The role of chemotherapy in the current treatment of gastric cancer

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Abstract

Metaanalyses of adjuvant systemic chemotherapy in gastric cancer have shown at best marginal benefits, although a recent trial of postoperative chemoradiotherapy has demonstrated significantly increased overall survival. Neoadjuvant chemotherapy and chemoradiotherapy are also feasible and are the subject of several ongoing studies. This setting may provide valuable evidence of the activity of new agents and the chemosensitivity of specific tumors. In metastatic disease, chemotherapy confers benefit when compared with best supportive care alone. No particular regimen has been shown to be superior to others in this context, and there is a pressing need for the evaluation of newer agents such as the oral fluoropyrimidines, taxanes, irinotecan, and oxaliplatin.

Key word Gastric cancer · Chemotherapy · Adjuvant treatment

Introduction

There have been no major improvements in the overall prognosis of gastric cancer over the past two decades. In advanced cancer particularly, prospects are poor, with an expected median survival in untreated patients of only 3–4 months.

Surgery is currently the only potentially curative option. However, relapse rates following surgical resection are high. More than 80% of patients develop intraabdominal metastases, typically in either the liver or peritoneum [1]. Between 40% and 80% of patients experience locoregional recurrence; and 20%–40% develop extraabdominal metastases. Among the known risk factors for recurrence are stage (lymph node involvement and serosal invasion) and histology, with

increased risk in tumors with poorly differentiated or diffuse infiltrative cell types.

Given this context, there is considerable opportunity for advances for perioperative chemotherapy or chemoradiotherapy. In locally advanced gastric cancer, there may be a role for preoperative chemotherapy or chemoradiotherapy, and the potential for improved chemotherapy in metastatic gastric cancer must also be evaluated.

The role of chemotherapy: the European and United States experience

Adjuvant therapy

Given the high incidence of local and distant tumor recurrence after surgery, the potential of adjuvant systemic chemotherapy in gastric cancer has been extensively investigated. Metaanalyses have shown, at best, a marginal survival benefit. The combined odds ratio of recurrence in one study for treatment relative to surgery alone lies somewhere between 0.72 and 1.08 [2]. However, it should be noted that many of the constituent studies in this analysis involved relatively small numbers of patients. The trials were predominantly of older chemotherapy regimens (such as 5-fluorouracil [FU] plus methyl lomustine [CCNU] and 5-fluorouracil doxorubicin mitomycin [FAM]). Further, the patient populations studied were heterogeneous, including patients with both high and low risk of recurrence.

The role of postoperative chemoradiotherapy is considered in greater detail elsewhere in this volume (see paper by Macdonald [3]). However, it is worth noting that a single large randomized trial was positive [4]. In this Intergroup study (INT-0116), 603 patients with resectable stage IB–IV gastric or gastroesophageal junction adenocarcinoma who underwent potentially curative surgery were randomized to either surgery or surgery plus postoperative chemoradiotherapy. The

chemotherapy regimen consisted of a cycle of bolus 5-FU and folinic acid (FA) followed by radiation given concurrently with chemotherapy, and then two further cycles of 5-FU/FA.

Median disease-free survival (DFS) was longer in the adjuvant chemoradiotherapy group than in patients treated with surgery alone (30 vs 19 months; $P = 0.001$), a greater proportion of patients receiving combined modality treatment survived to 3 years (50% vs 40%), and median overall survival (OS) was longer (35 vs 28 months; $P = 0.03$).

The benefit in DFS and OS seemed to have been achieved largely by improved local control, the local failure rate being reduced from 29% to 19%. The regimen of chemoradiotherapy used had acceptable toxicity. There are, therefore, grounds for considering postoperative chemoradiotherapy a new standard in treatment. However, the study has been criticized, for a number of reasons. Surgery was not optimal: 54% of patients had less than a D1 resection. Further, a small number of patients ($n = 39$) had stage IB disease, and the effect on failure pattern was not that expected. To introduce a radiotherapy regimen of the kind used requires careful planning and experience, and it can be argued that the chemotherapy involved in the trial was not optimal. Nevertheless, the study was well conducted, had a positive outcome, and constitutes a good foundation on which to build. In the United States, a new intergroup trial has begun, using the positive results from chemoradiotherapy in INT-0116 as the control arm, and comparing these treatments to a regimen of ECF (epirubicin, cisplatin, 5FU) with radiation and 5-FU.

Neoadjuvant therapy in locally advanced disease

Gastric cancer is relatively chemosensitive, suggesting that downstaging of disease is a possibility. Such treatment might result also in the eradication of micro-metastases. Further, it is likely that chemotherapy may be better tolerated before, rather than after, surgery. Neoadjuvant chemotherapy may also identify patients whose disease is potentially responsive to subsequent adjuvant cytotoxic treatment. The neoadjuvant setting is also an important setting in which to judge the activity of new agents. These considerations provide the rationale for neoadjuvant therapy.

Data from nonrandomized phase II studies and a small number of randomized trials show that neoadjuvant chemotherapy or chemotherapy in gastric cancer is feasible. However, there are no data from large, randomized studies, nor do we know how best to select patients for neoadjuvant therapy. Such treatment should therefore be regarded as investigational, and several trials are in progress. In Europe, a Swiss study is

comparing preoperative docetaxel, cisplatin, and 5-FU to surgery followed by the same chemotherapy regimen. A European Organization for Research and Treatment of Cancer (EORTC) trial is randomizing patients to cisplatin plus 5-FU/FA followed by surgery or surgery alone, a very similar French trial is comparing cisplatin plus 5-FU preoperatively with surgery, and the MRC adjuvant gastric infusional trial (MAGIC) trial is addressing the role of the ECF regimen in the neoadjuvant setting.

Chemotherapy in advanced gastric cancer

At least four small, randomized trials comparing chemotherapy with best supportive care (BSC) provide consistent evidence that cytotoxic treatment is of some benefit [5–8]. Chemotherapy using the 5-fluorouracil epirubicin methotrexate (FEMTX), 5-FU, doxorubicin, methotrexate (FAMTX), or etoposide leucovorin 5-fluorouracil (ELF) regimens increased median survival to 7–10 months from 3–4 months with BSC. Two trials which assessed quality of life also showed a benefit from active treatment [7,8].

In advanced gastric cancer, response rates (RRs) of 20%–30% have been reported with single agents such as 5-FU, mitomycin, doxorubicin, epirubicin, and cisplatin. With combinations such as FAM, FAMTX, and ELF, RRs may be as high as 30%–50%. However, the duration of response with these regimens tends to be short, and complete responses are rare. In addition, some regimens are relatively toxic, rendering them inappropriate for many patients.

Several large studies conducted in Europe and the United States have compared the benefits of different chemotherapy regimens. An EORTC trial, published in 1991, suggested that FAMTX was superior to FAM, with a median survival of 42 vs 29 weeks [9]. In a trial conducted at a similar time, 5-FU, FAM, and infusional 5-FU + cisplatin (FUP) were shown to have similar survival outcomes (30, 29, and 37 weeks, respectively) [10]. At Sloan Memorial Kettering, FAMTX produced a higher RR than etoposide doxorubicin cisplatin (EAP) (33% vs 20%) and longer OS (7.3 vs 6.1 months), but was more toxic [11].

In a subsequent randomized trial conducted in the United Kingdom, FAMTX, the accepted reference regimen, was compared with ECF [12]. ECF is a regimen which includes 5-FU and cisplatin, although epirubicin has not been universally available for tumors other than those of the breast. Preclinical data suggest synergy between cisplatin and 5-FU, and higher response rates have been seen in colorectal cancer using infusional rather than bolus 5-FU, which may, in part, explain the improved results seen in trials of ECF. ECF produced a higher RR (45 vs 21%), a longer time to progression

(7.4 vs 3.4 months), and a significantly longer median survival (8.9 vs 5.8 months). Patients randomized to ECF underwent more histologically complete surgical resections than those treated with FAMTX (10 vs 4 patients), which might reflect the higher RR. However, OS continued to be superior in the ECF group even when these resected patients were excluded from analysis (8.2 vs 6.0 months; $P = 0.004$).

During the same period as the ECF study, the EORTC compared FAMTX against ELF and a regimen of 5-FU and cisplatin [13]. Median survivals (ranging from 6.7 to 7.2 months) were not significantly different among the three groups.

It is reasonable to state that chemotherapy is of benefit to patients with advanced gastric cancer, but the extent of this benefit is limited, and there appears to be no standard, universally accepted regimen. Some form of 5-FU/cisplatin regimen has been considered standard treatment in clinical trials in the United States and Europe (but not in Japan, where 5-FU alone is still considered the reference regimen).

Other potential reference regimens exist, such as weekly 5-FU/FA and cisplatin, 5-FU/cisplatin given on days 1–5 monthly, and the French regimen of biweekly 48-h 5-FU/FA and cisplatin. None of these regimens has been proven superior to any other, and none has consistently achieved a median OS in excess of 6–9 months. In the REAL-1 trial, mitomycin was substituted for epirubicin in combination with cisplatin and 5-FU in the ECF regimen, and median OS was identical [14].

Given these results, it is clearly important to assess the potential contribution of newer cytotoxic agents in advanced gastric cancer. A modest initial aim would be to extend median survival beyond 12 months.

Three studies of single-agent docetaxel 60–100 mg/m² have shown RRs of 17%–24% and median survivals of 7.5–7.9 months [15–17]. Docetaxel, in combination with 5-FU or in combination with 5-FU and cisplatin, has shown RRs of 35%–55% and median survivals ranging from 8.6 to 10.5 months [18–20].

With paclitaxel used as a single agent, RRs of 11% and median survivals of 3 and 6.5 months have been reported [21–23]. In combination with 5-FU or carboplatin, trials have indicated a median survival of 9–11 months [23–25].

With single-agent irinotecan, RRs in gastric cancer are approximately 20% [26–28]. In combination with cisplatin, 5-FU, or mitomycin, RRs of up to 51% and median survival of up to 10.7 months have been reported in randomized phase II studies [29–34]. In a phase I/II study being conducted at the University of Pennsylvania Cancer Center, ECF is being modified in a regimen in which cisplatin is replaced by irinotecan. (See below for a detailed account of the Japanese experience of irinotecan plus cisplatin.)

In addition to these agents, there is the potential to explore oxaliplatin and the oral fluoropyrimidines S-1, capecitabine (Xeloda), and uracil-ftorafur (UFT). Thus, in the REAL-2 trial, ECF is being compared to ECX (epirubicin, cisplatin, and capecitabine), EEF (epirubicin plus oxaliplatin and 5-FU), or ECX (epirubicin, oxaliplatin, and capecitabine).

The Japanese experience of chemotherapy in locally advanced and metastatic gastric cancer

5-FU plus cisplatin

In the period from 1992 to 1997, the Japanese Clinical Oncology Group undertook a trial (JCOG 9205) in which patients were randomized to receive one of three chemotherapy regimens: 5-FU alone by continuous infusion, 5-FU plus cisplatin, or UFT plus mitomycin [35]. Patients were stratified by institution, performance status, and the presence or absence of measurable metastatic disease.

At an interim analysis, patients assigned to the UFT/mitomycin arm showed inferior survival compared to the control arm of 5-FU alone. Subsequent randomization was therefore confined to the 5-FU and 5-FU plus cisplatin arms.

The results of the study indicated that patients in the 5-FU/cisplatin group were significantly more likely to respond (RR, 34%) than those in the control arm of 5-FU alone (RR, 11%) or those assigned to UFT/mitomycin (RR, 9%). Median time to progression was also significantly longer among patients receiving 5-FU/cisplatin. However, there were no significant differences between these treatment arms in median OS. 5-FU therefore remains the reference regimen for use in future studies in Japan.

Factors associated with longterm survival

Prognostic factors have been investigated among 497 patients registered with the JCOG/Gastrointestinal Oncology Study Group (GIOSG). This group includes the 274 patients randomized in JCOG 9205, the remainder having been enrolled in five other trials in which the regimens used were ftorafur + mitomycin C (FTM), UFT plus mitomycin, EAP, or 5-fluorouracil + cisplatin (FP) [36].

The median age of this group was 61 years, 74% were male and 83% had a performance status of 0–1. Histology was of the scirrhous type in 28% of cases, and 17% of patients had a prior gastrectomy. Major metastatic sites were the liver in 47%, abdominal lymph nodes in 47%, and the peritoneum in 17%.

RRs across the studies ranged from 8% with FTM to

55% with EAP. Median survival ranged from 6 months in patients treated with FTM to 9.3 months in the nonrandomized study of the EAP regimen. For the entire group of 497 patients, the median survival was 7.2 months, with a 2-year survival rate of 8%, and 2% of patients were alive at 5 years. In 7 of the 9 5-year survivors, the paraaortic lymph nodes were the only site of measurable metastatic disease. Four of the longterm survivors had had a complete response to first-line chemotherapy, and two had a complete response to second-line treatment.

For the whole group, good performance status, small number of metastatic sites, and macroscopically nonscirrhous histology were all significantly favorable prognostic factors in the Cox regression analysis. Age, sex, history of gastrectomy, and histology (intestinal vs diffuse) were not predictive of outcome.

Irinotecan

Among the newer agents, irinotecan has attracted considerable interest in Japan. In a phase I/II trial, irinotecan was administered on days 1 and 15, with 80mg/m² of cisplatin on day 1 [37]. Treatment was repeated at intervals of 3-4 weeks. Hematological toxicity was dose-limiting, and 80mg/m² of irinotecan was the maximum tolerated dose.

In a multicenter phase II trial, 44 patients were treated with a combination of 80mg/m² of irinotecan and 80mg/m² of cisplatin [38]. Grade 4 neutropenia occurred in 36% of the first courses of chemotherapy, and in 22% of courses administered overall. The overall RR was 48% (59% in the 29 patients with no prior chemotherapy). Median survival was 9 months overall, and 10.7 months among patients for whom the regimen was first-line treatment. Median survival was 14.8 months in patients with intestinal histology and 8.6 months in those with diffuse disease ($P = 0.0057$).

S-1

The oral fluoropyrimidine S-1 appears also to have activity in advanced gastric cancer. In a late phase II study, in which 101 patients received doses of 40-60mg of S-1 twice daily for 28 days, followed by a 2-week interval between courses, the overall RR was 45%, median survival 8.1 months, and the rate of survival 37% at 1 year and 17% at 2 years [39]. There were no cases of grade 4 hematological or nonhematological toxicity, and 5% or fewer patients were affected by grade 3 toxicities.

This survival result has encouraged the JCOG to undertake an ongoing trial (9912) in which 450 patients will be randomized to receive either a three-drug combination of 5-FU, and cisplatin plus irinotecan, or single agent S-1.

In a further phase I/II trial, 25 patients received a dose of 80mg/m² twice daily of S-1 for 21 days plus 60-80mg/m² cisplatin on day 8, every 5 weeks [40]. An overall RR of 76% was observed. The median response duration is 4.2 months, and the median OS is 12 months. The combination of S-1 with cisplatin will now enter phase III testing.

Studies in patients normally excluded from trials

Patients with peritoneal metastases are generally excluded from clinical trials because their disease is not measurable, and because this condition is frequently associated with bowel obstruction. JCOG 9603 was specifically designed to address the question of how to treat patients with advanced gastric cancer and malignant ascites associated with peritoneal metastases [41].

A total of 37 patients (12 with intestinal histology and 25 with diffuse disease) received sequential methotrexate and 5-FU. Objective responses were seen in 35% of patients (11% experiencing a complete response), and median survival was 5 months.

This study has been followed by the initiation of a phase III trial in which 160 patients with peritoneal dissemination will be randomized to either 5-FU alone or sequential methotrexate and 5-FU.

Japanese neoadjuvant trials

The JCOG is also undertaking a trial (study 0001) of neoadjuvant chemotherapy for gastric cancer patients with paraaortic node metastases alone, a group of patients known to have good prognosis, comparable to other patients with metastatic disease. Such patients will receive two to three courses of cisplatin 80mg/m² on day 1 plus irinotecan 70mg/m² on days 1 and 15, followed by surgery in patients with resectable disease. In a second neoadjuvant study, patients with resectable scirrhous cancer will receive two courses of S-1 75mg/m² following laparoscopic staging and before surgery.

Discussion

A CancerNet search in the United States reveals a total of 39 voluntarily registered ongoing trials in gastric cancer, 28 of them in advanced disease. However, although 20 were phase II studies, none were phase III, indicating a lack of clearly superior regimens from phase II trials, including large-scale phase III testing.

Combination chemotherapy in advanced gastric cancer produces response rates (RRs) that range from 20% to 50%. The highest RRs reported are usually in the early history of the use of a new regimen, and it is important to consider those regimens that stand the test

of time. In evaluating the activity of new agents, the demographics of the population included must be carefully considered. These factors include the proportion of patients with locally advanced rather than metastatic disease, those with good performance status, and those who subsequently undergo surgical resection.

While major improvements in RRs and OS are expected using conventional cytotoxic regimens, treatment may be appreciably improved using regimens that are less toxic, more economical, and easier for patients to take. There is a trend (at least in the United States) towards avoiding the traditional bolus of fluoropyrimidines therapy (because of the mucositis seen in combination with radiotherapy), towards more easily administered regimens, and towards weekly treatments.

As in other areas of oncology, there is considerable interest in using agents acting on novel targets or with alternative mechanisms of action. Such drugs include the anti-angiogenic epithelial growth factor receptor (EGFR), vascular endothelial growth factor (VEGF), and cyclooxygenase (COX)-2 inhibitors and the matrix metalloproteinase inhibitors.

This range of new agents offers the possibility of tailoring treatment to the characteristics of a particular tumor, such as those with VEGF, thymidylate synthase (TS), p53, and bcl-2 expression, or to specific patterns of metastatic disease.

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