Chemotherapy for Gastric Carcinoma: New and Old Options

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Although gastric carcinoma is an uncommon disease in North America, its incidence is alarmingly high in Asia, South America, Eastern Europe, and countries of the former Soviet Union. Screening for gastric carcinoma is performed only on a limited basis in Japan; in the rest of the world, therefore, patients often present with advanced disease at the time of diagnosis.

Introduction

Gastric carcinoma is a major health problem around the world. Its incidence, however, has steadily dropped globally since World War II. This decreased incidence has been termed an “unplanned success.” Although the incidence of gastric cancer is lowest in North America, it still ranks as the eighth leading cause of cancer death in the United States. In 1998, more than 22,600 new cases of gastric cancer are expected to occur in the United States, and 13,700 deaths are anticipated as a result.[1] Patients with gastric carcinoma often present with advanced disease, because early detection is neither practiced nor possible in many countries. Screening for early detection of gastric cancer is carried out on a limited basis in Japan. Approximately 50% of patients are diagnosed with unresectable, locally advanced, or metastatic cancer. Median survival for patients with advanced disease ranges from 6 to 10 months.[2]

Although advanced gastric cancer is not curable, chemotherapy can have a palliative effect in symptomatic patients. In four randomized studies comparing combination chemotherapy with best supportive care in patients with advanced gastric carcinoma, quality of life and overall survival improved in patients receiving chemotherapy.[3-6] All four of these studies, however, were limited by small numbers of patients.

Single-Agent Therapy

Few drugs are active when used as single agents to treat gastric cancer. Response rates are usually ≤ 20%, with rare complete remissions and brief response durations. The pyrimidine analogue 5-fluorouracil (5-FU) has been studied most extensively, producing a response rate of less than 20%.[7] Other agents such as mitomycin,[7] etoposide,[8] and cisplatin[9] are also considered active, producing response rates of approximately < 20% when used as single agents.

Randomized Studies

In the early 1980s, the FAM (5-FU, doxorubicin, mitomycin) regimen was considered the gold standard for treatment of patients with advanced gastric carcinoma. In a revealing study performed by the North Central Cancer Therapy Group (NCCTG),[10] the FAM regimen was compared with single-agent 5-FU and 5-FU plus doxorubicin. No significant survival difference was detected among the three regimens; however, response rates were higher in patients receiving more than one agent (highest response rate seen with FAM, and higher response rate with 5-FU/doxorubicin than with 5-FU alone). These results suggest that combination chemotherapy is more appropriate than single-agent therapy for palliative treatment.

Several randomized studies, comparing FAM with FAMTX (5-FU, doxorubicin, methotrexate),[11] FAMTX with ECF (epirubicin, cisplatin, 5-FU),[12] and FAMTX vs ELF (etoposide, leucovorin, 5-FU) vs 5-FU/cisplatin have been reported.[13] No one standard therapy has emerged from these trials. The ECF regimen, which produced the best response rates in the most recent comparison, has not been widely accepted as standard therapy because it includes an experimental agent (epirubicin) and uses a prolonged infusion schedule of 5-FU. In addition, doxorubicin (a predecessor to epirubicin) is...
no longer a primary agent used to treat advanced gastric carcinoma. Epirubicin as a single agent is practically inactive against gastric carcinoma (with less than 10% response rate). In addition, survival data from ECF is similar to the survival data from FAMTX in a previous randomized trial.[11] This degree of overlap should cast some doubts in embracing ECF as a standard. Thus it would appear that infusional 5-FU in combination with cisplatin is likely to produce satisfactory palliation that is comparable to any combination studied thus far. Recommended treatment (outside of clinical trials) is usually with cisplatin-based or 5-FU-based combination chemotherapy. Clearly, more active agents are needed for the treatment of this disease.

New Single-Agent IV Drugs and Their Use In Combination

Chemotherapeutic approaches for gastric carcinoma, as for many solid tumors, are continually evolving. Several new agents have been studied recently in patients with gastric carcinoma, including paclitaxel and docetaxel, irinotecan, oral etoposide, and oral 5-FU biomodulators such as UFT and S-1.

Paclitaxel

Based on the activity of paclitaxel against adenocarcinoma of the esophagus and gastroesophageal junction,[14] a phase II study of single-agent paclitaxel in chemotherapy-naive patients with advanced, unresectable gastric carcinoma was undertaken at M. D. Anderson Cancer Center. A response rate of 17% was established.[15] Other studies of paclitaxel in advanced gastric carcinoma include a phase II trial performed by the Eastern Cooperative Oncology Group (ECOG), in which one partial response was achieved among 22 eligible patients (response rate 5%; 95% confidence interval [CI], 0% to 25%).[16] In a preliminary study by Tamura et al, three (21%) of 14 evaluable patients achieved a partial response when treated with 3-hour infusional single-agent paclitaxel.[17] All three responders had previously received chemotherapy. These preliminary reports suggest that paclitaxel is modestly active against gastric carcinoma. In addition, in a study of 34 patients treated with paclitaxel combined with 5-FU and cisplatin, 50% responded.[18]

Docetaxel

Docetaxel has also been studied in patients with advanced gastric carcinoma. The observed level of activity is similar to that reported with paclitaxel. Taguchi et al reported 9 (20%) partial responses among 45 evaluable patients with advanced gastric carcinoma who received only 60 mg/m2 of docetaxel administered every 3 weeks.[19] Sulkes et al treated 37 advanced gastric carcinoma patients with 100 mg/m2 of docetaxel every 3 weeks and reported a 24% (8 of 33 assessable patients) partial response rate.[20] In addition, a 17% response rate was observed in an ECOG study of 41 chemotherapy-naive patients with advanced gastric carcinoma.[21] More recently, assessment of combination chemotherapy including docetaxel (ie, docetaxel-cisplatin) has demonstrated substantial activity against advanced gastric carcinoma.[22]

Irinotecan

The topoisomerase-I inhibitor, irinotecan (CPT-11), has also demonstrated activity against gastric carcinoma when used as a single agent.[23] Interestingly, irinotecan was shown in this study to be active in patients previously treated with chemotherapy. In a study using a combination of irinotecan plus cisplatin, 42% of patients with gastric carcinoma responded[24]; this high response rate was confirmed in another study performed in Japan.[25] Similarly, the irinotecan/cisplatin combination appears to be active against carcinoma of the esophagus.[26]

Oral Agents

In evaluating treatment for cancer, increasing attention is being given to parameters such as quality of life, convenience of treatment, and symptom palliation. Oral chemotherapy, which is potentially more convenient than intravenous chemotherapy, has therefore come into focus. Most of the oral agents currently available are 5-FU prodrugs; therefore, their application in gastrointestinal malignancies is of interest. In addition, oral etoposide (topoisomerase-II inhibitor) has been studied
in gastric carcinoma.

**Oral Etoposide**

When the oral formulation of etoposide became available for investigation a few years ago, it was realized that chronic administration of this agent resulted in an improved pharmacokinetic profile compared with that of the traditional shorter intravenous infusion.[27] In a study of oral etoposide in chemotherapy-naive advanced gastric carcinoma patients, a response rate of 17% was observed among 26 evaluable patients, and the drug was extremely well tolerated.[28] Because oral etoposide has a modest level of activity against gastric carcinoma, it may be possible to combine it with other oral agents to achieve symptom palliation without adversely affecting quality of life.

**UFT**

UFT (uracil combined with tegafur in a 4:1 ratio) represents a second-generation, oral 5-FU prodrug. Biochemically, the combination of UFT and folinic acid appears to offer more than intravenous 5-FU and folinic acid because UFT incorporates uracil. Uracil prevents degradation of 5-FU by inhibiting dihydropyrimidine dehydrogenase (DPD), and this leads to increased levels of 5-FU in the plasma and tumor tissue. UFT has been widely available in Japan, Korea, Singapore, and Spain, and was currently made available in many South American countries. It appears that prolonged UFT administration results in similar or higher \( C_{\text{max}} \) (maximum concentration achieved) as well as AUC (area under the curve) compared with that achieved with continuous infusion 5-FU, although the pharmacokinetic patterns are different.[29,30]

In a recent review, we reported that the data on UFT alone and in combination were generated predominantly in Japan and Korea.[31] Phase II data suggest that UFT has activity against gastric carcinoma similar to that seen with 5-FU. It was also shown to be superior to tegafur (the first-generation 5-FU prodrug) in the adjuvant therapy of gastric carcinoma. The tolerability to UFT when given by a 28-day on and 7-day off schedule has been excellent. Commonly occurring toxicities include gastrointestinal effects such as anorexia (24%), nausea and vomiting (12.5%), and diarrhea (11%). Hematologic toxicity is rare. In the United States, UFT is undergoing extensive evaluation in several types of solid tumors including colon, gastric, esophageal, and breast carcinomas. UFT is combined with folinic acid in these studies.

**S-1**

S-1 is a combination of tegafur (5-FU prodrug), 5-chloro-2,4-dihydropyrimidine (a DPD inhibitor), and potassium oxonate (aimed at reducing diarrhea by inhibiting phosphorylation of 5-FU in the gastrointestinal mucosa). Preliminary data on S-1 for the treatment of advanced gastric cancer are encouraging. In a phase II study of 51 patients, Ohtsu et al administered S-1 80 mg/m² orally twice daily for 28 days followed by a 7-day rest period.[32] The overall response rate was 49% (95% CI, 36% to 62%), median duration of response was 4.6 months, and median survival of all patients was approximately 8.5 months. Another study by Kurihara et al has also demonstrated the activity of S-1 in patients with gastric carcinoma.[33] Currently, this agent is undergoing extensive evaluation in the United States.

**Capecitabine**

Capecitabine is also a second-generation 5-FU prodrug developed to improve intratumoral concentrations of 5-FU and reduce diarrhea. It is absorbed as an intact molecule from the small bowel mucosa and converted sequentially in a multistep process. The primary conversion step occurs in the liver and is mediated by carboxylesterase. The conversion into 5-FU is mediated by purine nucleoside phosphorylase (PNP).[34] Because PNP levels are higher in tumor cells than in normal tissues, a higher rate of conversion occurs there, resulting in greater concentrations of 5-FU in tumor than in normal tissues. Capecitabine has been approved in the United States for third-line treatment of breast cancer, and is undergoing extensive evaluation in patients with colon cancer. The advantage of this agent is that it can be effectively administered on a twice-daily schedule for 14 days followed by a 14-day break.
Eniluracil

Eniluracil (776C85) is among the newer oral agents developed to improve the efficacy of 5-FU. Eniluracil is a potent and irreversible inactivator of DPD, which is the first enzyme to degrade 5-FU.[34,35] Eniluracil is capable of inhibiting 99% of DPD; thus only a low concentration of 5-FU is needed to exert antitumor effect as well as toxicity. When administered with eniluracil, the half-life of 5-FU is prolonged from 15 minutes to up to 5 hours. Currently, several schedules combining eniluracil plus 5-FU are being studied. In a 28-day schedule, eniluracil 10 mg/m² and 5-FU 1.15 mg/m² are both given orally. In phase I studies, this oral combination was extremely well tolerated; toxicities included fatigue, nausea, vomiting, and rare mucositis. Eniluracil/5-FU is undergoing extensive evaluation in several malignancies including colorectal and pancreatic cancers.

Discussion

The interest in chemotherapy for gastric cancer has increased substantially in the past 15 years. The number of potentially active new agents has increased, and many investigators have been evaluating combinations of older agents or new agents. Based on results of comparative trials, single-agent chemotherapy with 5-FU may be as effective as combination chemotherapy. Recent randomized trials have not established a widely accepted standard therapy. Use of 5-FU-based combination or cisplatin-based combination chemotherapy is acceptable for palliation of patients with advanced gastric carcinoma who cannot be enrolled in a study. Several new drugs and new combinations have been identified in the past 4 years, and further research is needed to define the optimal role for these therapies.

Recently, increasing emphasis has been placed on patient convenience, quality of life, and effective palliation. A parallel focus has been on efforts to improve cytotoxicity of new therapies. In most Asian countries, patients with gastric cancer traditionally have received oral chemotherapy including drugs like UFT and tegafur, which have been in use there for several years. Studies of the antitumor efficacy of oral agents indicate that activity is not compromised with the oral formulations; however, results of ongoing studies are awaited to confirm this. The potential disadvantages of oral administration include patient noncompliance and predictability of gastrointestinal absorption.

For patients with gastric carcinoma, oral etoposide offers a convenient alternative while maintaining similar efficacy compared with its intravenous formulation. The toxicity profile of etoposide appears similar whether the drug is administered orally or intravenously. Combining oral etoposide with other oral or intravenous agents to develop an effective palliative regimen may be possible.

Other oral agents for the treatment of patients with gastric carcinoma are the 5-FU prodrugs. Among compounds that are being studied clinically, UFT has been investigated extensively, and S-1, capecitabine, and the DPD inactivator eniluracil are undergoing evaluation in several tumor types. In addition, oral formulations of topoisomerase inhibitors, metalloprotein inhibitors, antiangiogenic agents, and taxanes are expected; while intravenous agents including oxaliplatin, protein-C kinase inhibitors, and gene therapy will also increase the therapeutic options for patients with gastric cancer.

References:
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