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REVIEW

Chemotherapy for gastric cancer

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Abstract

Metastatic gastric cancer remains a non-curative disease. Palliative chemotherapy has been demonstrated to prolong survival without quality of life compromise. Many single-agents and combinations have been confirmed to be active in the treatment of metastatic disease. Objective response rates ranged from 10-30% for single-agent therapy and 30-60% for polychemotherapy. Results of phase II and III studies are reviewed in this paper as well as the potential efficacy of new drugs. For patients with localized disease, the role of adjuvant and neoadjuvant chemotherapy and radiation therapy is discussed. Most studies on adjuvant chemotherapy failed to demonstrate a survival advantage, and therefore, it is not considered as standard treatment in most centres. Adjuvant immunochemotherapy has been developed fundamentally in Korea and Japan. A meta-analysis of phase III trials with OK-432 suggested that immunochemotherapy may improve survival of patients with curatively resected gastric cancer. Based on the results of US Intergroup 0116 study, postoperative chemoradiation has been accepted as standard care in patients with resected gastric cancer in North America. However, the results are somewhat confounded by the fact that patients underwent less than a recommended D1 lymph node dissection and the pattern of recurrence suggested a positive effect derived from local radiotherapy without any effect on micrometastatic disease.

Neoadjuvant chemotherapy or chemoradiation therapy remains experimental, but several phase II studies are showing promising results. Phase III trials are needed.

Key words: Gastric cancer; Chemotherapy; Adjuvant treatment

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TREATMENT OF ADVANCED GASTRIC CANCER

Should chemotherapy be offered to patients with advanced gastric cancer?

Traditionally, although responses to chemotherapy have been reported in up to 60% of patients in phase II trials, most patients developed drug resistance within few months, and median survival of treated patients usually ranged from 7 to 9 mo. These disappointing results together with the toxic effects derived from chemotherapy prompted to several investigators to evaluate the benefit of chemotherapy in terms of survival and/or quality of life compared with best supportive care alone. Four randomized phase III studies were conducted during the last decade, showing a survival advantage in favour of chemotherapy of about 6 mo[1-4]. In the light of these findings, chemotherapy should be offered to patients with metastatic gastric cancer in good general conditions. Even in those patients with asymptomatic disease, a similar survival advantage derived from early chemotherapeutic treatment has been shown as compared with conservative attitude and therapy only when symptoms appear[5]. This benefit was obtained without quality of life compromise.

Which drugs can be considered active as single agents?

Many traditional and modern drugs have been tested as single-agent in advanced gastric cancer. Table 1 shows those agents that have obtained ⩾10% response rate. It is worth to remark that classical drugs were tested in the 1960s and 1970s and its true single-agent activity may be overestimated due to the methodology employed. In that sense, in the setting of a randomized trial reported in 1994, both epirubicin and 5-fluorouracil obtained less than 10% response rate[6]. Complete responses with single-agent therapy are uncommon, and partial responses ranged 10-20%, followed by a short period of time to disease progression.

Combination therapy for advanced gastric cancer patients

Several combination regimens have been developed with the aim of improving overall response rate and survival. Platinum compounds, 5-fluorouracil, and recently taxanes and irinotecan might be considered the mainstay of these

Table 1 Single agent activity in advanced gastric cancer

Agents	Response rate (%)
Mitomycin C	30
Doxorubicin	17
Epirubicin	19
Cisplatin	19
BCNU	18
5-Fluorouracil	21
Etoposide (oral)	21
Hydroxurea	19
UFT	27
Capecitabina	19
S-1	45
Paclitaxel	17-23
Docetaxel	17-29
CPT-11	18

Table 2 Combination therapy for advanced gastric cancer

	Response rat (%)	Median survival (mo)
FU-based combinations		
FAM	30-42	6-9
FAMTX	33-63	6
ELF	53	11
Modified-ELF	16-42	6-9.5
Cisplatin-5-FU CI synergism		
PF	40	9-10
ECF	59-71	8.7
P-5-FU 48-h CI	50	9.3
P-5FU 24-h CI	58	11
Cisplatin-based combinations		
EAP	33-64	9
FLEP	35	8
FLEP-type	39	11
LV5FU2-P	27	13.3
Combinations including new drugs		
P-CPT11	41-58	9-12
LOHP-CPT11	50	8.5
CPT11-bolus 5-FU	22	7.6
CPT11- 5-FU CI	20	7
P-Xeloda	54.8	10.1
ECC	59	9.6
P-S-1	73-74	12
TPFU/LV	50	11-14
DP	37-56	9-11
DPF	51	9.3

CI: Continuous infusion.

combinations (Table 2).

Fluorouracil-based combinations: The FAM (fluorouracil-doxorubicin-mitomycin C) combination was widely used in the 1980s. After the first publication where the authors reported an overall response rate of 42%[7], more than six hundred patients were treated with FAM or modified-FAM schedules reporting a cumulative response rate of 30%[8]. The concept of biochemical modulation of the activity of 5-FU led several authors to design schedules, such as FAMTX, FEMTX and EFL. In 1982, Klein *et al*[9] reported a response rate of 63%, administering sequentially high-dose methotrexate, with leucovorin rescue, and 5-FU followed by adriamycin (FAMTX) on day 15, with a median survival of 9 mo. In a subsequent study conducted by the EORTC with the same regimen, 22 out of 67 (33%) patients responded and nine of them achieved clinical complete responses. The median survival for all patients was 6 mo. Toxicity consisted mainly of leukopenia (WHO grade 4 in 14%), mucositis (WHO grade 3 in 11%), and alopecia[10]. When adriamycin was substituted by its analogue 4-epi-doxorubicin (FEMTX), no advantages were found in response rate or tolerance[2]. It is well known that 5-fluorouracil modulated by leucovorin combined with intravenous etoposide (EFL) is a well tolerated scheme, initially designed for elderly patients or those with cardiac risk. A phase II trial reported a 53% response rate, including 12% of complete responses[11]. Overall survival was 11 mo. The results of three modified-EFL regimens consisting of oral etoposide, oral leucovorin and either 5-FU continuous infusion or tegafur were controversial. Colleoni *et al* [12] and Feliu[14] reported 42% and 26% of partial remissions, and 8% and 9% complete responses respectively. Median survival times were 9.5 and 9 mo, respectively. Toxicity with these schedules was mild or moderate, mainly nausea and vomiting, and asymptomatic leukopenia. On the other hand, only 16% of patients treated with the entirely oral tefagur-containing schedule designed by Raderer *et al* [13] achieved partial remission, and overall survival was 6 mo. The investigators argued a low compliance due to severe emesis, in spite of prophylactic intake of 5-HT3 receptor antagonists, to explain these disappointing results.

Combinations based on cisplatin/5-FU continuous infusion (CI) synergism: The *in vitro* synergy between cisplatin and 5-FU, especially in continuous infusion administration, led several investigators to test the combination of both drugs with or without the addition of a third active agent. About 40% response rate and median survival of 9-10 mo were reported with the combination of cisplatin and 5-FU CI for 5 d[15,16]. Higher response rates (71% and 59%) were achieved in two phase II trials with the combination of protracted continuous 5-FU infusion, cisplatin and epirubicin (ECF), but apparently with a similar overall survival[17,18]. The Spanish Group for the Treatment of Digestive Tumors (TTD) conducted a phase II study with cisplatin every 3 wk in combination with a weekly 48-h infusion of 5-FU. Responses were achieved in 50% of patients and median survival reached 9.3 mo[19]. In theses schedules, moderate myelossupression appeared as the most relevant side effect with few patients requiring hospitalization for neutropenic fever. A multicenter study showed that a weekly 5-FU 24-h continuous infusion modulated by leucovorin and combined with bimonthly cisplatin obtained a 58% response rate and 11 mo of median survival[20].

Others cisplatin-based combinations: In 1989, a group of German investigators developed a combination regimen consisting of cisplatin + etoposide + doxorubic in (EAP). Responses were observed in 43 of 67 (64%) patients that included 21% clinical complete responses. Median survival time was 9 mo[21]. With exactly the same schedule employed by Preusser *et al*[8], 36 previously untreated patients with advanced gastric cancer were

involved in a phase II trial at the Dana-Farber Cancer Institute. Only 33% objective responses, including 8% clinical complete responses were reported. Median survival for the entire group was 8 mo[22]. Their revision of published experience with EAP-like regimens over 262 patients revealed a mean response rate of 41%. Although EAP is an active regimen, it should be noted the high hematologic toxicity reported with this schedule. Deaths due to treatment-related toxicity have been reported in the majority of series, ranging from 6% to 20%. The FLEP schedule developed by our group combined bolus 5-FU modulated by folinic acid (FA) for three consecutive days with epirubicin and cisplatin on day 2. Objective responses were observed in 32 of 90 patients (35%), including 9% clinical complete remissions, and median survival time was 8 mo. Ten patients presented episodes of febrile neutropenia, but no toxic deaths were observed[23]. Almost double response rate was reported with an intensive weekly FLEP-modified schedule, but median survival achieved seemed to be slightly better if so[24]. Other FLEP-type schedule in which cisplatin and 5-FU/FA were combined with etoposide, taking advantage of the three drugs synergism, obtained 39% responses and a median survival of 7 mo[25]. A well known active regimen in metastatic colorectal cancer (LV5FU2), combined with bimonthly cisplatin infusion obtained one of the higher overall survival of 13.3 mo in patients with advanced gastric cancer[26]. Hematologic toxicity was the most common adverse event (42.9% grade 3 or 4) but less than 5% of patients experienced febrile neutropenia and no toxic deaths were observed. Nausea and vomiting were also frequent side effects, despite systematic prophylaxis.

Combinations including new active drugs

Irinotecan shows a marked synergism with cisplatin as well as a lack of cross-resistance due to different mechanisms of action and a non-overlapping profile of adverse reactions. Shirao *et al* [27] reported a 41% response rate with a combination of irinotecan and cisplatin in a phase I-II trial. The recommended dose and schedule were 70 mg/m^2 of CPT-11 on days 1 and 15 and 80 mg/m^2 cisplatin on day 1 every 4 wk. The dose-limiting toxicity was neutropenia. A phase II study employing a combination of CPT-11 (70 mg/m^2) plus cisplatin (80 mg/m^2) in patients with metastatic gastric cancer achieved an overall response rate of 48%[28]. In Western countries, Ajani *et al* [29] obtained a very high response rate (58%) with a combination of irinotecan (65 mg/m^2) plus cisplatin (30 mg/m^2), both administered intravenously 1 d per week for 4 consecutive weeks, followed by a recovery period of two weeks. The median survival reported reached 9 mo. Compared with the classic cisplatin combination regimens, the introduction of CPT-11 as part of the treatment schedule increased the gastrointestinal toxicity. A recent pharmacokinetic study comparing two infusion schedules of irinotecan plus cisplatin suggested some advantages in favour of 24-h continuous infusion of CPT-11. The area under the plasma concentration-time curve of SN-38 was increased by 24-h infusion when compared with the 90-min infusion[30]. Irinotecan has also been combined with oxaliplatin as first-line treatment for locally advanced or metastatic gastric cancer patients. Oxaliplatin 85 mg/m^2 followed by CPT-11 200 mg/m^2 as a 30-min i.v. infusion achieved an overall response rate of 50% and a median survival of 8.5 mo in a phase II multicentre study conducted in Greece[31]. A weekly irinotecan plus bolus folinic acid and bolus[32] or infusion[33] 5-FU combination did not improve the outcome in patients with advanced gastric cancer in a non-randomised comparison with other CPT-11 combinations.Capecitabine is a novel oral fluoropyrimidine carbamate that mimics continuous infusion of 5-FU. The combination of capecitabine and cisplatin has been proven to be active and well tolerated in patients with advanced gastric cancer, giving an overall response rate of 54.8% in the intention-to-treat analysis[34]. Evans *et al.*[35] evaluated in a phase I trial the combination of epirubicin, cisplatin and capecitabine (ECC). With a fixed-dose of cisplatin 60 mg/m^2 and epirubicin 50 mg/m^2, both every 3 wk, the recommended dose for capecitabine was 1 000 mg/m^2 per 12 h on an intermittent schedule (two weeks of treatment, followed by one week rest). An overall response rate of 59% and median survival of 9.6 mo have recently been reported in a phase II trial carried out in Korea[36]. S-1 is an another fluoropyrimidine derivative developed mainly in Japan. A phase I/II study conducted by Koizumi *et al*[37] found a recommended dose for this combination of cisplatin 60 mg/m^2 on d 8 plus S-1 40 mg/m^2 b.i.d for 21 d, followed by a 2-wk rest. The response rate (74%) achieved was the highest published in the literature, and the median survival reached 12 mo. These encouraging results have been confirmed in another phase I/II trial carried out in Japan in which S-1 was administered orally at a dose of 80 mg/m^2 per d for 2 wk, followed by a 2-wk rest, plus cisplatin 70 mg/m^2 as the recommended dose. Among eleven evaluable patients for response, 8 achieved a partial response (73%) and 1 had stable disease. The main toxicities were neutropenia, nausea and anorexia, all of them not severe, reversible and manageable[38]. In Europe, the first phase II trial with S-1 as monotherapy for advanced gastric cancer revealed that the starting dose of 40 mg/m^2 was not tolerable due to significant diarrhoea. At 35 mg/m^2 twice daily a response rate of 26.1% was reported according to an independent radiology review[39]. A recent phase II trial conducted in the United States and Germany was presented at ASCO 2005, employing cisplatin 75 mg/m^2 on d 1 plus S-1 25 mg/m^2 p.o twice daily on d 1-21, followed by a 7-d of recovery[40]. Over 41 assessable patients, the overall confirmed response rate reached 51.2% and the median time to progression was 4.8 mo. The regimen showed a very favourable safety profile, with only 2.1% of patients suffering from febrile neutropenia and less than 15% experienced grade 3 or 4 gastrointestinal toxicities. A phase III trial comparing cisplatin plus S-1 *versus* cisplatin plus continuous infusion 5-FU is ongoing in Western countries. Similar results were reported by Iwase *et al*[41] in a phase II trial in which S-1 was given orally at 80 mg/m^2 dailly for 14 d and cisplatin was administered as a 24-h continuous infusion on day 8. Many randomized trials consisting of an S-1 based regimen are now being evaluated in Japan. Moreover, 5-FU alone is being compared with the combination of cisplatin plus irinotecan and with S-1 alone in a three- arms controlled study. The accrual of

a study comparing S-1 *versus* S-1 plus cisplatin has recently been completed[42].

Taxane-containing combinations have considerable activity in the treatment of gastric cancer. Kim *et al* [43] reported a 51% response rate with the combination of paclitaxel 175 mg/m^2 by 3-h, cisplatin 20 mg/m^2 per d for 5 d and 5-FU 750 mg/m^2 by 24-h continuous infusion for 5 d. In their treated population, there were patients included as second-line chemotherapy. Two consecutive studies from the University of Tuebingen Medical Center in Germany, in chemo-naïve advanced gastric cancer patients, employing weekly 24-h continuous intravenous infusion of 5-FU, modulated by leucovorin, plus 3-weekly cisplatin and either weekly or 3-weekly paclitaxel confirmed an overall response rate of 50% and survival times of 11 and 14 mo, respectively[44,45]. Docetaxel has also been combined with cisplatin, and in a three-drugs combination together with cisplatin and 5-FU. Two phase II trials combining docetaxel and cisplatin reported response rates of 37-56% and median survival times 9-11.5 mo[46,47]. Recently, Roth *et al* [48] have demonstrated that protracted infusion of 5-FU can be safely added to a docetaxel-cisplatin combination, showing a high response rate of 51%. Nevertheless, it should be remarked that although no treatment-related deaths were reported, 79% of patients experienced ≥grade 3 neutropenia and ten febrile neutropenia episodes were recorded. Grade 3 diarrhoea appeared in 19% of patients. The combination of docetaxel plus S-1 has recently been tested in Japan[49], showing a high activity (52.1% response rate and 93.8% tumour control rate), but probably it would be necessary to add hematopoietic growth factors due to the high rate of grade 4 neutropenia (22.9%).

Which of these combinations could be considered as a standard treatment?

Looking at the data of the phase II trials shown in Table 2, it can be concluded that we have made only marginal progress in the palliative treatment of advanced or metastatic gastric cancer. Despite a relatively high rate of objective responses achieved with cisplatin-based therapy and other combinations, including new agents, the time to treatment progression was usually short and the median survival ranged from 8 to 13 mo. Toxicity profile may be quite different depending on the schedule and it should be taken into account, mainly when great differences in progression-free survival and overall survival are unexpected. Relatively aggressive regimens, such as EAP-like, FLEP or DCF (Docetaxel-cisplatin-5-FU), commonly require regular use of colony-stimulating factors due to high medullar toxicity. ECF or cisplatin plus 5-FU CI seems to be less toxic but the need for central venous access and portable pumps make these schedules less comfortable. New oral fluoropyrimidines might play a role in the future to avoid central venous access.

Nowadays, data derived from randomized phase III studies do not convincingly support the use of a specific schedule as a standard treatment. During the early 1990s, especially in Europe, FAMTX became the gold standard because it was shown to be superior in overall survival when compared with the traditional FAM regimen (42 wk *vs.* 29 wk)[50]. The results of five subsequent randomized trials comparing FAMTX or FAM *versus* cisplatin-based combinations (EAP, EEP, FLEP, and PF) were disappointing[51-55]. The EORTC trial comparing FAMTX *versus* PF *versus* a non-cisplatin combination (ELF) showed a low activity in the three arms (≤20%), no differences in toxicity profile and similar modest survival times below 8 mo[54]. The authors concluded that none of theses schedules should be regarded as standard treatment for advanced gastric cancer and that new strategies should be found. The ECF regimen developed in United Kingdom was compared with FAMTX. Long-term results demonstrated that ECF yielded a significantly higher response rate (46% *vs* 21%, $P=0.00003$), median survival (8.7 mo *vs* 6.1 mo, $P=0.0005$) and two-year survival rates (14% *vs* 5%, $P=0.03$)[56]. However, the results are somewhat confounded by the fact that around one-third of patients included in both arms had locally advanced disease rather than metastatic disease. More patients in the ECF arm (12 out of 47) underwent surgery compared to the FAMTX arm (5 out of 51), and it is not clear in the study whether there were common criteria to perform a surgical rescue after neoadjuvant chemotherapy, reviewed by a surgical expert panel. On the other hand, ECF resulted in a more favourable toxicity profile than FAMTX. Therefore, many centres in Europe are now considering ECF as their standard practice. A later English study comparing ECF *versus* MCF (mitomicyn C, cisplatin and fluorouracil) over 574 eligible patients showed an equivalent response rate (42.4% for ECF *vs* 44.1% for MCF) as well as median survival times (9.4 mo for ECF *vs* 8.7 mo for MCF), although quality of life assessment suggested that ECF regimen was a more tolerable schedule[57].

Promising results of phase II studies containing new drugs have prompted to confirm these outcomes in phase III randomized trials. Data of a phase III study comparing DCF (docetaxel-cisplatin-5-FU) *versus* PF (cisplatin-5-FU) reported a significant advantage for DCF in response rate (37% *vs* 25%) and time to progression (5.6 mo for DCF *vs* 3.7 mo for PF, $P=0.0004$)[58]. Overall survival was longer with DCF (risk reduction 23%, $P=0.02$). Another randomized phase II study conducted by the SAKK Cooperative Group, comparing DCF *versus* DC *versus* ECF concluded that DCF is the more promising schedule and should be chosen for a formal comparison with ECF in a phase III study[59]. A recent three-arms randomized phase II study has compared LV 200 mg/m^2 (2-h infusion), followed by 5-FU 400 mg/m^2 bolus and 5-FU 600 mg/m^2 (22-h continuous infusion) on days 1 and 2, every 14 d (LV5FU2) *versus* LV5FU2 plus cisplatin 50 mg/m^2 or LV-5FU2 plus CPT-11 180 mg/m^2, and showed that the overall response rates were 13%, 27% and 40%, respectively[60]. The median progression-free survival (6.9 mo) and overall survival (11.3 mo) of the LV5FU2-irinotecan regimen were encouraging when compared with those of previous randomized studies. The accrual of a randomized phase III trial comparing irinotecan plus infusional 5-FU/LV *versus* cisplatin plus infusional 5-FU has been completed and the outcome is expected in the near future.

Finally, the ongoing REAL-2 study is testing the efficacy of oxaliplatin and capecitabine in a 2×2 design. Six

Table 3 Meta-analysis of randomized trials of adjuvant cytotoxic chemotherapy in gastric cancer

Author.Year	Number of patients/ number of trials included	Mortality risk ratio	95% confidence interval	*P* value
Hermans.1993	2 096/11	0.88	0.78-1.08	NS
Earle. 1999	1 190/13	0.80	0.66-0.97	0.024
Mari. 2000	3 658/20	0.82	0.75-0.89	<0.001
Panzini.2002	2 913/17	0.72	0.62-0.84	NA
Janunger.2002	3 962/21	0.84	0.74-0.96	NA

hundred patients will be recruited and randomized to receive ECF *versus* EOF (epirubicin-oxaliplatin-5FU) *vs* ECX (epirubicin-cisplatin-capecitabine) *vs* EOX (epirubicin-oxaliplatin-capecitabine). An interim analysis presented at ASCO 2003 reported an interesting response rate of 52% for EOX compared with 31% for ECF, 33% for EOF and 35% for ECX[61].

COMPLEMENTARY TREATMENT FOR LOCALIZED GASTRIC CANCER

Surgery remains the only potentially curative treatment, though it is associated with a high rate of locoregional failure. The surgical aim is the achievement of a curative resection (R0), which implies the removal of the primary tumour with clear resection margins and the removal of the regional lymph nodes[62,63].

There is an ongoing debate whether more extensive lymph node dissection (D2) improves survival when compared to less extensive lymph node dissection. The D2 dissection was developed from surgical practice in Japan. Retrospective studies from Japan, involving more than 10 000 patients, suggested that D2 dissection prolonged survival compared to limited resection[64-66]. However, two large phase III studies concluded that D2 dissection did not improve survival and was associated with higher surgical morbidity and mortality[67,68]. The complication rate of D2 dissection was reported to be higher in the Dutch trial than in the Japanese experience. Further studies should be designed to evaluate the extended nodular dissection.

Nevertheless, the effectiveness of surgical resection is poor. R0 resection can be only achieved in 40% of the cases. Globally, almost 60% of patients who undergo a R0 resection will relapse and succumb to their disease; consequently the overall 5-year survival rate of patients with resectable gastric cancer ranges from 10% to 30%[69,70]. The high risk of relapse after surgery has led to search strategies to prevent relapse and to improve survival for gastric cancer patients, as postoperative or adjuvant therapy strategies, or as preoperative or neoadjuvant approaches.

ADJUVANT CHEMOTHERAPY

The outcome of gastric cancer is related to a high incidence of both local recurrence and distant metastases after curative surgery, and has led to major efforts to explore different adjuvant therapies, such as adjuvant systemic chemotherapy, adjuvant peritoneal chemotherapy or adjuvant immunochemotherapy.

Gastric cancer would seem to be an ideal setting to test adjuvant cytotoxic regimens, as there are multiple significantly active chemotherapy drugs and combinations that show antitumoral activity in the metastasic disease. However, over the last three decades multiple phase III studies, including an observational arm, have been reported and failed to demonstrate a clear improvement in survival, and therefore, this strategy is far to be the standard management following curative surgery.

Before 1993, there were no analyses supporting the regular use of adjuvant chemotherapy for gastric cancer[71]. The minimal benefit of adjuvant cytotoxic chemotherapy alone has been published in several meta-analyses since 1993 (Table 3). The first meta-analysis published by Hermans *et al* [72] in 1993 revealed no conclusive value for adjuvant cytotoxic chemotherapy. Later on, a meta-analysis published by Earle *et al* [73] showed a marginal statistically significant, although clinically irrelevant, survival improvement for the adjuvant chemotherapy following surgical resection of gastric cancer. In 2000, Mari *et al*[74] concluded that chemotherapy might offer a small survival advantage in patients with curatively resected gastric cancer, however, the same authors pointed that, in regard to the limitations of literature-based meta-analyses, adjuvant chemotherapy must be considered as an investigational approach. The meta-analysis reported by Panzini *et al* [75] in 2002 showed that adjuvant chemotherapy resulted in a significant survival benefit in patients, though the authors suggested to confirm this conclusion in large prospective randomized trials. Finally, Jannuger *et al* [76] in 2002 did not recommend adjuvant chemotherapy as routine therapy in this setting.

Overall, there is insufficient evidence nowadays to recommend postoperative chemotherapy as adjuvant treatment.

As systemic postoperative chemotherapy has not been accepted as standard treatment, other adjuvant strategies have been explored for patients with curatively resected gastric cancer, as adjuvant immunochemotherapy and adjuvant intraperitoneal therapy.

The adjuvant immunochemotherapy approach has been developed, fundamentally, in Korea and Japan. The benefit of a streptococcal preparation (OK-432) immunochemotherapy in patients with curatively resected gastric cancer was assessed by a meta-analysis involving 1 522 patients from six clinical trials[77]. In these trials, chemotherapy was compared to the same chemotherapy plus immunotherapy. The 3-year survival rate was 67.5% in the immunochemotherapy group whereas 62.6% in the control group. The 3-year overall survival odds ratio was 0.81 (95% confidence interval: 0.65-0.99; $P=0.044$). The results of this meta-analysis suggested that immunochemotherapy with OK-432 after surgery may improve the survival of patients with curatively resected gastric cancer.

Intraperitoneal chemotherapy is a rational approach

Table 4 Phase II studies of preoperative chemotherapy in localized gastric cancer

Author.[Year]	Number of patients	Neoadjuvant chemotherapy regimen	Adjuvant chemotherapy regimen	R0 rate	pCR	Median survival (mo)	2-yr survival rate (%)
Wilke.[1989]	34	EAP × 2	EAP × 2	29	5	18	26
Leichman.[1992]	38	CF × 2	Intraperitoneal	76	3	17	NR
Ajani.[1993]	48	EAP × 3	EAP × 2	77	0	16	42
Kang.[1996]	53	EFP × 2-3	EFP × 3-6	71	4	43	NR
	54	Surgery	None	61		30	NR
Crookes.[1997]	59	CF × 2	Intraperitoneal	71	5	48	64
Songun.[1999]	27	FAMtx × 4	None	56	0	36	62
	29	Surgery	None	62		13.1	NR

EAP: etoposide, doxorubicin and cisplatin; CF: cisplatin and 5-fluoruracil; EFP: etoposide, 5-fluouracil and cisplatin; FAMtx: 5-fluoruracil, doxorubicin and methotrexate; pCR: pathological complete remission; NR: no reported

since the peritoneal cavity is the site of recurrence in more than half of the patients, and commonly the only one location of progression disease. In other tumours, such as ovarian cancer, in which peritoneal failure is common, clinical trials have demonstrated a small but significant advantage to intraperitoneal therapy[78,79]. Nevertheless, the trials reported in gastric cancer have been hampered by small size and limited statistical power and have not established a clear survival benefit from this strategy[80,82].

ADJUVANT CHEMORADIOTHERAPY

Taking into account that surgical resection of gastric cancer is curative in less than 40% of cases, and the fact that both locoregional and distant relapses are common, adjuvant chemoradiotherapy is a rational approach for these patients. Several preliminary studies have shown promising results[83,84]. The most important trial in this setting is the US Intergroup 0116 phase III study. Five-hundred and fifty six patients with adenocarcinoma of the stomach and esophagogastric junction were randomized to surgery alone or surgery plus postoperative chemoradiation (1 cycle of 5-FU modulated by leucovorin, followed by concomitant 5-FU/LV and radiation therapy (45 Gy), and one month after the completion of radiotherapy, two 5-d cycles of 5-FU/LV)[85]. Eighty-five percent of patients in both arms had node-positive carcinoma (stage III or IV). The toxicity in the study arm was: 41% of patients experienced grade III and 32% grade IV toxicity, with a 1% of toxic deaths. Median overall survival was significantly improved in the experimental arm compared to the surgery alone group (36 mo *vs* 27 mo; $P=0.005$). The 3-year overall survival (50% *vs*. 41%) and 3-year relapse-free (48% *vs* 31%) survival were significantly better in the study group. The survival improvement was mostly related to the decrease in locoregional rather than distant failure. Based on the results of US Intergroup 0116 study, postoperative chemoradiation has been accepted as standard care in patients with resected gastric cancer in North America.

However, this study is limited for both the surgical procedures and the chemotherapy regimen employed. Fifty-four percent of patients underwent less than D1 dissection (only partial removal of the N1 nodes) and only 10% of patients underwent a D2 dissection. On the other hand, 5-FU/LV is not a chemotherapeutic option in the management of patients with advanced gastric cancer. The benefit of the Intergroup 0116 may have primarily derived from the use of radiation therapy, since local control was improved without any effect in distant control. These data support a potential benefit of this chemoradiation schedule after inadequate surgical resection. Further studies employing D1 or D2 dissection alone *versus* the same surgery plus adjuvant cisplatin/5-FU-based combinations plus radiation therapy are needed.

NEOADJUVANT CHEMOTHERAPY

Neoadjuvant treatment, chemotherapy or chemoradiotherapy, has been tested in small studies. Preoperative chemotherapy may allow to improve in the R0 rate due to tumour down-staging, and also may contribute to eradicate micrometastasis. At present, neoadjuvant treatment is being tested in locally advanced non-resectable tumours and in those resectable tumours with a high risk of recurrence.

However, there are possible disadvantages of the neoadjuvant treatment. Patients with early gastric carcinoma (stages 0 and I) could be over-treated, and among the stages II-IV non-metastasic gastric cancers, the response to the preoperative therapy could be unsatisfactory; therefore, some patients could be exposed to an unnecessary morbidity, and furthermore, the success of surgical resection could be hampered. In this context, efforts to identify prognostic factors and more active and less toxic preoperative regimens are being searched.

Several small phase II trials with different cisplatin-based neoadjuvant chemotherapy regimens have been reported in the nineties, with the largest including only 59 patients (Table 4). The perioperative radiotherapy was not included in any trials, while postoperative systemic or intraperitoneal chemotherapy was administrated in some of these trials. The median survival ranged from 16 to 48 mo, and was significantly better in those patients who underwent an R0 resection[86-91]. Beyond these small trials, phase III prospective clinical trials are needed.

The large phase III UK Medical Research Council Adjuvant Gastric Infusional Chemotherapy (MAGIC)

trial was the first well-powered phase III neoadjuvant chemotherapy study to assess the efficacy of perioperative chemotherapy[92].

Five hundred and three patients with potentially resectable gastric cancer were randomized to both preoperative and postoperative EFC therapy chemotherapy *versus* surgery alone. EFC regimen consisted of epirubicin (50 mg/m^2) and cisplatin (60 mg/m^2) administered on day 1, and protracted venous infusion of 5-FU (200 mg/m^2 per d) on days 1 to 21, administered every 3 wk for three cycles before and after surgery. The results of this trial demonstrated statistically significant improvement of the study arm in disease-free survival (HR 0.7%, 95% confidence interval 0.56-0.88%) and a strong trend towards better overall survival compared to surgery alone (HR 0.8, 95% confidence interval 0.63-1.01). There were other important results from the MAGIC study. Although in the study group, the number of patients who underwent surgery was slightly lower (85% *vs* 92%), the rate of pathological complete response was significant better in this group (79% *vs.* 69%, $P=0.018$), and the surgical morbidity and mortality were not compromised. Furthermore, there was a significant tumour down-staging

However, it remains unclear how the neoadjuvant therapy may be integrated into the multimodality management of localized gastric cancer. Consequently, ongoing randomized controlled trials are evaluating this issue.

Meanwhile some clinicians may elect to offer patients preoperative chemotherapy. Taking into account, both INT-0116 study and MAGIC study, combining neoadjuvant and postoperative chemoradiation might result in improving the outcome of patients with resectable gastric cancer.

NEOADJUVANT CHEMORADIOTHERAPY

There are few phase I-II studies exploring the role of neoadjuvant chemoradiotherapy in resectable gastric cancer. In 2003, Roth *et al* [93] reported promising results of a phase I-II study with preoperative platinum and 5-FU plus radiotherapy in this setting. They found a 5% pathological complete responses, 80% resection rate without increasing the surgical morbidity, and 71% of 2-year survival[93]. Similar results were reported in a phase II study of MD Anderson group with 5-FU and concomitant preoperative radiotherapy[94].

Other approach is the three-step therapy, involving preoperative chemotherapy, followed by concomitant chemoradiation and finally the surgical procedure. The MD Anderson group reported two phase II studies. In the former study, the patients received a combination of cisplatin and 5-FU, and then radiotherapy concomitant with 5-FU, achieving a 29% rate of pathological complete response and 80% rate of resectability[95]. In the latter study, a combination of paclitaxel, cisplatin and 5-FU was used as neoadjuvant chemotherapy, followed by concomitant radiotherapy plus 5-FU. The resectability rate reported was 100%, with 26% of resections showing no viable tumour in the pathologic examination[96]. Finally, some other trials are exploring other chemotherapeutic agents, such as docetaxel or irinotecan.

CONCLUSIONS OF COMPLEMENTARY TREATMENT FOR LOCALIZED GASTRIC CANCER

Gastric cancer is a disease in which locoregional control is hardly achieved. The roles of adjuvant and neoadjuvant therapy have also been debated for a long time; there are some approaches that seem to be effective for the management of localized gastric cancer.

Currently, it remains unclear to agree the standard care, and even it differs in each country. In EEUU, adjuvant chemoradiation is considered the standard care and stands for the control arm for further trials. However, in Korea, the standard care is adjuvant immunochemotherapy. In Japan, a D2 lymph node dissection is the standard surgical procedure and the role of any adjuvant chemotherapy is controversial.

In Europe, there are the most different opinions. Some authors argue that following an optimal surgery (at least D1), none of the adjuvant strategies seem to be superior to surgery alone, but other authors do agree to the INT-0116 results.

On the other hand, the MAGIC trial added important information on adjuvant strategy, though it is required to wait for definitive survival results of the MAGIC and other phase III trials, to accept neoadjuvant chemotherapy as the new standard care. In addition, neoadjuvant chemoradiotherapy trials offer promising results and these schemes may be explored in large randomized phase III trials. Newer approaches to cancer management, including molecular-targeted therapies may be explored.

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