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TOPIC HIGHLIGHT

WJG 20th Anniversary Special Issues (8): Gastric cancer

What make differences in the outcome of adjuvant treatments for resected gastric cancer?

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Abstract

After a long history of Dark Age of adjuvant chemotherapy for gastric cancer, definite evidences of survival benefit from adjuvant treatment have been reported since 2000s. These survival benefits are likely attributed to something new approach different from pervious studies. In 2001, South West Oncology Group INT0116 trial yielded survival benefit in curatively resected gastric cancer patients with postoperative chemoradiotherapy [5-fluorouracil (5-FU) + Leucovorin + radiotherapy], followed by positive result by MAGIC Trial, employing perioperative(pre- and postoperative chemotherapy with Epirubicin, cisplatin (CDDP), 5-fluorouracil (ECF) regimen in patients with curative resection. A novel drug [S1: ACTS-GC (Adjuvant chemotherapy trial of TS-1 for gastric cancer) in 2007], or new drug combination chemotherapys [CDDP + 5-FU: FNCLCC/FFCD (Federation Nationale des Centres de Lutte contre le cancer/Federation Francophone de Cancerologie Digestive) in 2011, Capecitabine + Oxaliplatin: CLASSIC in 2012] also produced positive results in terms of improved prognosis. Neoadjuvant or perioperative chemotherapy, novel anti-cancer drugs, and chemoradiotherapy might be the key words to develop further improvement in the adjuvant treatment of resectable gastric cancer. Moreover, it is not new but still true to stress the importance of D2 surgery as the baseline treatment in order to minimize the amount of residual tumor after surgery.

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Key words: Resected gastric cancer; Phase Ⅲ clinical trial; Adjuvant and neo-adjuvant therapy; Chemoradiotherapy; Review

Core tip: Recent positive results of adjuvant clinical trials for gastric cancer are attributed to new approaches different from previous negative trials. Inclusion of novel effective drug (S-1: ACTS-GC) and new combination of drugs (capecitabine and oxaliplatin: CLASSIC/Cisplatin and 5-fluorouracil: FNCLCC/FFCD), combination of chemotherapy and radiotherapy (SWOG INT0116), and combination of different timing (pre- and postoperative: MAGICC), might have contributed to yield positive results after curative D2 surgery. D2 surgery is going to be adopted as recommended treatment in Eastern and Western countries, and should be the baseline treatment to minimize the amount of residual tumor in future trials of adjuvant treatment.

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INTRODUCTION

Previous review articles on the adjuvant treatment for gastric cancer have commonly stated that the prognosis of gastric cancer patients still remains poor even after

Table 1 Recent epoch making adjuvant trials showing survival benefit

Reporter/group	Regimen	Patients	3 ysr/ treated	3 ysr/ control
Macdonald/2001 (SWOG INT0116)	FL + (Rad. + FL)	Curat. D2	50	41
Cunningham/2006 (MAGIC)	EPF (peri-op.)	Curat.	36[1]	23[1]
Sakuramoto/2007 (ACTS-GC)	S-1	Ⅱ-Ⅲ	80.1	70.1
Ychou/2011 (FNCLCC/FFCD)	CDDP + 5-FU (peri-op.)	Curat.res.	38[1]	24[1]
Bang/2012 (CLASSIC)	Cape. + Oxal.	Ⅱ-ⅢB	74	51

[1]Five year survival rate. 3 ysr: 3 year survival rate (%); FL: 5fluorouracil + leucovorin, Rad.: Radiation; Curat.: Curative; EPF: Epirubicin + CDDP + 5-FU; Cape.: Capecitabine; Oxal.: Oxaliplatin; peri-op: Peri-operative.

curative resection was performed, and that adjuvant treatment almost failed in improving the prognosis of gastric cancer patients[1-3]. However, in resent years, a few clinical trials reported a certain survival benefit from adjuvant treatments[4-7]. What make differences in the outcome of adjuvant treatment for resected gastric cancer? Possible reasons may be attributed to the emergence of new effective drugs, new combination of chemotherapy, radiation or hyperthermia, different delivery timing (pre-, post- or perioperative) or route of drugs (intravenous, intra-arterial, or intra-peritoneal) which might increase the local drug concentration at tumor sites, less amount of residual tumor due to improved surgical technique, modified surgical indication for advanced diseases, or elaborate trial design, or increased compliance of drug administration.

Recent improvement in adjuvant treatment has been evaluated by the literature review in relation to the factors mentioned above with an aim of getting promising suggestions for future trials.

LITERATURE RESEARCH

Evaluation of treatment effect needs proper selection of endpoints. Survival benefit is principally evaluated by the phase Ⅲ trials with overall survival (OS), relapse free survival (RFS), or median survival time (MST) as primary endpoints. On reviewing the previous literatures through electronic database (PubMed), or referring to previous systemic reviews, inclusion criteria are as follows: (1) prospective randomized phase Ⅱ or Ⅲ trials with sufficient number of patients based on the statistics, elaborated analysis based on well-managed data, and clear conclusions as to the survival benefit in relation to the endpoints stated above; and (2) literatures published later than 2000 with a few exception for important reports published before 2000.

RESULTS AND DISCUSSION

Recent state of the arts in adjuvant treatments of resected gastric cancer

Adjuvant chemotherapy had failed in improving the prognosis of gastric cancer patients until the report of SWOG INT-0116 trial[4] with adjuvant chemoradiotherapy in 2001 (Table 1). This is the first report that the large-scale phase Ⅲ clinical trial in patients with curatively resected gastric cancer yielded the significant survival benefit from postoperative adjuvant chemoradiotherapy. Combination of chemotherapy (5-fluorouracil and leucovorin: FL) and radiotherapy + FL, a new approach to the adjuvant treatment, might decreased the amount of residual tumor after surgery. Although there are several criticisms that the results of this study could not be extrapolated to Asian countries where surgery alone produced better survival in curatively resected patients, the chemoradiotherapy has become the standard treatment of locally advanced gastric cancer in the United State. Clinical significance of postoperative chemoradiotherapy is to compensate underpowered surgery (D0 surgey in 54%)[3,8]. This success was followed by a perioperative adjuvant chemotherapy with ECF (epirubicin + cisplatin + 5-fluorouracil) in patients with curatively resected gastric cancer (MAGIC Trial)[9] in 2006. This treatment is new in terms of the combination of pre- and postoperative adjuvant chemotherapy. Comparing with ordinary postoperative chemotherapy, neoadjuvant chemotherapy has some theoretical advantages[10,11]: relatively high dose intensity available, down-staging of the tumor, eradication of micro-metastasis, reduction of residual tumor burden after curative surgery. Postoperative chemotherapy might also diminish minimal residual tumor after surgery. Low dose-compliance of this postoperative chemotherapy was the target of criticism, but it has become an European standard for locally advanced resectable gastric cancer. In 2007, a large-scale clinical trial in Japan compared S-1 (combined drug of tegafur, gimeracil, oteracil potassium) plus D2-surgery and D2-surgery alone in patients with Stage Ⅱ or Ⅲ gastric cancer, and reported significant survival benefit at the median follow-up time of 3 years (ACTS-GC trial)[5]. S-1 is a new oral drug: tegafur (5-fluorocuracil derivative), gimeracil (an inhibitor of dihydropyrimidine dehydrogenase) and oterasil (inhibitor of orotate phosphoribosyltansferase), and it is reported to be highly active with mild toxicities in advanced gastric cancer[12,13]. In 2011, another perioperative adjuvant chemotherapy with Cisplatin and 5-fuorouracil also reported a significant survival benefit in patients with curatively resected lower esophageal, esophago-gastric junction, and gastric cancer. The two drugs themselves were not new, but they were used before and after surgery (FNCLCC/FFCD)[6]. A new combination of adjuvant capecitabine and oxaliplatin (Adjuvant capecitabine and oxaliplatin for gastric cancer after D2 gastrectomy: CLASSIC Trial)[7] also yielded a significant survival benefit at 3 years after surgery in patients with stage Ⅱ-ⅢB gastric cancer after D2 surgery in Korea in 2012. Survival benefit in both ACTS-GC and CLASSIC trials continued later than 5 years after surgery[14]. Thus, these successful trials seems to commonly share something new in terms of a new drug or new combination regimen, or pre- and postoperative adjuvant chemotherapy, or a new combined

Table 2 Postoperative adjuvant chemotherapy

Reporter/year	Regimens *vs* Surgery alone	Patients	OS 5ysr (%)	
			Treated	Control
Nakajima/1984	MFC + F/MF′ C + F′	Curat. Res.	68.4/62.5	51.4
Coombes/1990	FAM	Curat. Res.	45.7	35.4
Krook/1991	FA	Curat. Res.	32	33
Macdonald/1995	FAM	Ⅰ-Ⅲ	37	32
Lise/1995	FAM2	Ⅱ, Ⅲ	42 mo[1]	36 mo[1]
Grau/1998	MMC + FT	Curat. Res.	67[2]	45
Nakajima/1999 (JACOG8801)	MF + UFT	S(+)	85.8	82.9
Neri/2001	ELF	N(+)	30.2[2]	12.6
Bajetta/2002	ELF	N(+)	52	48
Nashimoto/2003 (JCOG9206-1)	MFC + F	Curat. Res. S(-)	91.2	86.1
Chipponi/2004	FLP	S(+) or N(+)	39	39
Bouche/2005 (FFCD)	FP	Ⅱ-Ⅳ	46.6	41.9
De Vita/2007 (GOIM 9602)	ELFE	ⅠB-ⅢB	48	43.5
Nakajima/2007 (NSAS-GC)	UFT	T2/N1−2	86[2]	73
Di Costanza/ 2008 (GOIRC)	PELF	ⅠB-Ⅳ	47.6	48.7
Sasako/2011 (ACTS-GC)	S-1	Ⅱ-Ⅲ	71.7[2]	61.1
Miyashiro/2011	CDDPip + CFiv	S(+), curative	62	60.9
Noh/2013 (CLASSIC)	Cape. + Oxal.	Ⅱ-ⅢB	78[2]	69
Kang/2013 (AMC0201)	MMC + 5′ FUDR (MF′) *vs* MF′ + CDDP	Ⅱ-Ⅳ	61.1	57.9
Lee/2012 (ARTIST)	Cape. + CDDP(XP) *vs* XP + Rad. + XP	Curative, D2	78.2[3]	74.2

[1]Median survival time (month); [2]Statistically significant; [3]Three year Disease free survival. OS 5ysr: Overall 5 year survival rate; MFC/F: Mitomycin C (MMC) + 5-FU + Cytosine arabinoside(CA) iv, and oral 5-FU; MF′C/F′: MMC + Ftoraful (FT) + CA iv and oral ftoraful; FAM: 5-FU + Adriamycin + MMC; FA: 5-FU + Adriamycin; FAM2: Modified 5-FU + Doxorubicin + MMC; MF+UFT: MMC + 5-FU iv and oral UFT; ELF: Etoposide + Leucovorin + 5-FU; FLP: 5-FU + Leucovorin + CDDP; FP: 5-FU + CDDP; ELFE: Epirubicin + Leucovorin + 5-FY + Etoposide; PELF: 5-FU + Leucovorin + CDDP + Epidoxorubicin; CDDPip + CFiv: CDDP ip + CDDP + 5-FU iv; S(+): Serosa involved; Curat. Res.: Curative resection.

modality of chemotherapy and radiotherapy after high compliance D2 surgery.

What have made differences in the outcome of adjuvant treatments?

As stated above, reviewing previous papers is important to elucidate the reasons of obtaining survival benefit.

Type of surgery: Incomplete surgery does not produce permanent cure, and the treatment results seems inversely correlated with the amount of residual tumor behind surgery. There is no definite evidence for D2 superiority to D1[15], but D2 surgery has been accepted in recent adjuvant trials as base-line treatment. This is the reason why curative surgery (D2) combined with appropriate adjuvant treatment is the minimum requirement for better treatment results[16]. Since 1960s in Japan, D2 surgery has been adopted as the standard treatment choice in primarily resectable cancer[17]. D2 surgery has been accepted not only in Eastern but also in Western countries (NCCN and EORTC guidelines: http://www.nccn.org/professionals/physician_gls/f_guidelines.asp; http://www.medscape.com/viewarticle/751024).

Table 3 Phase Ⅲ Neoadjuvant chemotherapy trials

Reporter/year	Regimen	Patients	Survival benefit	
			Trial	Control
Songun/1999	FAMTX	Curat. Res.	15/27[1]	18/29
Stahl/2009	PLF + rad. *vs* PLF	Curat. Res. (E-G J)	47.4[2]	27.7
Schumacher/2010	PL	Curat. Res.	72.7[3]	69.9

[1]R0 surgery rate; [2]Three year survival rate, P = NS; [3]Two year survival rate. FAMTX: 5-FU + Adriamycin + Methotrexate; PLF + rad.: CDDP + Leucovorin + 5-FU and radiation; E-G J: Esophago-gastric junction; Curat. Res.: Curative resection.

Postoperative chemotherapy with new drugs: Curative resection and postoperative adjuvant chemotherapy has been the ordinary treatment modality for a long time. Table 2 shows the summary of recent phase Ⅲ trials of postoperative chemotherapy[14,18-34]. Most of adjuvant trials reported around 2000 were using mitomycin C-, 5-fluorouracil- or Adriamycin-based regimens, most of which failed to produce survival benefit. Statistically significant survival benefit was reported in a trial done before 2000[35], but the sample was too small to confirm the survival benefit. However, a new drug such as S-1, or a new combination such as Capecitabine and Oxaliplatin yielded positive results in terms of survival benefit in the ordinary settings of postoperative adjuvant chemotherapy. It suggests that previous treatment failure is not always attributed to the trial setting itself, but to ineffective drugs. Clinicians' pessimism in 1990s led statisticians to make meta-analysis of phase Ⅲ trials of adjuvant chemotherapy[36-41], which somehow encouraged clinicians by showing a marginal survival benefit, and at the same time caused a paradigm shift from postoperative to neoadjuvant chemotherapy in 1990s[3,42,43].

Neoadjuvant chemotherapy: According to the delivery routes of drugs, neoadjuvant chemotherapy employs systemic[44-49], intra-arterial (ia), or intra-peritoneal (ip) delivery, or combination of different deliveries. Though numerous small size phase Ⅱ trials have been reported in 1990s, but large scale phase Ⅲ trials are not so much done as shown in Table 3[48,50]. It is because that neoadjuvant chemotherapy has generally been indicated to patients with high risk of relapse. Ia or ip chemotherapy has advantage to increase in the local drug concentration at the tumor site[51]. Ia chemotherapy through hepatic artery has been used to control hepatic metastasis, and sometimes induce drastic tumor shrinkage. Ip chemo-

therapy is sometimes done at the time of surgery, or *via* a catheter placed into the peritoneal cavity connected with a delivery device implanted in the subcutaneous tissue[52]. These local delivery methods rarely be done in single use, but they were combined with systemic administration (iv or oral), and ip administration was sometimes combined with hyperthermia[53].

Combination of different delivery timings, or delivery routes: Past postoperative adjuvant chemotherapy failed to improve the prognosis, but as stated before, MAGIC trial used a combined regimen of pre-and postoperative (peri-operative) adjuvant chemotherapy regimen and succeeded to yield survival benefit. Referring to the result of INT 0116 study and Magic trial, a phase Ⅱ trial of combined preoperative chemotherapy and radiotherapy was done for locally advanced gastric cancer with favorable results[54], and a phase Ⅲ trial by EORTC (CRITICS) is now conducted to determine which chemotherapy or chemoradiotherapy should be chosen in postoperative treatment[55]. Combination of systemic and local delivery (ia or ip chemotherapy) is sometimes employed in adjuvant or neoadjuvant settings[32,56-63]. Some of them produced favorable results in terms of local effect and survival benefit. Ia chemotherapy was seldom used as neoadjuvant setting for resectable gastric cancer, but was sometimes applied to patients with unresectable diseases such as large T4, liver metastasis, or peritoneal dissemination[64-66]. The author tried a combined systemic and ia chemotherapy[67] (FLEP regimen: 5-FU + leucovorin, systemic, and etoposide + CDDP, ia) for preliminarily unresectable gastric cancer associated with hepatic metastasis, paraaortic lymph node metastasis, or peritoneal dissemination. Response rate was 50%, and some of responders were subjected to radical surgery, and survived more than 5 years. Phase Ⅱ trials generally reported good local response which sometimes resulted in prolonged survivals, but survival benefit of neoadjuvant chemotherapy had not been confirmed by phase Ⅲ setting until Magic trial.

Clinical response to chemotherapy is reportedly correlate with postoperative survival[43,68], but histologic response to chemotherapy was not always the surrogate endpoint of better survival[46,69,70].

Improvement in the methodology of clinical trial: Clinical trial design has been elaborated during the long history of adjuvant treatments. Proper selection of subjects, appropriate sample size, adequate endpoints, adherence to protocol, elaborate follow-up schedule and excellent data management, proper interim and final analyses are important elements to carry out high quality clinical trials.

Previous trials often failed to show positive results in terms of survival benefit due to underpowered sample size. Recent collaboration between physicians and statisticians has opened the right way to statistical basis of clinical trials.

Five-year survival rate has been employed as the true endpoint of survival benefit in the past trials. In recent trials such as ACTS-GC or CLASSIC trials, three-year survival rate was employed as the early predictor of survival benefit based on the result of interim analysis. Later follow-up study revealed that the survival benefit has been kept later than 5 years.

In AVAGAST trial[71], significant survival benefit was observed by RFS (relapse free survival), but not by overall survival (OS). OS is influenced by the effect of subsequent treatment, but RFS is not. It is a difficult issue whether to choose RFS or OS as the primary endpoint, but recent trials tend to choose RFS.

Future perspective

Recent positive results in adjuvant treatment of gastric cancer after resection have encouraged physicians to develop further effective treatments. It may be rational and efficient way to employ in adjuvant setting a drug or combination of drugs which yielded good response in advanced gastric cancer. Combination of chemotherapeutic drugs and molecular targeting drugs, such as trastuzumab[28], bevacizusmab[71], or apatinib[72] may be promising in adjuvant trials.

Determination of proper duration of adjuvant chemotherapy[49] is another important issue in a positive regimen. It is important from the point of patient' quality of life, and medical economics, if shorter or less aggressive regimens are equivalent or superior to standard regimen.

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