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REVIEW

Current status of adjuvant chemotherapy for gastric cancer

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Abstract

Although radical gastrectomy is a standard treatment for advanced gastric cancer, recurrence remains high. After several large-scale controlled studies have shown the beneficial effects of adjuvant chemotherapy, that treatment emerged as a standard option for advanced gastric cancer after gastrectomy. However, various guidelines from different countries have suggested different adjuvant chemotherapies. Understanding the differences between guidelines is very important for investigating further therapeutic strategies. Fortunately, because there are many ongoing studies about new regimens for adjuvant treatment, it is expected that patients with gastric cancer after surgery will have better outcome.

Key words: Gastric cancer; Adjuvant chemotherapy; Perioperative chemotherapy; Chemoradiotherapy; Guidelines

Core tip: There are differences in preferred adjuvant therapy for gastric cancer according to the guidelines from different countries. These include the National Comprehensive Cancer Network recommending chemoradiotherapy, the European Society for Medical Oncology recommending perioperative chemotherapy, and the Japanese recommending postoperative chemotherapy. Understanding the differences between guidelines can help in the future investigations of further regimens for adjuvant treatment of gastric cancer.

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INTRODUCTION

Although radical gastrectomy is a standard treatment for advanced gastric cancer, recurrence is a critical issue for long-term survival of patients. Gastric cancer is still one of the most common causes of death due to malignancy[1]. In the past, most researchers mentioned in their reviews that adjuvant treatment was not beneficial for improving survival after gastric cancer surgery. Some studies had found that adjuvant therapies did not improve the prognosis of patients with gastric cancer[2,3].

After the 2000s, several large-scale controlled studies showed beneficial effects of adjuvant chemotherapy on the survival of patients with gastric cancer[4,5]. These studies demonstrated better survival rates for patients who had received adjuvant therapies after gastrectomy for gastric cancer, as compared with patients who received surgery alone. Many subsequent studies also found the beneficial effects of adjuvant chemotherapy for patients with gastric cancer[6,7]. Therefore, adjuvant chemotherapy for gastric cancer has gained both research and clinical attention in the last 20 years, and it has become one of the standard treatment options for advanced gastric cancer after gastrectomy.

However, adjuvant therapies for gastric cancers are developed and studied separately among the various countries, without international guidelines. These various guidelines have suggested different adjuvant chemotherapies (Table 1). The differences among each might be the result of differences in race, epidemiology, etiologic factor, diagnostic tool, and clinical situation[8].

The purpose of this review is to summarize the previous studies about adjuvant chemotherapy for gastric cancer, describe the present treatment guidelines with regional differences, and discuss the ongoing studies and new regimens for adjuvant treatment of gastric cancer.

PREVIOUS STUDIES ON ADJUVANT CHEMOTHERAPY FOR GASTRIC CANCER

The SWOG INT-0116 trial by Macdonald *et al*[4] in 2001 was the first large-scale controlled study that provided positive results of adjuvant chemotherapy for gastric cancer. The investigators had made a comparison between surgery plus postoperative chemoradiotherapy and surgery alone for 556 patients with adenocarcinoma at the stomach or gastroesophageal junction. The results showed better overall and relapse-free survivals in the chemoradiotherapy group. However, that study had been criticized by many Asian researchers, in the aspect of low rates of D2 lymph node dissection. Most Asian surgeons believed that D2 lymph node dissection should be performed for locally advanced gastric cancer. Those authors have mentioned that results of the SWOG INT-0116 trial should be validated in patients who have undergone D2 lymph node dissection[9,10]. Despite its limitation, however, the SWOG INT-0116 trial has played a key role in furthering efforts to investigate postoperative therapy for gastric cancer. Its results are supported by several studies showing that postoperative chemotherapy plays a significant role in compensating undertreated surgery[11,12].

In 2006, the MAGIC trial showed that perioperative adjuvant chemotherapy using a triplet combination regimen produced a successful result in improving survival rates of patients with gastric cancer[5]. Ultimately, that trial supported a new concept in terms of using both preoperative and postoperative chemotherapy for gastric cancer. Neoadjuvant chemotherapy also has some advantages, such as relatively high dose with better compliance and down-staging before surgery[13,14]. After the MAGIC trial, perioperative chemotherapy became a standard treatment for locally advanced gastric cancer in the European society[15].

In Asian countries, radical gastrectomy with D2 lymph node dissection has been considered as a standard treatment for advanced gastric cancer applied earlier than that in Western countries. Therefore, many Asian studies have investigated postoperative adjuvant chemotherapy regimens after D2 lymph node dissection without radiotherapy or neoadjuvant therapy. The ACTS-GC trial has reported better survival rates with S-1 monotherapy in Japan[16,17]. The CLASSIC trial has shown beneficial effect of the capecitabine plus oxaliplatin chemotherapy regimen (XELOX) in Korea[18,19]. Both of these two regimens have been widely used in Asian countries for advanced gastric cancer after curative resection[20]. They have also been adopted in Western guidelines as a treatment option[15,21]. Kim *et al*[22] have reported that there are no differences in survival rates for patients with gastric cancer at earlier stages between these two chemotherapeutic regimens, although XELOX chemotherapy is more effective than S-1 for patients with higher stages of gastric cancer, including 3B

Table 1 Comparison of guidelines of adjuvant chemotherapy for gastric cancer

Guideline	Methods of adjuvant therapy	Regimen
NCCN	Postoperative chemoradiation (preferred)	5-FU plus irradiation
	Perioperative chemotherapy	ECF
		Modification of ECF
	Postoperative chemotherapy (only after D2 lymph node dissection)	XELOX
		Capecitabine plus cisplatin
ESMO	Perioperative chemotherapy (preferred)	ECF
		Modification of ECF
	Postoperative chemotherapy (patients without preoperative therapy)	S-1 monotherapy
		XELOX
	Postoperative chemoradiation (for undertreatment surgery)	5-FU plus irradiation
Japanese	Postoperative chemotherapy	S-1 monotherapy (preferred)
		S-1 plus oxaliplatin
		XELOX

5-FU: 5-Fluorouracil; ECF: Epirubicin, cisplatin, and 5-fluorouracil; ESMO: European Society for Medical Oncology; NCCN: National Comprehensive Cancer Network; XELOX: Capecitabine plus oxaliplatin.

and 3C.

GUIDELINES OF ADJUVANT TREATMENT FOR GASTRIC CANCER

There are several strategies for adjuvant treatments available, including chemoradiation, perioperative chemotherapy, and postoperative chemotherapy. Chemoradiation consists of intravenous 5-fluorouracil (5-FU) and irradiation being administered postoperatively. Oral administration of capecitabine is also accepted in combination with irradiation as an alternative to infused 5-FU[21]. Recommended regimens for perioperative chemotherapies are combination of epirubicin, cisplatin, and 5-FU (known as ECF) and its modification that includes the so-called ECX regimen of epirubicin, cisplatin, capecitabine, and EOX, which is epirubicin, oxaliplatin, capecitabine[15]. Postoperative adjuvant chemotherapies with S-1 monotherapy, or XELOX chemotherapy are accepted as treatment options for advanced gastric cancer after curative resection[20].

Because adjuvant treatments for advanced gastric cancer after gastrectomy were developed separately among countries, there are many differences in recommendations from the guidelines according to the various countries they were developed in.

National Comprehensive Cancer Network clinical practice guidelines

The National Comprehensive Cancer Network (NCCN) clinical practice guidelines provide standard treatment strategies for many cancers, including breast and colorectal cancers, for use not only in United States but also around the world[21]. Although the incidence of gastric cancer is low in the United States, its mortality is still high. Therefore, the NCCN guidelines for treatment of gastric cancer have some differences compared to others[23]. Although the NCCN guidelines agree that D2 lymph node dissection is associated with low mortality and reasonable survival benefit, they recommend gastrectomy with D1 or modified D2 lymph node dissection and emphasize that D2 lymph node dissection should be performed only by experienced surgeons because of its technical difficulty[24,25]. They recommend postoperative chemoradiation for cases that have not received preoperative chemotherapy, although the evidence of efficacy of using chemotherapy after R1 or R2 resection is unclear[26]. They also recommend perioperative chemotherapy, according to results from the MAGIC trial. For the postoperative chemotherapy, the NCCN guidelines state that it is difficult to apply results of the ACTS-GC and CLASSIC trials because D2 lymph node dissection is rarely performed in many of the United States cancer centers. They only include postoperative chemotherapy with XELOX as an option for cases that have undergone D2 or modified D2 dissection, with emphasis on chemoradiation[9]. S-1 is still regarded as an investigational agent in

north America.

European Society for Medical Oncology clinical practice guidelines

The European Society for Medical Oncology (ESMO) clinical practice guidelines suggest that D2 lymph node dissection should be performed for patients with stage IB-III gastric cancer. They recommend perioperative chemotherapy preferentially. Although fluoropyrimidine plus platinum-based doublet or triplet regimens are reasonable, combination of fluorouracil, epirubicin, and cisplatin is mostly recommended with strong evidence[27]. The ESMO guidelines recommend postoperative chemoradiotherapy or chemotherapy for patients who have undergone gastrectomy without preoperative therapy. Postoperative chemotherapy has been adopted according to results from the ACTS-GC and CLASSIC trials. Although postoperative chemoradiotherapy is a standard treatment in the United States, they state that this therapeutic option has not gained acceptance in Europe because of toxicity and difference in surgical quality. However, they recommend chemoradiotherapy in the case of suboptimal surgery with less lymphadenectomy or suspicious micrometastasis[26,28].

Japanese gastric cancer treatment guidelines

The Japanese gastric cancer treatment guidelines suggest that standard gastrectomy is curative gastric resection with D2 lymph node dissection for stage 1B or higher gastric cancer[20]. They recommend postoperative chemotherapy with S-1 monotherapy preferentially because the efficacy of S-1 has been proven in Japan. Although the CLASSIC trial showed good result from XELOX, oxaliplatin has not been approved for gastric cancer in Japan. After Japanese studies with oxaliplatin were published, combination therapy of capecitabine or S-1 plus oxaliplatin was adopted as an option for postoperative chemotherapy[29,30]. Because curative radical gastrectomy with D2 lymph node dissection has been the standard treatment in Asian countries for a long time, the Japanese guidelines did not mention radiotherapy as an adjuvant treatment at all, even for cases of noncurative resection.

ONGOING STUDIES AND NEW REGIMENS FOR ADJUVANT CHEMOTHERAPY

During the last 20 years, a variety of adjuvant therapies for gastric cancers have been investigated. Although the development of adjuvant treatment has been different among countries, there are several efforts to adopt different therapeutic strategies from the others. Most importantly, surgical treatment has become more standardized; for example, the European society has already accepted D2 lymph node dissection as a standard treatment. The NCCN clinical practice guidelines have also provided recommendation of D2 dissection in certain situations[15,20,21].

Today, several ongoing Asian studies, in Korea and China in particular, are investigating the efficacy of perioperative chemotherapy and/or postoperative chemoradiotherapy[31]. Studies investigating new regimens of combination with S-1 are ongoing. In Japan, the safety and feasibility of S-1 plus cisplatin as an adjuvant chemotherapy has been proven[32], and a phase II study of S-1 plus oxaliplatin as combination therapy has also been approved[30]. In China, a large-scale randomized controlled trial (referred to as the RESCUE-GC) is ongoing, to investigate the efficacy of S-1 plus oxaliplatin as adjuvant therapy for gastric cancer[33]. There is also a phase III study evaluating the significance of preoperative chemoradiation therapy for locally advanced gastric cancer. This study is designed to investigate addition of radiotherapy to the MAGIC trial[34].

After the ToGA trial found survival gain for advanced gastric cancer with trastuzumab combination[35], the significance of combination therapies with molecular target agents gained much interest in the field of adjuvant treatment. However, targeted agents have failed to show their efficacies as adjuvant treatment for gastric cancer. The ST03 trial showed no significant difference between the group who received chemotherapy alone and the group who received combination of chemotherapy plus bevacizumab but did find an increased rate of anastomotic leakage in the combination group[36]. To date, several studies are ongoing to investigate efficacies of target therapeutic agents as adjuvant treatment for gastric cancer[31].

Although adjuvant treatments have been developed and are widely used, recurrence and metastasis are still critical problems for survival of patients after gastrectomy. Drug resistance is one of the most important causes of therapeutic failure in gastric cancer patients. Although many researchers have studied the

mechanisms of drug resistance in gastric cancer, the regulation of these mechanisms has not been completely elucidated. Recently, several researchers have reported precise mechanisms of chemoresistance in gastric cancer and showed the possibility of advances in prediction of failure of chemotherapeutic agents[37,38]. These efforts can lead to the future development of individual therapeutic plans for patients with gastric cancer and novel strategies to overcome chemoresistance.

CONCLUSION

After the development of adjuvant chemotherapy for gastric cancer, there has been a years-long steady improvement in survival after gastric cancer surgery. In accordance with the many ongoing studies investigating new regimens as adjuvant therapy for gastric cancer, better prognosis of patients after surgery is expected in the future.

Because there are several differences in the various national and regional guidelines, it is very important to know and understand their differences and to make an effort to provide better treatment strategies by communication among each other. Unfortunately, this review cannot suggest the best strategy for the patients with gastric cancer; this is due to the results of studies between Western and Asian countries being difficult to compare directly in the present situation. For further advances and worldwide consensus in adjuvant treatment of gastric cancer, new studies are warranted, including studies about racial or genetic differences in patients with gastric cancer, worldwide studies to determine surgical and therapeutic standards, and studies to investigate the mechanisms of the oncology of gastric cancer.

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