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REVIEW

Chemotherapy as a component of multimodal therapy for gastric carcinoma

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Abstract

Prognosis of locally advanced gastric cancer remains poor, and several multimodality strategies involving surgery, chemotherapy, and radiation have been tested in clinical trials. Phase III trial testing the benefit of postoperative adjuvant chemotherapy over treatment with surgery alone have revealed little impact on survival, with the exception of some small trials in Western nations. A large trial from the United States exploring postoperative chemoradiation was the first major success in this category. Results from Japanese trials suggest that moderate chemotherapy with oral fluoropyrimidines may be effective against less-advanced (T2-stage) cancer, although another confirmative trial is needed to prove this point. Investigators have recently turned to neoadjuvant chemotherapy, and some promising results have been reported from phase II trials using active drug combinations. In 2005, a large phase III trial testing pre- and postoperative chemotherapy has proven its survival benefit for resectable gastric cancer. Since the rate of pathologic complete response is considered to affect treatment results of this strategy, neoadjuvant chemoradiation that further increases the incidence of pathologic complete response could be a breakthrough, and phase III studies testing this strategy may be warranted in the near future.

Key words: Surgery; Radiation; Anticancer drug; Adjuvant chemotherapy; Neoadjuvant chemotherapy

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INTRODUCTION

Despite its declining incidence in Western Europe[1] and the United States[2], gastric carcinoma remains the second most common cause of cancer death worldwide with over 600 000 deaths per year[3]. The curative treatment of gastric carcinoma remains primarily surgical. Although developments in surgery have been slowed in the West by the large percentage of patients presenting at advanced stages[4] radical gastrectomy with extended lymphadenectomy[5,6] has been performed in Japan and other East Asian countries[7] as well as at specialized centers in the West[8-12] and is now recognized as a reasonably safe procedure in experienced hands[13,14]. However, the survival benefit of extended lymphadenectomy is yet to be proven in a large-scale randomized trial[15,16], and the prognosis of patients with locally advanced gastric cancer remains dismal even after potentially curative resection. Consequently, multimodal treatment strategies involving surgery, chemotherapy, and radiation have been explored to improve on the survival of the patients with resectable advanced cancer. The current review focuses on the development and states of the art of chemotherapy given as a component of such multimodal treatments. It is not within the scope of this review to describe in detail the chemotherapeutic regimens given concurrently with radiation.

Postoperative adjuvant chemotherapy

One straightforward strategy against resectable advanced gastric cancer is to do the best that can be done by surgery and then supplement it with chemotherapy to eliminate micrometastases that may have developed before the surgery or viable cells that may have been disseminated during the surgical procedure. Based on the fractional cell kill hypothesis [17], it would be expected that the highest tolerable drug doses given at the shortest possible interval after surgery would maximize the rate of cell kill[18, 19]. The authors have shown through an in vivo model of peritoneal carcinomatosis that either oral S-1 (1M tegafur-0.4M gimestat-1M otastat potassium)[20] or intraperitoneal paclitaxel[21] can control viable intraperitoneal cancer cells at an early stage of the metastatic process, although the therapeutic effect proved limited once they have developed into gross metastases. This strategy has long been a standard of care in other cancer types including colorectal cancer, reflecting the results of several randomized phase III trials. In the case of gastric carcinoma, however, the results of phase III trials testing this strategy have been inconsistent. An early success was reported from Japan in the 1970s, where a treatment by twice weekly intravenous administrations of

0.08 mg/kg mitomycin for 5 weeks reportedly improved the 5-year survival of curatively resected Stages I~IV gastric carcinoma by 13.5%[22]. This was the result of a large-scale nationwide trial in which 714 patients had been enrolled. Survival analysis, however, showed that the number of patients receiving chemotherapy was 242, whereas the number treated by surgery alone was 283. Details of a large number of patients who had been excluded from the survival analysis have not been reported, and the reliability of the study is questionable from the current point of view. Nevertheless, the result was taken seriously at the time, and several trials in the decade to follow explored the benefits of new combinations, mostly with oral fluoropyrimidines, as well as of new routes of delivery versus intravenous mitomycin, the gold standard. It was only in late 1980s after a long dispute that the Gastric Cancer Surgery Study Group in the Japan Clinical Oncology Group (JCOG) declared that treatment with surgery alone should once again be considered as the standard of care for curatively resected gastric cancer. Since that time, several new phase III trials have been launched in Japan with surgery alone as a standard arm. However, these new generation studies have repeatedly produced negative results. The failure to prove a survival benefit may be attributed to inadequate eligibility criteria that allowed the inclusion of early-stage cancers[23], faulty study design[24], and selection of ineffective antineoplastic agents[25]. The first JCOG study to be reported was a phase III study testing the impact of intravenous mitomycin (1.4 mg/m^2) and fluorouracil (166.7 mg/m^2) twice weekly for 3 week followed by oral UFT for 18 months[23]. From subset analyses of this negative study that enrolled 579 patients, Nakajima suggested that T1 stage cancer should be excluded from future trials, whereas T2 stage cancer could be a promising target for postoperative adjuvant chemotherapy. However, eligibility criteria of the next JCOG trial testing intravenous mitomycin 1.33 mg/m^2, fluorouracil 166.7 mg/m^2, and cytosine arabinoside 13.3 mg/m^2 given twice weekly for 3 wk followed by oral fluorouracil 134 mg/m^2 daily for the next 18 mo were based on surgical rather than histopathologic findings, and this again resulted in the inclusion of several T1 stage cancers. Consequently, the excellent survival achieved by surgery alone left little room for improvement by adjuvant chemotherapy, and the study, designed unfortunately to detect a large difference of 15% in 5-year survival, wasdestined to be under-powered[24]. Another JCOG phase III trial testing the survival benefit of a combination chemotherapy with intraperitoneal CDDP (70 mg/m^2) on d1, intravenous CDDP at 70 mg/m^2 on d14, and continuous 5FU at 700 mg/m^2 on d14~16 followed by one year of oral UFT (267 mg/m^2) over surgery alone for T3~T4 stage cancer had been powered to detect a difference of 12% in 5-year survival[25]. Survival curves in this study that were found to be almost identical suggest that this trial failed because of an inadequate regimen rather than a flaw in the statistical considerations, since intraperitoneal CDDP had already proven ineffective as was reported in 1994 by a much smaller Austrian study[26].

After the aforementioned JCOG trials, a trial testing oral UFT (350 g/m^2) to be continued for 16 months was conducted for pathological T2/N1 and T2/N2 stage cancer (NSAS-GC). Although there were several new participants in the study in addition to the members of JCOG (33 institutions in all), the patient accrual was poor with only 199 patients participating in 4 years, whereas 488 were needed to detect an 8.8% difference in 5-year survival. The trial was eventually discontinued in order to carry out the next randomized trial testing a new and more promising drug, S-1[27], in the adjuvant setting (ACTS-GC). Nevertheless, a planned interim analysis at the median follow-up of 3.8 years revealed significant improvements in overall and relapse-free survival in the chemotherapy arm[28]. Patient characteristics had been well-balanced between the arms, and the study had been carefully conducted. However, this was considered too small a study to definitively prove the benefit of postoperative chemotherapy in gastric cancer. In the meantime, ACTS-GC, a nationwide trial comparing postoperative adjuvant chemotherapy by oral S-1 with surgery alone for Stages II and III gastric cancer, completed a planned enrollment of 1000 patients in the year 2005. It is hoped that the results of this trial will in the near future provide a decisive answer regarding the survival benefit of adjuvant chemotherapy with oral fluoropyrimidines following formal D2 dissection. Since the result of ACTS-GC could turn out to be negative after all, another confirmative phase III trial testing the benefit of UFT is currently planned by JCOG so that the enrollment may be completed before the interim analysis for the ACTS-GC study due to take place in 2008. Although the response rate of S-1 in cancer with measurable lesions was higher than that of UFT, there is currently no guarantee that S-1 is more effective than UFT in the adjuvant setting.

In the meantime, two randomized trials in the West have shown the advantage of adjuvant chemotherapy, one with mitomycin and tegafur[29], and the other with epidoxorubicin, 5FU and leucovorin[30]. However, prognosis of those patients treated with surgery alone in these trials had been so dismal that the patients enrolled for the trial might have been treated with or inadequately staged by suboptimal surgery. On the contrary, an adjuvant postoperative chemotherapy regimen consisting of EAP (etoposide, doxorubicin, cisplatin) followed by intravenous 5FU/LV had no survival benefit in a trial by the Italian Medical Oncology Group. Interestingly, the 5-year survival rate of the surgery alone group in that trial was relatively good at 44% [31]. Survival benefit was not proven in other modern adjuvant trials exploring the FAM (5-FU, doxorubicin, mitomycin) regimen[32] or 5FU/LV and cisplatin[33], though meta-analyses of the Western trials demonstrated some potential of this strategy[34-38]. A meta-analysis of the three Japanese randomized trials with serosa-negative cancer as a target[23, 24, 27] also suggested a survival advantage[39]. Thus, attempts to confirm a definitive survival advantage of postoperative adjuvant chemotherapy should be continued.

There is a significant difference between the Japanese and Western principles for the selection of chemotherapeutic regimens to be used in the postoperative adjuvant setting. In the West, any regimen found to be active in the treatment for unresectable/metastatic cancer could also be regarded as a candidate to be tested in the adjuvant setting. For instance, the EAP regimen tested in the Italian Trials in the Medical Oncology group study[33] had caused

concern due to its severe toxicity[40]. A Swiss study currently exploring the impact in both a neoadjuvant and adjuvant setting of a combination of 5-FU, cisplatin and docetaxel which has revealed a superior response rate compared with 5FU and cisplatin among advanced gastric cancers [41] but has also been recognized as highly toxic. The Gruppo Onocologico Italia Merideionale (GOIM) recently conducted a trial to explore the efficacy and tolerability of the addition of epirubicin to a combination of etoposide, leucovorin and 5FU (ELF), and found this regimen (ELFE) to be active for advanced gastric cancer[42]. Here again, the next step they took was to test this regimen in the adjuvant setting in a phase III study with surgery alone as a control arm[43]. Since most of the patients treated with potentially curative surgery still have dismal prognosis in the West, investigators there do not hesitate to introduce toxic regimens that were nevertheless found to be active against advanced cancer into trials for postoperative adjuvant chemotherapy.

The situation is different in Japan where regimens used in adjuvant settings tend to be relatively mild. This is because a larger proportion of patients to be treated with postoperative adjuvant chemotherapy will survive by surgery alone, so that treatment-related toxicities and impairment of patient's quality of life are less likely to be tolerated. For these reasons, adjuvant chemotherapies in Japan have centered around oral fluoropyrimidine-based regimens with mild toxicities. The aforementioned regimen of intravenous mitomycin, fluorouracil, and cytosine arabinoside followed by oral fluorouracil, for example, induced Grade III leucopenia in 1.6% and Grade III gastrointestinal symptoms in 0% of patients treated in the adjuvant setting[24]. A highly regarded combination of oral S-1 (80 mg/m^2 for 21 d with 14 d of rest) and cisplatin (60 mg/m^2 on d8) that achieved a response rate of >70%[44], for instance, had been frequently used in Japan for unresectable/metastatic cancer, but has not been considered as a candidate for postoperative adjuvant chemotherapy. Use of mild regimens demonstrating moderate reponse rates are regarded by some investigators as old-fashioned[45], but as described earlier, the possibility that these regimens may still prove useful in pT2 stage cancers treated with adequate surgery cannot be currently denied.

Finally, a positive result in a trial testing adjuvant chemoradiation needs to be mentioned. In the United States, an Intergroup Trial (SWOG-9008/INT0116) was launched in 1991 to test the effect of combined radiation and fluorinated pyrimidine in the adjuvant setting[46]. The treatment consisted of five consecutive days of bolus 5FU (425 mg/m^2) /LV (20 mg/m^2) before and after 45 Gy of radiation given for 5 weeks, with intravenous 5FU (400 mg/m^2) /LV (20 mg/m^2) on the first four and last three days of radiotherapy. The trial enrolled 556 patients, and the median overall survival in the surgery-only group was 27 mo as compared with 36 mo in the chemoradiotherapy group, showing a significant survival benefit for chemoradiation. Since radiation was delivered to the gastric bed and regional lymph nodes, the object of chemoradiation would seem to have been to combat any locoregional residual disease, and it was indeed for this pattern of recurrence that a significant decrease in the incidence was observed among the treatment group. The extent of lymph node dissection being D0 in 54% of the patients enrolled, some skepticism arose as to whether chemoradiotherapy might have effectively compensated for the suboptimal surgery in terms of local control[47, 48]. These observations point to the importance of quality control in surgery even when multimodality treatments are being discussed[26]. Although postoperative chemoradiation has not been seriously explored in Japan where investigators believe that local control can be achieved through extended lymphadenectomy, this may be a useful option in countries where systematic lymphadenectomy has not become a standard practice.

Future perspective regarding postoperative adjuvant chemotherapy

A breakthrough in clinical trials testing postoperative adjuvant chemotherapy may be achieved through a customized approach in which the candidates for adjuvant chemotherapy are more meticulously selected. Detection of minimal residual disease may be one of the options, since chemotherapy given to a patient with no residual disease would only be needlessly harmful. This detection can be done through immunostaining or polymerase chain reaction of protein, gene mutation, or mRNA expression that may be present in cancer cells while absent in non-cancer cells that may be included in the samples[49]. Although the prognostic value of micrometastasis detected in the lymph node through immunostaining remains controversial[50, 51], detection of free cancer cells in peritoneal washing samples by a conventional cytologic examination is a strong prognostic factor predicting the risk for peritoneal carcinomatosis[52]. Enhanced detection through reverse-transcriptase polymerase chain reaction was found to be even more potent as a prognostic factor[53-55].

Identification of patients at risk will have little value unless effective drugs are available. Adequate selection of anticancer drugs could be achieved through *in vitro* chemosensitivity testing in which the rates of growth in relation to a control of viable cancer cells from the surgical specimens are tested in culture media containing various antineoplastic drugs. A retrospective study has shown that patients treated with postoperative adjuvant chemotherapy using a certain drug had a better outcome when the result of *in vitro* chemosensitivity testing for that drug had been positive[56]. Prospective studies to confirm this phenomenon are currently underway by several study groups in Japan. However, a randomized trial comparing patients whose treatments are selected based on chemosensitivity testing and those who were treated with empirical treatments is still needed to definitively assess the benefit of this costly and time-consuming procedure[57,58].

Neoadjuvant chemotherapy for resectable gastric cancer

Due to the consistently poor outcome of patients treated with a strategy of surgery followed by chemotherapy, preoperative chemotherapy has for several years attracted the attention of investigators in the West[59]. This is considered effective for patients in advanced T and N stages, and may result in downstaging of the tumors and consequently improving the curative resection rate. Since the best response is likely to be achieved within a few months from

the initiation of therapy, 2 to 3 courses of preoperative chemotherapy are usually performed in most clinical trials. Naturally, a high response rate is required for the chemotherapeutic regimens to be used in this setting in order to achieve downstaging. Chemotherapeutic regimens with high response rates usually are associated with greater toxicity and may not be feasible in the postoperative adjuvant setting, since chemotherapy performed immediately after gastric surgery is often marred by surgery-related gastrointestinal symptoms. Preoperative delivery of chemotherapy would be much less problematic, and this underscores the major appeal of neoadjuvant therapy[60]. Another theoretical benefit of neoadjuvant chemotherapy concerns micrometastases that are undetected at the initiation of treatment. Patients with locally advanced cancer are more or less likely to harbor distant micrometastases which could remain untreated for several weeks when the surgery-first strategy is selected.

It appears so far that survival rates are excellent among patients who respond to neoadjuvant chemotherapy[60]. However, whether a group of patients as a whole benefits from this strategy needs to be carefully elucidated, and several phase III trials are ongoing after producing promising phase II results[61-63]. Of these, a MAGIC trial exploring pre- and postoperative ECF regimens (a combination of epirubicin, CDDP, and continuous infusion of 5FU) has enrolled patients as planned and has proved the significant benefit of chemotherapy (improvement of 13% in a 5-year survival rate)[64]. Although three cycles each of ECF were to be performed before and after surgery, compliance with chemotherapy was unexpectedly lower after surgery (only 42% of patients completed postoperative chemotherapy), so that the result of MAGIC trial is considered mainly to reflect the effect of preoperative ECF. Tumor diameter, depth of invasion, and nodal status of the surgical specimens were significantly decreased or improved in the chemotherapy group, indicating that downstaging actually took place in a significant proportion of patients. Despite the toxicity of neoadjuvant chemotherapy, the mortality and morbidity in surgery following chemotherapy seems to have been comparable to what it would have been without preoperative chemotherapy.

In Japan, two phase II studies await survival analysis after enrollment as planned: one is exploring a combination of CPT-11 and CDDP[65] performed against gastric cancer with bulky nodal metastasis, and the other is testing CDDP and oral S-1[44] against linitis plastica type (type 4) and large type 3 cancers. A phase III trial comparing neoadjuvant chemotherapy by CDDP and S-1 with surgery alone for types 3 and 4 cancers will soon be launched. The concept of chemotherapy in the neoadjuvant setting is similar between Japan and Western countries in that regimens with high response rates have usually been selected. It has been proven in other types of cancer that only neoadjuvant chemotherapy using a regimen with a high pCR (pathological complete response) rate can really affect survival[66]. A high incidence of PR (partial response) was reported in a phase II trial of chemotherapy with CDDP and S-1, but CR was seldom observed as a result of treatment with this combination[44]. Thus, there is a theoretical concern that the expected survival benefit may not be obtained by a neoadjuvant chemotherapy relying on this regimen, although the consequences of neoadjuvant chemotherapy followed by gastrectomy plus extended lymphadenectomy with sufficient nodal clearance remain of interest.

The pCR rate can be enhanced by the addition of radiation, which has been shown to have a beneficial impact on the surgical outcome in esophageal and rectal cancer. Anticancer drugs in this case are in part considered as radiosensitizers, and 5FU, cisplatin, and paclitaxel have been used alone and in combination[67-69]. A pCR was achieved in 20% of patients who received two cycles of continuous 5FU, paclitaxel, and cisplatin followed by 45 Gy radiotherapy with concurrent 5FU and paclitaxel[70]. Although chemotherapy performed concurrently with radiation may be somewhat inadequate against potential micrometastases that may exist outside the field of radiation, a three- step strategy with intense induction chemotherapy prior to the preoperative chemoradiation and surgery may overcome this weakness. The validity of this strategy needs to be proven by a well-designed phase III trial.

CONCLUSIONS

Since the prognosis of locally advanced gastric cancer remains poor, several multimodality strategies involving surgery, chemotherapy, and radiation have been tested in clinical trials. Postoperative adjuvant chemotherapy with highly active regimens generally had disappointingly little impact on survival for advanced cancer, although there is a hard evidence that locoregional control could be improved by postoperative chemoradiation where systemic removal of the regional lymph nodes has not been conducted.

Moderate chemotherapy with oral fluoropyrimidines may be effective against T2 N+ stage cancer, although another confirmative trial is needed to prove this point. For more advanced disease, investigators have turned to neoadjuvant chemotherapy in the hope that downstaging might facilitate an R0 resection and that distant micrometastasis could be eliminated. A large randomized study testing pre- and postoperative ECF has confirmed the survival benefit of this strategy, and several phase III trials exploring other promising regimens are ongoing. The outlook is even brighter with neoadjvant chemoradiation that further increases the incidence of pathologic CR, and phase III studies testing this strategy are warranted.

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