Current Status of Therapy for Advanced Gastric Carcinoma

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Advanced gastric carcinoma remains an incurable disease with a median survival of 6 to 9 months, and available therapeutic approaches are predominantly palliative. In small controlled trials, systemic chemotherapy has

Introduction

Gastric carcinoma continues to be a serious health problem throughout the world. The decline in its incidence is a global, consistent phenomenon, although this decrease has been more noticeable in the western world than in Asia and eastern Europe. Despite the fact that the United States has one of the lowest incidences of gastric cancer in the world, more than 22,600 new cases of this cancer are anticipated in this country in 1998, and a total of 13,700 patients are expected to die as a result of it.[1] Gastric carcinoma also remains the eighth leading cause of cancer death in the United States.[1]

Since the stomach is a rather large organ, a space-occupying lesion often does not cause symptoms until it has reached a substantial size. Early detection is neither carried out nor financially feasible in most countries around the globe. Thus, it is not uncommon for a significant number of patients with gastric carcinoma to have widely disseminated cancer at diagnosis. It is estimated that nearly one-half of US patients have gastric carcinoma beyond the local confines at diagnosis.

Advanced gastric carcinoma is incurable, and chemotherapy remains palliative. The median survival of patients with advanced disease is 6 to 9 months.

Conventional Agents

In patients with metastatic gastric carcinoma, chemotherapy appears to provide a significant survival advantage over best supportive care.[2] However, all four published prospective randomized trials of chemotherapy vs supportive care involved only a small number of patients.[3-6]

Single Agents

Although a number of conventional agents are used to treat gastric carcinoma, there is no standard chemotherapy. The use of fluorouracil- or cisplatin-based combinations in patients with good performance status (Zubrod ≤ 2) may be considered acceptable. The response rate to fluorouracil alone is less than 20%.[7] Other agents, such as mitomycin (Mutamycin),[7] etoposide (VePesid),[8] and cisplatin (Platinol),[9] are also considered active and result in response rates of approximately 20% when used as single agents. However, responses are short-lived.

Combination Regimens

Combination chemotherapy for advanced gastric cancer has been attractive to investigators for many decades. In a pivotal study performed by the North Central Cancer Therapy Group (NCCTG) comparing the FAM (fluorouracil, Adriamycin, and mitomycin) regimen to fluorouracil alone and fluorouracil plus doxorubicin, no significant survival difference was detected among the three regimens.[10] Combination chemotherapy produced a higher response rate, however. In the United States, there have been no further comparisons of any combination vs fluorouracil alone.

On the other hand, many comparative studies have been carried out in Europe. In a phase III trial conducted by the European Organization for Research and Treatment of Cancer (EORTC), in which FAMTX (fluorouracil, Adriamycin, and methotrexate) was compared to FAM, FAMTX resulted in a
superior response rate (41% vs 9%) and a superior median survival (40 vs 29 weeks).[11]

More recently, researchers at the Royal Marsden Hospital compared FAMTX to ECF (epirubicin, cisplatin, and fluorouracil) in a total of 274 patients.[12] In this study, ECF produced a higher response rate than FAMTX (45% vs 22%), as well as a better median survival (8.9 vs < 6 months).

Thus, in the EORTC study, FAM performed less than optimally (9% response rate) compared to FAMTX (33% response rate), whereas in the Royal Marsden study, FAMTX performed less optimally (22% response rate) than expected compared to ECF (45% response rate). To date, however, the median survival barrier of approximately 9 months has not been overcome in any randomized trial.

A trial reported by Wilke et al prospectively compared FAMTX, ELF (etoposide, leucovorin, and fluorouracil), and cisplatin plus fluorouracil in patients with advanced gastric carcinoma and found no advantage in any of the regimens.[13] The response rate was less than 28% and the median survival, again, was less than 9 months.

**Standard Chemotherapy**

Patients with poor performance status should be offered only best supportive care and those with good performance status (Zubrod ≤ 2) may be offered best supportive care or combination chemotherapy. There is not an accepted standard chemotherapy regimen for patients with advanced gastric carcinoma. Previously proposed standards are not widely practiced. Every effort should be made to enter all eligible and willing patients into approved protocols. For patients who are not entered on any protocols, either 5-FU-based therapy (eg, 5-FU plus leucovorin) or cisplatin-based therapy (eg, 5-FU plus cisplatin) may be considered standard.

An argument can be made for the use of single-agent 5-FU as standard therapy, however, the use of 5-FU alone poses some limitations: (a) higher response rate (thus higher rate of palliation) has been reported with combination chemotherapy in the NCCTG randomized trial[10]; (b) all studies comparing best supportive care with chemotherapy have demonstrated advantage to the use of combination chemotherapy. Such trials have not been done with single-agent therapy, and (c) reluctance of physicians and patients to accept single-agent 5-FU as standard for patients with advanced gastric carcinoma. Such a proposal is very likely to cripple a randomized trial.

The combination of cisplatin and 5-FU is widely used around the world as "standard" therapy. Regimens like ELF, FAMTX, and EAP should be considered outdated for the treatment of patients with advanced gastric carcinoma. ECF does deserve a mention here. ECF has been proposed as a possible "standard" recently, however, it is neither used widely in Europe nor considered standard by many investigators. Since, epirubicin is an investigational agent, ECF is not used in North America. In addition, it is a cumbersome regimen and the value of anthracyclines in this disease at present is considered quite limited. Most likely, the benefit of ECF is due to cisplatin and 5-FU. Therefore, at present, use of cisplatin plus 5-FU is justifiable. For patients in whom cisplatin is contraindicated, use of 5-FU-based therapy is recommended to achieve palliation. Clearly, new active agents are needed in the treatment of gastric carcinoma.

**New Agents**

**Taxanes**

The taxanes represent a new class of antimitotic agents that preferentially bind to microtubules.[14] These drugs promote microtubular assembly and stabilize microtubules.[15] Both paclitaxel (Taxol) and docetaxel (Taxotere) are broad-spectrum anticancer agents that have demonstrated significant clinical activity against a variety of solid tumors.

Paclitaxel—Based on paclitaxel’s activity against adenocarcinoma of the esophagus and gastroesophageal junction,[16] a phase II study of this taxane in chemotherapy-naive patients with advanced, unresectable gastric carcinoma was initiated at the University of Texas M. D. Anderson Cancer Center. In 30 evaluable patients treated with single-agent paclitaxel, the overall response...
rate was 17% (95% confidence interval [CI], 6% to 35%).[17] The drug was well tolerated, and toxicities in patients with gastric carcinoma were similar to those described in other patient groups.[18]

Both 3- and 24-hour schedules of paclitaxel (starting dose, 200 mg/m²) were studied in this protocol. The study was not intended to compare the efficacy of different schedules of administration.

Other groups also have studied paclitaxel in advanced gastric carcinoma. An Eastern Cooperative Oncology Group (ECOG) phase II study of paclitaxel resulted in one partial response among 22 eligible patients (response rate 5%; 95% confidence interval, 0% to 25%).[19] In a preliminary study by Tamura et al, 3 of 14 evaluable patients (21%) achieved a partial response when treated with a 3-hour infusion of single-agent paclitaxel.[20] All three responders had received prior chemotherapy.

These preliminary reports suggest that paclitaxel has modest activity against gastric carcinoma. In addition, treatment with paclitaxel in combination with fluorouracil and cisplatin produced a response rate of 50% in 34 patients.[21]

Docetaxel has also been studied in patients with advanced gastric carcinoma and has demonstrated a level of activity similar to that of paclitaxel.[22-24] Taguchi reported 9 partial responses (22%) among 45 evaluable patients with advanced gastric carcinoma treated with 60 mg/m² of docetaxel administered every 3 weeks.[22] Sulkes et al treated 37 patients with advanced gastric carcinoma with 100 mg/m² of docetaxel every 3 weeks and achieved a partial response rate of 24% (8 of 33 assessable patients).[23] In addition, an ECOG study of 41 eligible chemotherapy-naive patients with advanced gastric carcinoma demonstrated a 17% response rate.[24] These data suggest that taxanes may be useful in the treatment of patients with advanced gastric carcinoma.

**Camptothecins: Irinotecan**

Among the camptothecins, irinotecan, formerly known as (CPT-11 [Camptosar]), is active in patients with advanced gastric carcinoma. Irinotecan is a topoisomerase-I inhibitor with demonstrated activity against colorectal and lung carcinomas.

In one of the first phase I-II trials of irinotecan in advanced gastric carcinoma,[25] 81 patients were treated, 56 of whom had previously received chemotherapy. Irinotecan was administered at a dose of either 100 mg/m² weekly or 150 mg/m² every 2 weeks.

In the 66 patients who were evaluated for response, the overall response rate was 23% (95% CI, 13% to 34%). Among the 45 evaluable patients who had received prior chemotherapy, the response rate was 20%. Overall, the median duration of response was 68 days (range, 32 to 644 days). Thus, irinotecan alone was found to be active in previously treated as well as untreated patients with gastric carcinoma.

Of the 81 patients, 76 were evaluable for toxicity. Major toxicities were neutropenia, diarrhea, and nausea and vomiting.

The combination of irinotecan and cisplatin has also been studied in patients with advanced gastric carcinoma. In a phase I-II study of irinotecan plus cisplatin conducted by Shirao et al, irinotecan 60 to 80 mg/m² was infused over 90 minutes on days 1 and 15.[26] On day 1, 80 mg/m² of cisplatin was infused over 2 hours beginning 2 hours after the irinotecan infusion. In the phase I portion of the study, the starting dose of irinotecan was 60 mg/m²; if tolerable, this was increased by 10 mg/m².

A total of 24 patients were enrolled in this study, 20 of whom had received prior chemotherapy. Tolerance was excellent at irinotecan doses of 60 and 70 mg/m², and the maximum tolerated dose was determined to be 80 mg/m². Neutropenia was the dose-limiting toxicity. Severe diarrhea occurred in 4% of patients.

The overall response rate was 42% (95% CI, 22% to 61%). The median duration of response was 4.5 months, and the median survival of all patients was 9.5 months.
In a follow-up study, 44 patients with advanced gastric carcinoma were treated with irinotecan (70 mg/m² infused over 90 minutes on days 1 and 15) and cisplatin (80 mg/m² infused over 2 hours beginning 2 hours after irinotecan on day 1).\[N. Boku and A. Ohtsu, personal communication, January 1998\] The overall response rate was 48% (95% CI, 33% to 63%). Two patients achieved a complete response. Among the 29 patients who had received no prior chemotherapy, the response rate was 59% (95% CI, 39% to 77%). The median survival was between 8 and 9 months for the entire group and 10+ months for the untreated group. Major toxic effects included neutropenia, diarrhea, and nausea and vomiting.

At M. D. Anderson, we are currently evaluating the combination of irinotecan and cisplatin (both drugs administered weekly for 4 weeks followed by a 2-week break) in patients with advanced gastric and gastroesophageal junction adenocarcinoma.

**Fluorouracil Prodrugs**

There is also interest in second- and third-generation oral prodrugs of fluorouracil. These include UFT, S-1, and other similar oral agents.

UFT is a combination of uracil and tegafur (a fluorouracil prodrug). Studied extensively in Japan, UFT is considered to be active in 20% of patients with gastric carcinoma.[27] UFT is better tolerated than intravenous fluorouracil and appears to be just as efficacious.

S-1 is a combination of tegafur, 5-chloro-2,4-dihydropyrimidine (a dihydropyrimidine dehydrogenase [DPD] inhibitor), and potassium oxonate (which supposedly reduces diarrhea). In a phase II study of 51 patients, Ohtsu et al administered S-1 at 80 mg/m² orally twice daily for 28 days followed by a 7-day rest period.[28] The overall response rate was 49% (95% CI, 36% to 62%). The median duration of response was 4.6 months, and the median survival of all patients was approximately 8.5 months.

**Conclusions**

A number of new active agents against gastric carcinoma are now on the horizon. A concerted effort must be made to evaluate their efficacy and toxicity. Many studies evaluating combinations that include these new agents are now under way around the world. Properly designed phase III trials using appropriate controls will be necessary to place the new drugs and newer combinations in proper perspective.

A number of new agents have radioenhancement properties and may find utility, in conjunction with radiation therapy, in the treatment of locoregional disease. In addition, if the new agents, combinations of new and older agents, and combined-modality approaches prove useful in advanced disease, they are likely to be studied in the preoperative setting for patients with potentially resectable gastric carcinoma. The next several years of research in the treatment of gastric carcinoma are likely to be very exciting and hopefully will yield significant progress for patients.

**References:**


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