combination trials with docetaxel described above, irinotecan has also been evaluated in combination with continuous infusion 5-FU in recent single-arm and randomized phase II trials in esophageal and gastric cancer. One trial combined irinotecan 180 mg/m^2 every 2 weeks with bolus 5-FU 400 mg/m^2, leucovorin 125 mg/m^2, and a 48-hour continuous infusion of 5-FU dosed at 1,200 mg/m^2/day, cycled every 2 weeks.[68] The regimen was well tolerated, and a response rate of 29% was reported in patients with esophageal and gastric cancer who had progressed on at least one prior chemotherapy regimen.

The tolerability and activity of irinotecan and continuous-infusion 5-FU was also reported in a randomized phase II trial in gastric cancer, in which the 5-FU combination was compared to irinotecan and cisplatin.[69] A total of 115 patients with adenocarcinoma of the stomach or gastroesophageal cancer were randomized to receive irinotecan 80 mg/m^2 in combination with leucovorin 500 mg/m^2 and a 22-hour infusion of 5-FU at a dose of 2,000 mg/m^2 cycled weekly for 6 weeks with a 1-week break, or to irinotecan 200 mg/m^2 and cisplatin 60 mg/m^2 once every 3 weeks. The irinotecan plus 5-FU arm had a superior toxicity profile, with less hematologic toxicity but slightly more diarrhea than the irinotecan/cisplatin arm. Response rates were comparable for the 5-FU arm (42%) and the cisplatin arm (34%), but time to progression (6.5 vs. 4.2 months) and median survival (10.7 vs. 6.9 months) favored the irinotecan/5-FU combination.

Irinotecan in combination with mitomycin was assessed in a recent phase II trial in esophageal and gastroesophageal junction cancer.[70] Irinotecan administered at a dose of 125 mg/m^2 day 1 and day 8, every 3 weeks, was combined with one of two dose schedules of mitomycin: mitomycin 6 mg/m^2 on day 2, or mitomycin 3 mg/m^2 on days 2 and 9, cycled every 3 weeks. Patients with both locally advanced and metastatic disease were treated, and 17 responses were reported in 37 patients (46%).

TARGETED AGENTS

Of great interest is the identification of biochemical markers in tumors that may be predictive of chemotherapy response and resistance. Thymidylate synthase, the enzyme targeted by 5-FU, appears to be a potential marker of chemotherapy response. An increase in expression of thymidylate synthase may lead to resistance to 5-FU in gastroesophageal cancers.[71] In addition to evaluation of potential chemotherapy target expression with immunohistochemical analysis or mRNA expression in tumors, studies are now looking at variations in individual genetic polymorphisms of tumor targets expressed in patients using pharmacogenetic analysis. It is hoped that advances in pharmacogenomics, the study of individual patient metabolism of chemotherapy agents, and pharmacogenetics, the germline variation of tumor target expression in each patient, will lead to better tailoring of therapy to the individual patient.

The search for effective antitumor agents in the treatment of esophageal cancer continues, given the modest activity of currently available agents and brief duration of antitumor responses observed. Future strategies in the treatment of esophageal carcinoma will undoubtedly be based on advances in the understanding of the molecular biology of the disease. Ongoing studies indicate a role for numerous oncogenes and tumor suppressor genes in the mechanism of tumorigenesis; these factors may be important biologic prognostic factors as well as potential targets for the development of new antitumor drugs. Over the past decade, the field of drug development has been transformed with the identification of, and ability to direct treatment at, specific molecular targets.

For squamous cell esophageal carcinoma and gastroesophageal adenocarcinoma, potential tumor targets/markers have been described, including those related to growth regulation (epidermal growth factor receptors [EGFR, HER2/neu] and Ki-67), angiogenesis (vascular endothelial growth factor [VEGF]), inflammation (COX-2 pathway), cell cycle control (p16, p21, cyclin D1), apoptosis (p53, bax, and bcl-2), metastatic potential (tissue inhibitor of metalloproteinase, E-cadherin), and sensitivity to chemotherapy (p-glycoprotein, thymidylate synthase, glutathione S-transferase, metallothionine, ERCC-1). Most have been studied solely as markers to predict clinical outcomes, such as pathologic response after preoperative chemotherapy or chemoradiotherapy.[72-77]

EGFR Therapy

Multiple targeted therapies for esophageal cancer are in various phase I/II clinical trials, including monoclonal antibodies and signal transduction/tyrosine kinase inhibitors for EGFR, monoclonal antibodies to the HER2/neu receptor and VEGF ligand, oral COX-2 inhibitors, and other novel drugs. Multiple phase II trials have been reported for the tyrosine kinase inhibitors erlotinib

and gefitinib. Gefitinib appeared to have no activity in adenocarcinoma of the esophagus or gastroesophageal junction, but limited activity was observed for patients with squamous cell cancer.[78] In phase II trials of erlotinib, activity has also been reported in squamous cell cancer of the esophagus,[79] but adenocarcinoma trials have indicated either no activity[79] or modest activity.[80] Phase II trials have reported combinations of EGFR-targeted monoclonal antibodies with chemotherapy, including the combination of FOLFIRI (leucovorin/5-FU/irinotecan) with cetuximab[81] and matuzumab as a single agent[82] or in combination with ECF.[83]

VEGF-Targeted Therapy

Of the identified angiogenic factors, VEGF is the most potent and specific and has been identified as a crucial regulator of both normal and pathologic angiogenesis. VEGF is overexpressed in 30% to 60% of patients with esophageal cancers and multiple studies have demonstrated a correlation between high levels of VEGF expression, advanced stage, and poor overall survival in patients undergoing a potentially curative esophagectomy.[84-87]

Trials combining VEGF-targeted therapy, including bevacizumab, are ongoing or planned in the treatment of both metastatic and locally advanced esophageal cancer. A recent phase II trial combined bevacizumab, which targets the VEGF ligand, with weekly irinotecan and cisplatin in metastatic gastric and gastroesophageal junction cancer.[88] A response rate of 65% was observed with a median time to progression of 8.9 months, significantly greater than historical control results for this regimen. Although toxicity was not increased with the addition of bevacizumab to chemotherapy, two gastric perforations and one near perforation (6%) were seen in this trial. Further phase II and III evaluation of bevacizumab in esophagogastric cancer is planned.

NEOADJUVANT CHEMOTHERAPY

Collectively, data from European and American studies suggest that administering systemic chemotherapy prior to surgery for esophagogastric cancer improves survival compared to surgery alone,[89–91] and that the addition of concurrent radiotherapy improves rates of curative resection, increases rates of pathologic complete response, reduces rates of local tumor recurrence, and may also translate into a modest incremental improvement in survival.[92-96] The absolute improvements in survival, however, with preoperative chemotherapy with or without concurrent radiotherapy are marginal and likely to be less than 5% to 15%, making survival differences difficult to demonstrate in the context of small randomized trials. The relative merits of preoperative chemotherapy alone, or preoperative chemotherapy combined with radiation therapy, will ultimately need to be addressed with a randomized trial comparing treatment with or without radiotherapy.

For patients with adenocarcinoma of the gastroesophageal junction, or cancers of the stomach with extension into the gastroesophageal junction, another potential treatment alternative has emerged with publication of the results of Intergroup trial 0116 in gastric cancer.[97] The Intergroup trial indicated a significant improvement in median, overall, and disease-free survival for the delivery of postoperative radiation and chemotherapy with 5-FU and leucovorin compared to surgery alone. Twenty percent of patients treated on study had proximal gastric cancers and tumors of the gastroesophageal junction, and these data justify the use of postoperative therapy in these patients.

DISCUSSION

Modest advances have been made in chemotherapy for esophageal cancer. A spectrum of single agents are active in esophageal cancer, including fluorinated pyrimidines, taxanes, platinum drugs, irinotecan, and mitomycin. Two-drug combinations modestly increase response rates, but translate into only a limited improvement in survival compared to single-agent therapy. The combination of 5-FU and cisplatin is widely used, and alternative two-drug regimens using either 5-FU or cisplatin as a backbone typically add either a taxane or irinotecan. Recent phase III trials, also treating patients with gastric cancer, indicate modest 10% to 15% improvements in response and 1–2 month improvements in median survival with the addition of a third agent to conventional infusional 5-FU/cisplatin — either epirubicin on the ECF regimen or docetaxel on the DCF regimen.

Cisplatin/5-FU-based chemotherapy is now a therapy standard in the preoperative treatment of esophageal and gastroesophageal junction adenocarcinoma. Combined chemotherapy and radiation therapy are given preoperatively for esophageal adenocarcinoma and squamous cell carcinoma, and chemoradiotherapy without surgery is an accepted therapy standard for squamous cell cancer. Future research will focus on incorporating novel, molecularly targeted agents in the treatment of advanced disease and in the preoperative treatment of locally advanced disease.

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