Table 2. Toxicity profile

Toxicity	Incidence (n = 3808)	
	All adverse events	≧Grade 3 events
Leukopenia	26.0% (991)	2.6% (99)
Neutropenia	21.3% (810)	6.1% (231)
Anemia	15.7% (597)	4.6% (176)
Hemoglobin decreased	9.0% (343)	1.6% (60)
Red blood cell count decreased	8.1% (310)	1.9% (73)
Hematocrit decreased	5.2% (199)	0.8% (29)
Thrombocytopenia	8.3% (317)	1.5% (59)
Aspartate aminotransferase increased	5.2% (198)	0.6% (22)
Alanine aminotransferase increased	4.6% (175)	0.4% (16)
Nausea / Vomiting	19.3% (734)	2.2% (85)
Anorexia	26.4% (1004)	5.9% (226)
Fatigue	17.5% (666)	3.5% (132)
Diarrhea	16.5% (629)	2.0% (77)
Stomatitis	12.5% (476)	1.2% (46)
Pigmentation	14.6% (557)	1.1% (43)
Rash	8.4% (318)	0.9% (34)
Overall	74.3% (2831)	25.0% (952)

Actual numbers of cases are shown in parentheses

Table 3. Incidence of toxicities in three patient groups classified by administration eligibility status

Toxicity		Incidence in patient groups according to eligibility status			Hazard ratio (95% CI)*	P value*
		Appropriate (n = 2778)	Careful-use (n = 909)	Inappropriate (n = 121)		
Leukopenia/Neutropenia	All	29.7%	32.5%	32.2%	2.314	P = 0.0001
	≧Grade 3	5.5%	11.9%	10.7%	(1.823–2.938)	
Anemia	All	25.5%	28.3%	24.8%	2.325	P = 0.0001
	≧Grade 3	5.2%	11.0%	9.9%	(1.816–2.977)	
Thrombocytopenia	All	7.5%	10.7%	9.1%	1.824	P = 0.0243
	≧Grade 3	1.3%	2.2%	2.5%	(1.081–3.079)	
Aspartate/alanine aminotransferase increased blood bilirubin increased	All	12.3%	10.1%	4.1%	1.352	P = 0.2428
	≧Grade 3	1.7%	2.2%	1.7%	(0.815–2.244)	
Nausea, vomiting, anorexia	All	31.5%	33.2%	34.7%	1.42	P = 0.0095
	≧Grade 3	5.9%	7.6%	10.7%	(1.089–1.852)	
Fatigue	All	16.3%	20.2%	23.1%	1.637	P = 0.0064
	≧Grade 3	3.0%	4.4%	6.6%	(1.148–2.335)	
Diarrhea	All	15.9%	17.9%	19.0%	1.276	P = 0.3219
	≧Grade 3	1.9%	2.3%	2.5%	(0.788–2.067)	
Stomatitis	All	12.3%	13.4%	10.7%	1.225	P = 0.5269
	≧Grade 3	1.2%	1.4%	0.8%	(0.654–2.296)	
Pigmentation	All	14.9%	13.6%	14.9%	1.225	P = 0.5417
	≧Grade 3	1.1%	1.0%	3.3%	(0.639–2.348)	
Rash	All	8.4%	7.9%	9.9%	0.86	P = 0.7097
	≧Grade 3	0.9%	0.7%	1.7%	(0.389–1.900)	

* Appropriate group vs careful-use and inappropriate groups

coagulopathy; 1 died of neutropenic sepsis; 1 died of hepatic failure; and 1 died of hyperglycemia with metabolic acidosis. Of these 5 patients, those patients who died of neutropenic sepsis and hyperglycemia were in the appropriate group; and the 2 patients who died of serious thrombocytopenia and the patient who died of hepatic failure were in the careful-use group.

The incidences of hematological toxicities (leukopenia, neutropenia, anemia thrombocytopenia) in relation to creatinine clearance, calculated using the Cockcroft-

Table 4. Incidence of hematological toxicities in four patient groups classified by creatinine clearance[a]

Creatinine clearance (ml/min)	Patients administered at standard initial dose		Patients administered at reduced initial dose	
	Overall incidence	≧Grade 3	Overall incidence	≧Grade 3
<30	70.0% (14/20)	45.0% (9/20)	41.2% (7/17)	23.5% (4/17)
≧30 to <50	56.4% (206/365)	23.3% (85/365)	45.5% (70/154)	18.8% (29/154)
≧50 to <80	47.6% (640/1345)	13.8% (185/1345)	40.1% (173/431)	12.1% (52/431)
≧80	40.7% (429/1054)	9.2% (97/1054)	36.3% (115/317)	10.7% (34/317)

[a] Patients with unknown baseline creatinine level or who received inadequate dose were excluded from this analysis

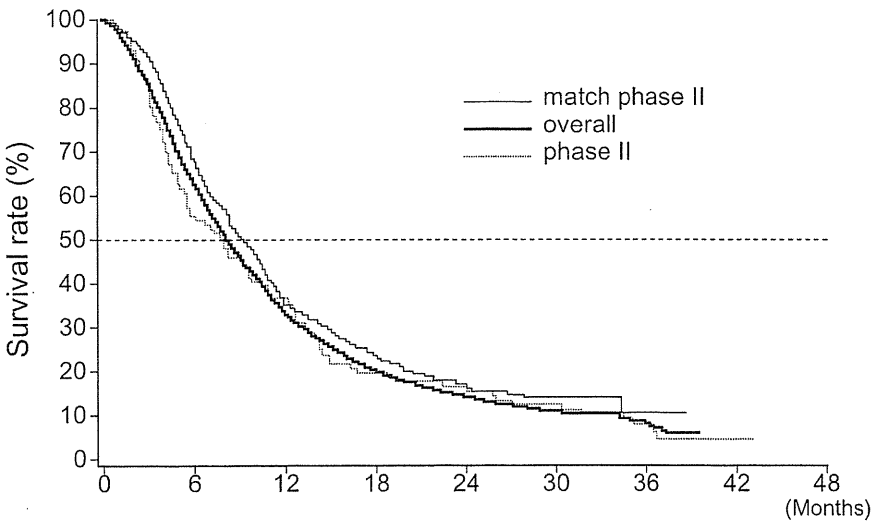

Fig. 1. Survival curves, for patients *overall* (n = 3801), for those with criteria that matched phase II criteria (*match phase II*; n = 483), and for patients in the original phase II study (*phase II*; n = 101)

Gault formula, are shown in Table 4. In the patients with lower creatinine clearance, the incidences of adverse reactions were higher for all grades combined, as well as for grades 3 or worse. Additionally, in the patients who initially received administration at a reduced dose, the incidence of adverse reactions was lower.

Efficacy results

For the efficacy analysis, 280 (7.3%) of the 3801 patients suitable for the analysis were lost to follow up. The MST of these 3801 patients was 8.3 months (95% confidence interval [CI], 8.0–8.6 months), and the 1-year survival rate was 33.3% (95% CI, 31.8%–34.9%) (Fig. 1). Among these 3801 patients, 1540 patients had had no prior chemotherapy and 483 of these patients had baseline data which met the eligibility criteria of the prior registration phase II studies (age, 20–74 years; PS, 2 or better; WBC, 4000–12000/μl; hemoglobin, >9.0 g/dl; platelets, >100000/μl; total bilirubin, ≦1.5 mg/dl; AST and ALT, ≦100 IU/l; alkaline phosphatase [ALP], within two times the upper limit; serum creatinine, within the normal upper limit; and no history of prior chemotherapy [2,3]). The MST and 1-year survival rate of these 483 patients were 9.3 months (95% CI, 8.4–10.3 months) and 36.1% (95% CI, 31.7%–40.6%), respectively.

Discussion

There have been several scandals around new drug approvals in Japan. Eighteen people died as a result of the combined use of sorivudine (an anti-herpes drug that completely inhibits dihydropyrimidine dehydrogenase) with fluorouracil-based anticancer drugs. Twenty of 477 patients died of toxicity during phase I and phase II registration studies of CPT-11, which was approved in 1994. These unfortunate results prompted the MHLW to change the Japanese drug approval system; new guidelines, "the Revised Good Clinical Practice", which recommended very strict safety monitoring during the registration studies, were adopted in 1997. In these guidelines, the MHLW requires two independent phase II studies for new drug approval, while the applicant is required to perform a post-marketing survey and studies to demonstrate the clinical benefit of the approved drug. In accordance with the Japanese approval system,

the company (Taiho Pharmaceutical Company) sponsored two independent phase II studies of S-1, which demonstrated high activity for gastric cancer, and achieved an accelerated approval in Japan. Then, as recommended by the MHLW, the company conducted a nationwide post-marketing survey in a strict manner to prevent the improper use of this agent from causing serious toxicities in general use.

Limitations are inevitable in obtaining information (particularly regarding the safety profile) for a new agent before its approval. In the Japanese system, the safety data of this new agent were obtained from only about 100 patients before marketing. In addition, only 31% (483/1540) of the chemo-naive patients in this present survey met the eligibility criteria of the prior registration study. Considering these limitations, it seems essential to keep the introduction of this agent under careful survey. Discrepancies in safety profiles are likely to occur between clinical studies and general use, particularly when the agent is indicated for gastric cancer. There are major differences in patient populations between these two settings. Although patients with peritoneal dissemination constitute a major proportion of gastric cancer patients, they are usually excluded as candidates for phase II studies because of difficulties in measuring the size of their metastatic lesions. These patients also have serious associated complications, such as bowel obstruction, hydronephrosis, and ascites, due to the peritoneal dissemination; these undesirable conditions are likely to delay the elimination of pharmacological components and may cause serious toxicities. Additionally, there are only a limited number of chemotherapy experts in Japan; the number of medical oncologists is still small in this country. Therefore, the use of newly approved agents, particularly for gastric cancer, should be carefully monitored under survey by the pharmaceutical company and the MHLW.

The overall incidences of adverse events in the present survey and in the phase II studies were 74.3% and 75.2%, respectively [2,3]. These results suggest that the power of the present post-marketing survey was similar to that of the phase II studies. On the other hand, the incidences of adverse events of grade 3 or worse were 25.0% and 14.9%, respectively. A possible cause of this discrepancy was the exclusion of patients potentially in the careful-use or inappropriate groups from the clinical studies, which rejected patients with a PS of 3 or WBC of less than 3500/μl. This interpretation fits well with the higher incidences of grade 3 or worse hematological toxicities in the careful-use and inappropriate groups than in the appropriate group in the present study. Another compromising factor could be impaired renal function; the incidences of grade 3 or worse hematological toxicities were also higher in the low-creatinine-clearance group. CDHP, a component of S-1 that sustains the concentration of tegafur-derived 5-FU by inhibiting dihydropyrimidine dehydrogenase, is known to be eliminated by renal excretion [7,8]. Therefore, S-1 should be particularly carefully administered in patients with impaired renal function, particularly in those with creatinine clearance of 50 ml/min or less.

As for the efficacy analyses, the MST and 1-year survival rate in the present survey were 8.3 months and 33.3%, respectively. Although the present population included patients with a prior history of chemotherapy and those with peritoneal dissemination, these survival results were comparable to those obtained in the phase II studies, i.e., 8.0 months and 36.6%, respectively. The efficacy of S-1 seen in the clinical studies was thus shown to translate into real clinical benefits. These results have proven the utility of this post-marketing survey in assessing the reproducibility of the efficacy results obtained from prior clinical studies.

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Special article

Current status and future prospects f chemotherapy for metastatic gastric cancer: a review

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Abstract
Although many randomized trials of chemotherapy for metastatic gastric cancer have been reported during the past two decades, no standard regimens worldwide have been established yet. Reference arms vary depending on the region and cultural differences. To date, a combination of 5-fluorouracil (5-FU) and cisplatin is most widely used. However, no confirmation of survival advantage over single-agent 5-FU in a randomized trial has been proved yet, and there remain limitations of efficacy results in older-generation regimens. Recently developed new agents such as irinotecan, taxanes (paclitaxel and docetaxel), and new oral fluorouracil (S-1 and capecitabine) provided more promising results: a response rate over 50% and median survival time (MST) over 10 months in their preliminary combination studies. These newer combination regimens are now being investigated in various randomized phase III studies, which will clarify whether the newer-generation regimens provide survival advantage over older-generation regimens. The MST of the new standard should exceed 11 months to be considered a definite improvement, and overall survival seems to be a more desirable primary end point than progression-free survival in a randomized trial. Molecular targeting agents are another concern to improve the treatment outcomes of this disease and are now under investigation in combination with conventional cytotoxic agents. Both clinical and biological research will be more important in future studies.

Key words Gastric cancer · Chemotherapy · Treatment · Molecular targeting agent

Introduction

Unresectable advanced or recurrent gastric cancer still has a poor prognosis, with a median survival of less than 9 months. Randomized trials demonstrated that -fluorouracil (5-FU)-based regimens provide superior ırvival and quality of life in patients with advanced ıstric cancer when compared with the best supportive ıre [1–3]. However, this survival advantage appears to e marginal, and no standard regimens worldwide have een established yet.

Recently developed new agents, such as irinotecan, -1, capecitabine, docetaxel, paclitaxel, and oxaliplatin ıay have potentials that will break through this status. 'ewer-generation regimens with these agents are now eing investigated in randomized trials throughout the 'orld. Molecular targeting agents are another new topic ı the field of chemotherapy and are also under devel- pment for gastric cancer treatment. This review fo- ıses on the results of newer-generation regimens with brief summary of older-generation regimens.

)verview of the older-generation regimens

'esults from randomized controlled trials (Table 1)

)uring the past two decades, various randomized trials ave been carried out for metastatic gastric cancer.)espite the numerous efforts, there is no accepted lobal standard regimen at present, and reference :gimens differ according to cultural and regional dif- :rences. In Europe, a combination of fluorouracil, oxorubicin, and high-dose methotrexate (FAMTX) sed to be a standard regimen based on the European)rganization for Research and Treatment of Cancer EORTC) trials [4]. However, this regimen failed to emonstrate any superiority over other combination :gimens (5-FU plus cisplatin or etoposide plus 5-FU/ :ucovorin) in the subsequent EORTC randomized :udy [5]. Another randomized study in the United :ingdom revealed superiority of a combination of pirubicin, cisplatin, and 5-FU (ECF) over FAMTX in :rms of survival [6], while survival results of these

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Table 1. Results of randomized trials using older-generatio gimens

Study (ref #)	Treatment	). of ients	Response rate (%)	Median survival (months)	*P* value
Wils 1991 [4]	5FU+ADM+MMC	03	7	6.7	0.004
	5FU+ADM+MTX	05	33	9.6	
Kim 1993 [8]	5FU	94	26	6.9	ns
	5FU+ADM+MMC	98	25	6.6	
	5FU+CDDP	03	51	8.5	
Webb 1999 [6]	5FU+ADM+MTX	30	21	5.7	0.0009
	Epirubicin+CDDP+5FU	26	45	8.9	
Vanhoefer 2000 [5]	5FU+CDDP	34	20	7.2	ns
	Etoposide+LV/5FU	32	9	7.2	
	5FU+ADM+MTX	33	12	6.7	
Ohtsu 2003 [9]	5FU	06	11	7.1	ns
	5FU+CDDP	04	34	7.3	
	UFT+MMC	70	9	6.0	

ns, not significant; 5FU, 5-fluorouracil; ADM, doxorubicin; MMC, ›mycin C; MTX, methotrexate; CDDP, cisplatin; LV, leucovorin; UFT, uracil and tegafur

Table 2. Treatment results of new age monotherapy

Agent	No. of patients	Response rate	MST (M)
CPT-11	76 (20)	18% (25%)	NS (NS)
S-1	101 (101)	45% (45%)	8.3 (8.3)
Capecitabine	44 (44)	34% (34%)	9.5 (9.5)
Docetaxel	40 (40)	18% (18%)	11.0 (11.0)
Paclitaxel	60 (28)	23% (21%)	11.5 (11.4)

MST, median survival time; NS, not stated: ˜-11, irinotecan
Parentheses indicate results in the chemon: ›atients

studies were limited with a median survival time (MS' ranging from 6 to 8 months and no confirmation superiority of ECF over two-drug combinations such cisplatin (CDDP) plus 5-FU (CF). Other trials includi using 5-FU alone as a reference arm and comparing with FU-based combination regimens have been r ported from the United States, Korea, and Japan [7–' All three trials showed similar results: combinati regimens failed to demonstrate survival prolongatio as compared with 5-FU alone, while response rates a progression-free survival in the CF arm were superior single-agent 5-FU.

Based on the results of these randomized trials, (could be a reasonable reference arm. However, ev this regimen has not shown superiority to 5-FU alone terms of overall survival, and there still are limitatio on efficacy results in older-generation regimens: t response rates ranged from 10% to 35%, and the MS from 6 to 8 months with around 10% in 2-year surviv To overcome these limitations, new active agents we essential.

Current status of new-generation regimens

Single-agent studies

Recently, new-generation agents such as irinotecan, S-1, capecitabine, docetaxel, paclitaxel, and oxaliplatin have been developed and investigated for gastric cancer with promising activities [10–15]. Results of single-agent studies are summarized in Table 2. Of the five agents, S-1 achieved the highest response rate, 45%; and the other agents also showed moderate activity, with response rates of 18% to 34%. These active agents are now being investigated in combination with other agents.

Combination studies (Tables 3, 4)

Irinotecan and its combinations

Irinotecan is an inhibitor of DNA-topoisomerase I, which is a crucial enzyme involved in DNA replication and transcription. At first this agent was investigated in combination with CDDP in Japan [16,17]. A phase II study of this combination (irinotecan at 70 mg/m^2, day 1 and 15, and CDDP at 80 mg/m^2, day1 every 4 weeks)

Table 3. Treatment results of newer-gene on regimens: two-drug combinations

Regimen	Phase	*n*	R	nse rate	MST (M)	Reference (year)
Irinotecan+CDDP	II	29		9%	10.8	17 (1999)
Irinotecan+5-FU/LV	II	59		2%	10.7	35 (2004)
S-1+CDDP	I/II	25		6%	12.5	22 (2003)
S-1+irinotecan	I/II	24		0%	NS	23 (2002)
Capecitabine+CDDP	II	42		5%	10.1	27 (2002)
Capecitabine+docetaxel	II	47		0%	12	28 (2004)
Docetaxel+CDDP	II	48		6%	9	31 (2000)
Oxaliplatin+5-FU/LV	II	41		3%	9.6	33 (2004)

NS, not stated

Table 4. Treatment results of newer-generation regimens: thr rug combinations

Regimen	Phase	*n*	Response rate	MST (M)	Reference (year)
Paclitaxel+CDDP+5-FU	II	41	55%	6	30 (1999)
Docetaxel+capecitabine+CDDP	II	40	68%	17	35 (2004)
Docetaxel+CDDP+5FU	III	111	39%	10.2	34 (2003)

achieved a high response rate of 48% with an MST of 9 months in all patients, and of 59% with an MST of 11 months in chemonaive patients. Toxicities were substantial, the major ones being neutropenia and diarrhea: grade 4 neutropenia was observed in 57% of patients and grade 3 or 4 diarrhea in 20%. This combination has been modified to a weekly schedule in order to reduce toxicity and has been followed in Western countries. Both of the phase II studies in the United States showed similar activity, with response rates of 58% and 57% [18,19]. This combination is now being investigated in a randomized phase III trial in Japan.

Another combination was conducted with mitomycin C; the phase I/II study of this combination revealed similar efficacy results and less toxicity than an irinotecan/CDDP regimen [20]. This regimen was then evaluated in the phase II study as a second-line setting after the failure of FU-based regimens [21]. Of the 45 patients registered, 13 achieved partial response, with a response rate of 29%. Median progression-free survival was 4 months. Toxicities were moderate: grade 4 neutropenia was observed in 29% of patients and grade 3 anorexia in 24%. This study concluded that this regimen could be a treatment option in patients resistant to an FU-based regimen.

Oral fluoropyrimidines and their combinations

S-1 is a new oral fluoropyrimidine consisting of three components: tegafur, which is a prodrug of 5-FU; 5-chloro-2,4-dihydroxypyridine (CDHP), which competes with dihydropyrimidine dehydrogenase; and oxonic acid, which suppresses the gastrointestinal toxicity of tegafur. Various attempts in combination with other agents such as CDDP, irinotecan, and taxanes have been conducted, particularly in Japan. At first, this agent was combined with CDDP. This combination phase I/II study was scheduled as S-1 40 mg/m² twice daily for 21 consecutive days and 2-h infusion of CDDP at 60–70 mg/m² on day 8, which was repeated every 5 weeks [22]. This study revealed an excellent response rate of 76% with an MST of 12.6 months. Toxicities were moderate but easily manageable: grade 3 or 4 hematological and nonhematological toxicities were 15.8% and 26.3%, respectively. Another combination, S-1+CPT-11, is also promising. A phase I/II study of this combination revealed similar response rates of around 50% with an MST of 14 months [23].

In spite of the promising results in Japan, the development of this agent in Western countries has been interrupted due to severe diarrhea as a side effect. The first European single-agent phase II study had to be decreased from 40 to 35 mg/m² owing to significant diarrhea [24]. These differences might be caused by higher susceptibility to diarrhea or lower absorption of oxonic acid in Western populations [25]. However, this agent is now being retested using lower doses in the United States. Ajani et al. reported a phase I study of S-1 in combination with CDDP [26]. The predominant dose-limiting toxicities were fatigue, diarrhea, and mucositis. Although the maximum tolerated dose of the study (S-1 at 25 mg b.i.d for 3 weeks and CDDP at 75 mg/m² every 4 weeks) was different from that of the Japanese study, the preliminary results were promising and a phase II study is now underway in the United States.

The activity of capecitabine for gastric cancer has also been reported, particularly from Korea. This agent

Table 5. Ongoing large-scale randomized phase III trials fo ɛtastatic gastric cancer

Regimen	Target accrual (patients)
Western trials	
CDDP+5-FU vs. docetaxel+CDDP+5-FU	462
CDDP+5-FU vs. irinotecan+5-FU/LV	337
Epirubicin+CDDP+5-FU vs. epirubicin+oxaliplatin+5-I 's.	600
Epirubicin+CDDP+capecitabine vs. epirubicin+oxalipla ·capecitabine	
Asian trials	
CDDP+5-FU vs. capecitabine+CDDP	300
Japanese trials	
5-FU vs. irinotecan+CDDP vs. S-1	690
S-1 vs. S-1+CDDP	300
S-1 vs. S-1+irinotecan	300

was first investigated in combination with CDD (capecitabine at 1250 mg/m², days 1–14, and CDDP ɛ 60 mg/m², day 1 every 3 weeks), showing a response rat of 55% with an MST of 12 months in a phase II stuc [27]. Similar promising results were observed with combination of capecitabine and docetaxel [28]. Kar et al. reported three drug combinations consisting ɛ capecitabine at 1125 mg/m², days 1–14, docetaxel ɛ 60 mg/m², day 1, and CDDP at 60 mg/m², day 1, repeate every 3 weeks, which resulted in a high response rat of 68% (27/40) with a long MST of 17 months [29 These results warrant further investigations of thes capecitabine-based combinations and should be evalı ated in large-scale randomized trials.

Taxanes and their combinations

The taxanes docetaxel and paclitaxel inhibit microtı bule depolymerization and have moderate activi against gastric cancer, with a response rate of arour 20% in single-agent studies. Paclitaxel was combine with a CF regimen in the Korean phase II study [3C Although this three-drug combination achieved a hig response rate of 51% (21/41), an MST of 6 montl seemed disappointing. The Swiss Group for Clinic Cancer Research has reported a phase II study ɛ docetaxel 85 mg/m² with CDDP 75 mg/m² administere once every 3 weeks for advanced gastric cancer, achie ing a response rate of 52%, median time to progressic of 6.6 months, and an MST of 9 months [31]. This con bination was then followed by three-drug combinatioı adding 5-FU and has been investigated in the randı mized trial described later.

Oxaliplatin and its combinations

Oxaliplatin is an alkylating agent inhibiting DN replication by forming adducts between two adjace guanines or guanine and adenine molecules. With tl success of the combination of oxaliplatin and 5-FI leucovorin (LV) for colorectal cancers, this combin tion was tested for gastric cancer. Louvet et al. reporte a phase II study of oxaliplatin in combination with infusional 5-FU/LV (FOLFOX6) for advanced or metastatic gastric cancer, which resulted in a response rate of 45% and an MST of 8.6 months [32]. However, FOLFOX6 caused significant toxicity including myelosuppression and peripheral neuropathy. Subsequently the regimen was revised with a reduced dose of oxaliplatin and without bolus infusion of 5-FU. The revised phase II revealed a similar response rate and MST of 9.6 months, with less toxicity than those in the previous study [33]. The authors concluded that the modified FOLFOX6 regimen provided efficacy results comparable with other combination regimens with significantly less toxicity.

Randomized controlled trials including newer-generation regimens

As mentioned above, various combination regimens including new agents showed promising results in the phase II studies, with response rates of around or above 50%. Most of the new-generation regimens are now being evaluated to determine whether they would provide significant survival prolongations as compared with older-generation regimens (Table 5). Recently, an international randomized controlled trial (V-325) comparing a docetaxel-based regimen with the reference regimen of CF was reported following an interim analysis [34]. The phase II randomized portion of the study revealed an overall response rate of 28% with docetaxel/CDDP, and of 43% with docetaxel/CDDP/5-FU (DCF). Subsequently the DCF regimen was chosen as the experimental arm for the phase III stage. The doses and schedule of the DCF arm were: docetaxel 75 mg/m² on day 1, CDDP 75 mg/m² on day 1, and 5-FU 750 mg/m² per day as continuous infusion on days 1–5, repeated every 3 weeks. The dose and schedule of the CF arm were CDDP 100 mg/m² day 1 and 5-FU 1000 mg/m² per day as continuous infusion on days 1–5, administered every 4 weeks. At the interim analysis on

232 patients, time to progression was superior (P = 0.0008) for DCF (5.2 months vs 3.7 months for CF). The MST was also longer for patients receiving DCF (10.2 months) than for those receiving CF (8.5 months). Neutropenic fever, infections, diarrhea, and mucositis were also higher from DCF than from CF. To date, however, the interpretation of the V-325 study results appears to be controversial. Although this study confirmed the superiority of DCF over CF in terms of efficacy, the MST of the DCF arm was 10.2 months, which did not seem a marked improvement. The latest combination studies, as listed in Tables 3 and 4, yielded 12 months or longer MST, although patient numbers were low. Additionally, toxicity of DCF was significant, with grade 3/4 neutropenia of 84%. The decision of whether the superiority of DCF can be accepted should wait until publication of final results. Another international randomized phase II/III study (V306), which compared irinotecan/CDDP with irinotecan plus infusional 5-FU/leucovorin in the phase II portion is now under investigation, mostly in European countries [35]. In that study, 200 mg/m^2 of irinotecan and 60 mg/m^2 of CDDP were administered every 3 weeks, compared with 80 mg/m^2 of irinotecan, 500 mg/m^2 of folinic acid (leucovorin, LV), and 2000 mg/m^2 of 5-FU as a 24-h infusion per week for 6 weeks followed by 1 week of rest. The overall response rates and MSTs of irinotecan/CDDP and irinotecan/5-FU/LV were 32% and 42% and 6.9 and 10.7 months, respectively. Toxicity results also revealed more favorable profiles in irinotecan/5-FU/LV than in irinotecan/CDDP; therefore, the former regimen has been chosen as the experimental arm for the phase III portion in comparison with the control arm of CF. Superiority of the irinotecan/5-FU/LV has also been observed in a French randomized phase II study comparing 5-FU/LV with CDDP/5-FU/LV and with irinotecan/5-FU/LV [36]. These two randomized phase II studies suggest that irinotecan/5-FU/LV is the most promising combination regimen; however, confirmation by a phase III study is necessary. In Europe, there is another ongoing study with oxaliplatin used in combination with epirubicin and capecitabine. Patients are randomly assigned to one of the four regimens: ECF (epirubicin/CDDP/5-FU), EOF (epirubicin/oxaliplatin/5-FU), ECX (epirubicin/CDDP/capecitabine), and EOX (epirubicin/oxaliplatin/capecitabine). The preliminary results available in 2003 showed response rates of 31%, 33%, 35%, and 52% for ECF, EOF, ECX, and EOX, respectively [37]. Complete results will be expected in the near future. The fourth trial is now underway in Asian countries, mostly in Korea, in a study comparing 5-FU/CDDP with capecitabine/CDDP.

In the meantime, many randomized trials consisting of an S-1 based regimen are now being evaluated in Japan. Based on the results of JCOG9205 [9], the JCOG ɔnsidered single-agent 5-FU as the reference arm and as initiated three-arm randomizations (JCOG9912) ɔmparing 5-FU alone with a combination of inotecan/CDDP and with S-1 alone. This study reuires a sample size of 690 and the accrual will be ɔmpleted at the end of 2005. The second study is a ɔstmarketing randomized trial comparing S-1 alone ith S-1+CDDP (sponsored by the Taiho Pharmaceuti-ıl Company), with a sample size of 300. The accrual to ıis study has been recently completed. The other studs are also designed to have S-1 as the reference arm: S- versus 5-FU/LV sponsored by Weiss, and S-1 versus ·1/irinotecan sponsored by the Yakult-Daiichi Phar-ıaceutical Company.

There may be significant differences between Japan ıd other countries in interpreting the reference arm. lost countries consider CF, some regions ECF, as the ·ference arm for metastatic gastric cancer. However, ngle-agent 5-FU is considered the reference arm in ƆOG based on the results of the previous randomized ial (JCOG9205) as well as the Korean and North merican trials [7–9], and S-1 monotherapy has been ·lected as the reference arm in the later trials in Japan. his difference was caused by the different interpreta-ɔn of the trials comparing single-agent 5-FU with CF, fferent histories of randomized trials, and cultural dif-rences between the regions. One might say that high ·sponse rate and long progression-free survival would ·ovide better quality of life, but another could say that FU alone would provide the same survival as CF, with ss toxicity, which seemed to provide better quality of ·e. In addition, there might be some questions raised: hether combination regimens as front-line therapy ıve survival advantages over single-agent therapy; ·termining which is better, simultaneous or sequential ɔmbinations; and whether we have to change the pri-ary end point to progression-free survival rather than /erall survival. The above ongoing trials will answer ese questions, and the MST of the new standard ould exceed 11 months to be considered a definite ıprovement. Contrary to the recent advances in ɔlorectal cancer, no confirmation of improving results ith newer-generation regimens as compared with der-generation ones has been achieved yet. It is likely at at first we should confirm definite overall survival ·olongation.

ɔndomized trials in patients with peritoneal metastasis

ıe peritoneum is the major site of metastasis from ıstric cancer. However, patients with peritoneal me-stasis usually are in poor general condition, with im-ıirment of oral intake and complications such as bowel ɔstruction and hydronephrosis, which may prolong imination of the agents. Patients with peritoneal dis-

semination are excluded from a phase II study becau these studies usually require response evaluation a primary end point, whereas these patients usua have no measurable lesions. Thus, a specifica targeted study should be conducted. A phase II study sequential combination of methotrexate (MTX) pl 5-FU (JCOG9603) has been carried out in patients wi malignant ascites [38]. A total of 37 patients were reg tered; remarkable decreases of ascites were observed 13 patients (35%), including 4 (11%) with disappe ance of ascites, while 2 (5%) patients died of treatme related toxicity. Based on the results, a phase III stu comparing 5-FU alone with MTX/5-FU (JCOG0106) patients with peritoneal dissemination has been ini ated in the JCOG and the accrual will be complet in 2005. Another randomized trial to investigate efficacy of paclitaxel for this disease is now bei conducted as a second-line therapy in JCOG.

Molecular targeting agents under investigation

Recently developed molecular targeting agents m provide a significant impact in this field, as success results of bevacizumab and cetuximab have been c served in colorectal cancer [39,40].

Gefitinib is an orally active epidermal growth fac receptor–tyrosine kinase inhibitor that has sho single-agent action against non-small-cell lung canc A Japan–Europe joint phase II study was conducted investigate the efficacy, tolerability, and pharmaco netics of gefitinib in patients with metastatic gastric a enocarcinoma [41]. Seventy-five patients (32 Japane 43 non-Japanese) were randomized to receive 250 m day or 500 mg/day gefitinib orally. Disease control v achieved in 13 patients: 1 (250 mg/day) had a part response and 12 had stable disease (4 at 250 mg/day, 8 500 mg/day), with a disease control rate of 18%. T most common drug-related adverse events were di rhea (45.9%), rash (35.1%), and anorexia (12.2% Drug-related grade 3/4 adverse events were expe enced by 11.1% and 23.7% of patients given 250 mg/c and 500 mg/day gefitinib, respectively. Gefitinib exp sure appeared to be unaffected by ethnicity or previc gastric surgery. Furthermore, there was no marked c ference in plasma concentration in patients with dise control (partial response plus stable disease) versus p gressive disease. In conclusion, gefitinib monothera was generally well tolerated but its action seemed to limited.

Investigations of two other molecular target agents are now being planned. EMD72000 is a 9 humanized monocloncal antibody against EGFR t showed promising activity for colorectal adenoca noma in a phase I study [42]. This agent has less toxic particularly in allergic reaction and skin rash, than cetuximab, which is a chimeric antibody against EGFR. This agent in combination with a cytotoxic agent will be evaluated in patients with EGFR-positive gastric cancer. Another planned agent is trastuzumab, a monoclonal antibody to Her2 protein, which is widely used in patients with Her2-overexpressing breast cancer. We have evaluated the frequency of Her2 overexpression and the concordance between protein expression and gene amplification in 200 surgical and endoscopic biopsy specimens using two commercial immunohistochemical (IHC) kits (Dako Cytomation, Glostrup, Denmark) and fluorescence in situ hybridization (FISH) (VYSIS, Abbott Laboratories, Downers Grove, IL, USA) [43]. Among these 200 cases, 46 (23%) of the patients were found to exhibit Her2 protein overexpression. The following IHC scores were obtained: 0: 126 (63%); 1+: 28 (14%); 2+: 12 (6%); and 3+: 34 (17%). Gene amplification examined with FISH was observed in 54 cases (27.1%). Her2 protein overexpression was observed in 21.5% of the 200 biopsy specimens (2+: 7.5%; 3+: 14%). The concordance rate between the surgically resected materials and the biopsy specimens was 88.7%. From these background results, trastuzumab can be applied for clinical trial in patients with Her 2 overexpressed gastric cancer, and a randomized trial is now being conducted as an international study.

Although the efficacy of the molecular targeting agents is still limited, these agents are the other new hopes for improving efficacy results with less toxicity than conventional cytotoxic agents. Understanding of the biology of gastric cancer may result in better targets or cellular pathways being modified or blocked by therapeutic interventions. Additionally, improvement of the clinical trial design and molecular surrogate into clinical research will lead to the development of better treatments. Both clinical and biological research will be more important.

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ORIGINAL ARTICLE

Photodynamic therapy as salvage treatment for local failures after definitive chemoradiotherapy for esophageal cancer

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Background: Although definitive chemoradiotherapy for esophageal cancer shows a high response rate, persistent or recurrent locoregional disease remains a major problem. Salvage esophagectomy is the only curative intent treatment option; however, it carries higher morbidity and mortality rates than primary esophagectomy. Response to second-line chemotherapy is quite dismal.

Methods: From December 2002 to November 2003, we applied salvage photodynamic therapy to 13 patients with local failures after completion of chemoradiotherapy, 4 patients had local recurrence after achieving a complete response, and 9 had a persistent tumor after chemoradiotherapy. The decision to treat was based on patients' refusal of salvage surgery or chemotherapy. After the intravenous administration of 2 mg/kg of Photofrin, photoradiation treatment with an excimer dye laser was performed for 48 hours and 72 hours after the injection. Written informed consent was obtained from all patients.

Results: Eight patients (62%) achieved a complete response. After a median follow-up period of 12 months after photodynamic therapy, 6 patients were still free of disease, and the overall survival rate at 1 year was 68.4%. There were no treatment-related deaths.

Conclusions: Our results show that salvage photodynamic therapy could be a promising curative intent treatment option with low morbidity and mortality rates. (Gastrointest Endosc 2005;62:31-6.)

Although definitive chemoradiotherapy (CRT) is now commonly used for the treatment of esophageal cancer, persistent or recurrent locoregional disease occurs in more than 40% of patients and remains one of the major unsolved problems.[1] The survival of the patients who did not achieve complete response (CR) is dismal. Most of them (over 80%) would die within 1 year.[2] Esophagectomy as a salvage treatment has a curative potential; however, it is a more difficult and risky procedure than primary esophagectomy.[3] Postoperative mortality rates within 30 days of surgery also are higher.[3,4] Moreover, there are no curative chemotherapy protocols currently available for treatment of residual tumor.

Some patients with persistent or recurrent locoregional disease have truly local failures without distant metastasis. In such patients, local treatment seems to be sufficient. We have previously reported that EMR could be a salvage option.[5] In that paper, the 3-year survival rate from the initial EMR for all 16 patients was 56%, and there were no serious complications.[5] However, the application of salvage EMR is limited by its requirement for tumor recurrence that is focal in nature, and a high skill level is required for this procedure.

Photodynamic therapy (PDT) is a potential alternative, nonsurgical treatment that eliminates superficial esophageal cancer.[6,7] This method uses a photosensitizing chemical agent that is activated by light to selectively destroy the neoplastic cells.[8-10] Theoretically, PDT may cure T1 and possibly T2 tumors, as classified by the TNM classification,[11] and this procedure is relatively simple to perform. Therefore, we postulated that PDT could be a more effective salvage option than EMR. However, there have been no reports published to date that use this method to treat local failures after definitive CRT. Herein, we report our experience of esophageal cancer patients treated with salvage PDT for local failure after completion of definitive CRT.

PATIENTS AND METHODS

Between December 2002 and November 2003, 13 patients underwent salvage PDT at the National Cancer Center Hospital East, Kashiwa, Japan. All patients initially

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were treated with definitive CRT at our hospital. The CRT consisted of 60 Gy irradiation, along with two cycles of continuous infusion with 5-fluorouracil (5FU) and cisplatin (CDDP) or nedaplatin (NED). The 5FU (400 mg/m^2, 24-hour intravenous infusion) was administered on days 1 to 5 and 8 to 12. CDDP (40 mg/m^2, 2-hour intravenous infusion) was administered with hydration on day 1 and day 8. This schedule was repeated twice, every 5 weeks. Radiotherapy was initiated concurrently on the first day of the first and second course of chemotherapy and was delivered in 30 fractions of 2 Gy for a total of 60 Gy. In addition, two courses of chemotherapy were added for the patients who showed good initial response to treatment. In the cases with renal insufficiency or cardiovascular disease, we used NED instead of CDDP, because NED did not require hydration and showed a low risk of renal toxicity.[12]

Baseline staging of esophageal cancer was determined by the TNM classification of the International Union Against Cancer.[11] Clinical T stage was evaluated by endoscopy and EUS, and clinical N and M stage were evaluated mainly by CT of the neck, the chest, and the abdomen. The definition of complete response after CRT was determined as follows: (1) disappearance of tumor lesion or ulcer of primary site with confirmed cancer negative histology, and (2) disappearance of measurable or assessable metastatic lesion confirmed by CT.

Although all persistent or recurrent tumors were surgically resectable, the decision to undergo nonsurgical treatment was based on the patients' refusal of surgery. All patients gave written informed consent. The criteria for salvage PDT were specific and included the following: (1) no lymph node or distant metastases was detected; (2) tumor staging by a 20-MHz US probe (UM-3R; Olympus Optical Co, Ltd, Tokyo, Japan) was limited to the following categories of uT1 or uT2, uT1 when the tumor invasion was within mucosal and/or submucosal layer, or uT2 when the tumor invaded into the muscularis propria layer; (3) other nonsurgical treatments, e.g., EMR, were not indicated for reasons of difficulty or noncurability; and (4) written informed consent was obtained from the patient.

The PDT procedure commenced with intravenous administration of 2 mg/kg of Photofrin (Wyeth K. K., Tokyo, Japan) followed by dye laser irradiation. The 630-nm-wavelength laser beam was emitted by an excimer dye laser (EDL-1; Hamamatsu Photonics, Hamamatsu, Japan). The laser treatment was performed 48 and 72 hours after injection of the drug. The excimer dye laser was delivered via a microlens fiber introduced into the operative channel of the fiberscope (GIF-Q20; Olympus) and was positioned in the esophagus. The distal tip of the fiber was maintained to keep the distance about 1 cm from the surface of the lesion. The total light density was 75 J/cm^2, with 4 mJ/pulse maximum pulse energy and 40 Hz pulse frequency.

All patients were instructed to avoid direct exposure to sunlight for 1 month after the injection of Photofrin for the purpose of protection from skin photosensitization. Patients were examined endoscopically 7 to 8 days after treatment to confirm the development of tissue necrosis. To evaluate the response and the luminal toxicity of PDT, endoscopic examination with biopsy was repeated at least every month until confirmation of the response. The response to PDT was classified as a CR if there was no macroscopic or microscopic evidence of cancer, or non-CR if a tumor was seen at endoscopy and was confirmed histologically. Recurrence was defined as a relapse after achieving CR. CT was used to evaluate the distant organ or lymph-node metastasis at 3, 6, and 12 months after PDT.

The progression-free survival was measured from the date of PDT to the date of confirmation of the recurrence or the progression of the disease. Overall survival was measured from the date of PDT to death or at last follow-up visit. Survival time was calculated by the Kaplan-Meier method. In addition, we assessed the period of hospital stay, antibiotics usage, and fasting after salvage PDT. If the toxicity occurred within 7 days after PDT, we defined it as acute toxicity. In contrast, if it occurred 8 days after PDT, it was defined as a late toxicity. All information was collected from medical records and was provided by the patient's physicians.

Capsule Summary

What is already known on this topic

- Persistent or recurrent loco-regional disease occurs in more than 40% of esophageal cancers after chemoradiotherapy.
- Photodynamic therapy (PDT) may cure T1 or T2 esophageal tumors and may be a salvage option.

What this study adds to our knowledge

- In an uncontrolled case series from Japan, salvage PDT with curative intent was used in 13 patients, achieving 62% complete response and a 68% 1-year survival.

RESULTS

Baseline patient and lesion characteristics before CRT and those before PDT are summarized in Table 1. Median age was 67 years (range 51-75 years). There were 12 men and one woman. The baseline clinical stage before CRT was as follows: T1, T2, T3, and T4 in 0, 4, 9, and 0 patients, respectively; N0 and N1 in 5 and 8 patients, respectively; and stage I, stage IIA, stage IIB, stage III, and stage IV in 0, 5, 1, 6, and 1 patients, respectively. Nine patients were treated with 5FU, CDDP, and radiation; and 4 patients were treated with 5FU, NED, and radiation. Four patients suffered local recurrence after achieving CR, and the remaining 9 patients had persistent tumor after completion of CRT. Six patients

TABLE 1. Patient and lesion characteristics

Patient	Age (y)	Gender	Baseline TNM stage*†	Tumor status after CRT	TNM stage before PDT†	Histologic confirmation of residual cancer	Tumor length before PDT (cm)
1	64	Male	T2N0M0	Recurrent	T1N0M0	Positive	1
2	59	Male	T3N1M0	Persistent	T1N0M0	Positive	2
3	74	Male	T3N0M0	Persistent	T2N0M0	Positive	4
4	51	Male	T2N0M0	Recurrent	T1N0M0	Positive	2
5	58	Male	T3N1M0	Persistent	T2N0M0	Positive	2.5
6	74	Male	T2N1M1a	Persistent	T1N0M0	Positive	4
7	68	Male	T3N1M0	Persistent	T2N0M0	Negative	7
8	75	Male	T3N1M0	Recurrent	T2N0M0	Positive	3
9	61	Female	T3N0M0	Persistent	T1N0M0	Negative	2
10	71	Male	T2N1M0	Recurrent	T1N0M0	Positive	2
11	64	Male	T3N0M0	Persistent	T2N0M0	Positive	5
12	67	Male	T3N1M0	Persistent	T2N0M0	Positive	6
13	69	Male	T3N1M0	Persistent	T2N0M0	Negative	5

CRT, Chemoradiotherapy; *PDT*, photodynamic therapy.
*Based on the criteria of the TNM classification of malignant tumors by the International Union Against Cancer.
†The tumor stage was evaluated by EUS.

had uT1 tumors (all of them were assessed as having massive submucosal invasion), and 7 patients had uT2 tumors. Three patients were judged to have persistent tumor without histologic confirmation of carcinoma according to the endoscopic and EUS findings of submucosal tumor-like lesions. The median length of tumor before salvage PDT was 3 cm (range 1-7 cm). Seven patients had ulceration on the lesions before PDT.

Clinical outcomes after salvage PDT are summarized in Table 2. The median total delivered light dose was 750 J (range 300-1000 J). A response of the tumors to salvage PDT was seen in all patients. CR was attained in 8 (62%) of the 13 patients. Among the cases with histologically confirmed residual cancer, the CR rate was 60% (6/10). We show the representative case of a patient who achieved CR after salvage PDT in Figure 1. All patients with uT1 tumors achieved CR, whereas two of 7 patients with uT2 also achieved CR. The median time to confirm CR was 3 months (range 1-4 months). Two patients experienced local recurrence after salvage PDT and were re-treated with PDT; however, their recurrent lesions did not disappear. They died of esophageal cancer progression. Of the 5 patients who did not achieve CR, 3 patients were re-treated with PDT, and the remaining two were followed with appropriate best-supportive care. At a median follow-up period of 12 months (range 6-19 months) after application of salvage PDT, 9 patients were still alive and 6 of them were free of disease. The overall survival rate after salvage PDT after 1 year was 68.4% (Fig. 2).

In all cases, intravenous injection of the Photofrin was well tolerated. There were no allergic reactions or injection site irritation. For all 13 patients, the median hospital stay was 13 days (range 6-20 days), the fasting period was 1 day (range 0-6 days), and the antibiotics-required period was 4 days (range 0-10 days). As for acute complication within the 7 days after salvage PDT, high fever (>38.5°C), and chest pain that needed pain killers was observed in 4 and 7 patients, respectively. White blood count (WBC) and C-reactive protein (CRP) were elevated after initial salvage PDT. Median WBC and CRP at 2 days after salvage PDT were 9400/mm^3 (range 5300-15900/mm^3) (normal 4500-8500/mm^3) and 11.2 mg/dL (range 2.3-18.8 mg/dL); (<0.5 mg/dL), respectively. Six patients experienced significant complications: one mediastinitis, one esophagotracheal fistula, 3 stenosis that required repeated balloon dilation, one cutaneous phototoxicity, and one increase of radiation-induced pericardial effusion that required drainage. The patient who developed mediastinitis was cured by intravenous administration of antibiotics and fasting for 1 week. The patient who developed a fistula died of the progression of esophageal cancer. There were no occurrences of treatment-related death.

DISCUSSION

Definitive CRT is considered the standard non-surgical treatment for esophageal cancer, because it shows

TABLE 2. Clinical outcome after salvage PDT

Patient	Total light dose (J)	Best response for PDT	Time to confirm CR (mo)	Recurrence after PDT (site)	Treatment to persistent or recurrent tumor	Major complications	Outcome	Tumor status	Survival from PDT (mo)
1	600	CR	1	No	—	—	Alive	Disease free	19
2	1000	CR	4	Yes (primary)	PDT	—	Dead	With disease	14
3	840	Non-CR	—	—	Palliation	Fistula	Dead	With disease	3
4	750	CR	3	No	—	Stenosis	Alive	Disease free	15
5	750	Non-CR	—	—	Palliation	Mediastinitis	Dead	With disease	8
6	450	CR	3	No	—	Increase of PE	Alive	Disease free	15
7	900	CR	2	Yes (primary)	PDT	—	Dead	With disease	5
8	525	Non-CR	—	Yes (brain)	PDT	—	Dead	With disease	6
9	300	CR	2	No	—	—	Alive	Disease free	13
10	450	CR	2	No	—	—	Alive	Disease free	11
11	825	Non-CR	—	Yes (primary)	PDT	Stenosis	Alive	With disease	6
12	900	Non-CR	—	Yes (primary)	PDT	—	Alive	With disease	9
13	625	CR	3	No	—	Stenosis, phototoxicity	Alive	Disease free	8

PDT, Photodynamic therapy; *CR,* complete response; *NON-CR,* non-complete response; *PE,* pericardial effusion.

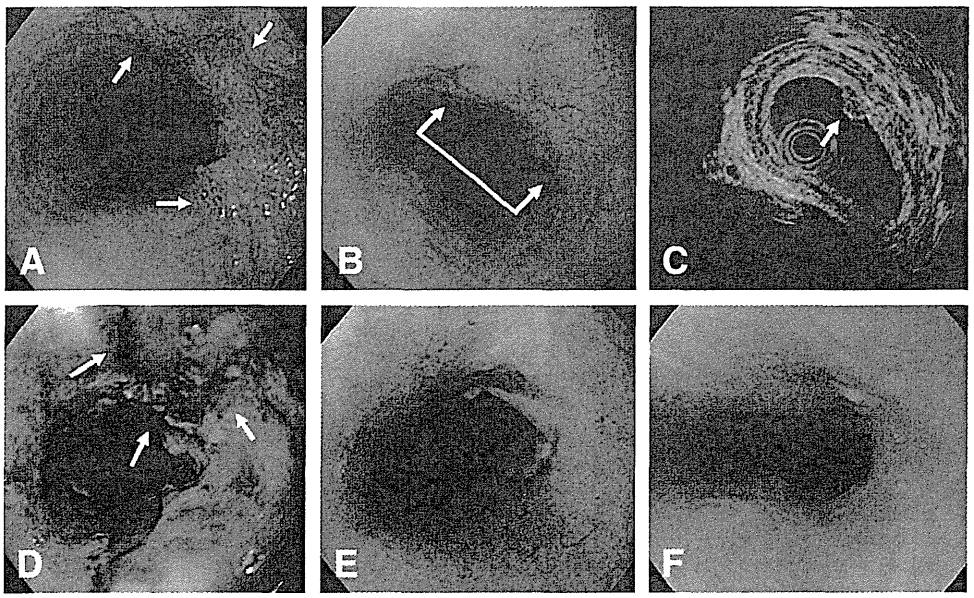

Figure 1. Endoscopic pictures of the patient with esophageal cancer. Baseline clinical stage was assessed as cT2N0M0. **A,** Depressed tumor with surrounding mound *(arrows)* is seen before definitive CRT. **B,** After completion of CRT, a submucosal tumor-like elevation *(arrows)* was persistent at the primary site, and residual cancer was confirmed by biopsy specimen. **C,** EUS image showed a hypoechoic lesion both in the mucosal and submucosal layer *(arrow)*; then, the depth of the residual tumor was assessed as uT1. **D,** At the primary site, tumor necrosis can be recognized by ischemic changes in color *(arrows)*; ulcerative change also can be seen in the background mucosa at 3 days after salvage PDT. **E,** Primary site still shows deep ulceration at 1 month after salvage PDT; however, no cancerous tissue was found by biopsy specimen. **F,** Primary site showed a scar of ulceration at 3 months after salvage PDT; no residual cancer could be found in the biopsy specimen.

comparable survival results to esophagectomy. However, the long-term follow-up results of the prospective randomized trial (Radiation Therapy Oncology Group 85-01) showed that persistence of disease and locoregional failure after definitive CRT were 25% and 13%, respectively.[13] In our previous report, local failure occurred in 34% (18/53)

of the patients treated with definitive CRT.[1-4] Therefore, improvement of local control is one of the major factors in producing better survival for patients who are treated with definitive CRT.

In our case series, 8 of 13 patients (62%) achieved CR by salvage PDT. Furthermore, the overall survival rate after salvage PDT at 1 year was 68.4%, whereas our previous report showed that overall survival data for patients with non-CR at 3 years was 6%.[2] While, all tumors were assessed as having massive invasion to the submucosal layer or invasion to the muscularis propria layer in this study, salvage PDT showed a relatively high CR rate and excellent short-term survival. These results indicate that carefully selected patients might have a chance of cure by salvage PDT even though they had persistent or recurrent tumor after definitive CRT.

We also previously reported that the overall survival rate of the patients treated by salvage EMR for locoregional failure after definitive CRT was 56% at 3 years.[5] These results might suggest that local treatment by endoscopic modalities such as EMR and PDT could be a treatment option for selected patients.

From a technical point of view, PDT seems to be superior to EMR. If the persistent or the recurrent lesion has an ulceration or severe fibrosis or stenosis, salvage EMR is quite difficult or impossible to perform. If the depth of the residual tumor is limited within the submucosal layer, salvage EMR is relatively difficult and has a risk of being incomplete. Even in such cases, salvage PDT could be indicated in addition to the primary treatment.

Generally, most locoregional failures after definitive CRT are detected at an advanced stage. Endoscopic treatment may not be indicated in such cases because it lacks curative potential. To date, surgical resection is considered to be the only curative treatment in these cases. However, Swisher et al[3] reported that the patients treated by salvage esophagectomy had a significantly higher incidence of anastomotic leaks (39% vs. 7%) and a longer hospital stay (29 days vs. 18 days) than those treated with planned esophagectomy. To treat malignant neoplasms, early detection is very important to cure the patient. Indeed, in our experience, all of the uT1 cases achieved CR. To detect the locoregional failure at earlier stage, the appropriate follow-up schedule after definitive CRT needs to be clarified.

As for the complications of salvage PDT, most of them were manageable with medical treatments. However, one patient developed an esophagotracheal fistula. It is unknown whether the fistula was PDT related or because of the natural progression of disease. Because the tumor in this case was non-CR, we could not deny the possibility of the latter. An esophagotracheal fistula could develop by PDT even for naïve early esophageal cancer cases, and an incidence of 6.5% has been previously reported.[7] Sanfilippo et al[15] reported two patients with esophageal cancer who had developed a fistula after PDT. One received prior external beam irradiation, and the other had intraluminal brachytherapy.[15] Similarly, the reason for mediastinitis or the increase in pericardial effusion occurring after salvage PDT is unknown. One possibility is that radiation-induced esophageal damage and heart disease,[16,17] are potentiated by PDT and that structural damage occurs by transmural necrosis. Nevertheless, it is important to elucidate their mechanism to prevent the potential complications of PDT.

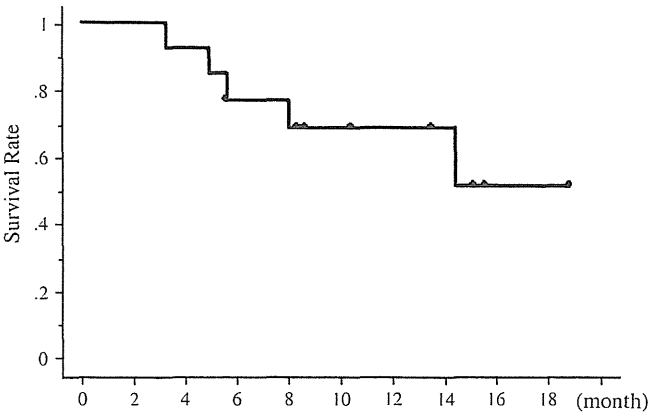

Figure 2. Overall survival of all patients from initiation of salvage PDT.

We have shown the acceptable short-term safety and worthwhile curative properties of salvage PDT when applied to the local failures after definitive CRT. Although further long-term follow-up studies will be required, salvage PDT represents a potentially new and promising treatment option. Large studies will be necessary to define the population of patients who are most likely to benefit from this treatment. Furthermore, we should confirm the efficacy of PDT as a salvage treatment for local failure after definitive CRT.

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Seminars in Oncology

Overview of Adjuvant Therapy for Resected Gastric Cancer: Differences in Japan and the United States

Atsushi Ohtsu[a] and Mitsuru Sasako[b]

Survival in adjuvant chemotherapy following resected gastric cancer has been studied by both Japanese and Western investigators using varied chemotherapy regimens in different target patients. Gastrectomy with D2 lymphadenectomy is the standard in Japan, and trials of adjuvant therapy in these patients have shown no survival advantages over surgery alone. In the United States, where 5-year survival rates in patients with gastric cancer are much lower following potentially curative surgery, adjuvant therapy has shown a survival benefit. The differences observed in these trials may result from the additional experience that Japanese surgeons have gained because of the higher incidence of gastric cancer there, or because of this increased incidence, there are more stringent screening guidelines in place and these cancers are possibly being diagnosed at an earlier stage. The Japanese viewpoint on the use of adjuvant therapy in patients with gastric cancer following potentially curative resection is that the quality of surgery, including diagnostic and pathologic procedures, is a more important prognostic factor than adjuvant chemotherapy. Also, they have determined from previously conducted clinical trials that patients with stage 1–2 tumors should be excluded from the target populations of randomized trials. Until the results of INT-0116 became available, there had been no improvement, or only marginal improvement, in overall or disease-free survival for patients receiving adjuvant chemotherapy following gastric cancer resection in the United States and Europe.
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Gastric cancer is the fourth most common cancer worldwide and the second leading cause of cancer death, accounting for 10.4% of cancer deaths globally. In 2000, there were an estimated 865,000 new cases of gastric cancer.[1] Approximately 50% of patients with gastric cancer have metastasis at diagnosis, and of those without metastasis at diagnosis, only 50% are eligible for gastric resection. In fact, gastric cancer resection typically occurs in late-stage cancer, when the cancer has already spread to the peritoneal cavity, lymph nodes, or blood vessels.[2] The 5-year survival rate in the United States and most Western countries is between 5% and 15%.[3] Age-standardized incidence rates of gastric cancer are highest in Japan; however, because of mass screening that leads to earlier disease stage at diagnosis, the 5-year survival rate is approximately 52%.[1] Adjuvant therapy for gastric cancer after surgical resection has been investigated for many years. Its efficacy in gastric cancer remains questionable because no concrete evidence exists to show that adjuvant therapy for resected gastric cancer improves survival. Questions exist regarding the necessity, most useful chemotherapy combinations, worldwide standardization of lymph node dissection grade, eligibility for surgery based on tumor stage, and the benefit of individualization of therapy for adjuvant chemotherapy for gastric cancer.

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Adjuvant Therapy for Resected Gastric Cancer

Early trials of adjuvant therapy for gastric cancer in Japan evaluated the use of mitomycin-C (MMC), and later, a combination of MMC and oral fluoropyrimidines. These studies showed a small survival benefit compared with surgery alone. Re-examination of these data led to additional studies of these agents. Pooled data showed borderline survival benefit for oral fluoropyrimidines compared with surgery alone.

Recent studies have shown either no differences or marginal improvement in overall survival (OS) with adjuvant chemotherapy compared with surgery alone.[4–6] Three meta-analyses of randomized, controlled clinical trials comparing surgery alone with adjuvant chemotherapy showed only

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Table 1 Meta-Analyses Randomized Clinical Trials in Patients With Resected Gastric Cancer (Adjuvant Chemotherapy *v* Surgery Alone)

Study	Trials Analyzed (No.)	HR	95% CI
Hermans et al (1993)[7]	11	0.82	0.68–0.97
Earle and Maroun (1999)[8]	13	0.80	0.66–0.97
Mari et al (2000)[6]	20	0.82	0.75–0.89

Abbreviations: CI, confidence interval; HR, hazard ratio.

marginal advantages of adjuvant chemotherapy (Table 1).[6–8] As a result of these meta-analyses, adjuvant chemotherapy following curative surgery for gastric cancer continues to be an investigational approach.[6] The use of meta-analysis has been the trend in determining benefits of adjuvant chemotherapy for resected gastric cancer, but recent studies suggest standardization of lymph node dissection protocols worldwide, tumor stage qualification for target populations of randomized trials, and surgery quality along with diagnostic procedures are all needed to qualify the results of these meta-analyses.

Adjuvant Therapy for Resected Gastric Cancer in Japan

Three randomized controlled clinical trials have been conducted or are currently underway in Japan comparing surgery with or without adjuvant chemotherapy (Table 2).[9,10]

Nashimoto et al[9] conducted a randomized, multicenter, phase III study ([Japan Clinical Oncology Group] JCOG-9206-1) to evaluate the survival benefit of adjuvant chemotherapy in patients with serosa-negative gastric cancer following curative resection. Patients were randomly assigned to observation or chemotherapy with MMC 1.33 mg/m^2, 5-fluorouracil (5-FU) 166.7 mg/m^2, and cytarabine 13.3 mg/m^2 twice weekly for the first 3 weeks after surgery, and oral 5-FU 134 mg/m^2 daily for the next 18 months. The primary endpoint was relapse-free survival. The 5-year relapse-free survival among patients who received chemotherapy in addition to surgery was 88.8% versus 83.7% in patients who underwent surgery alone; these differences were not statistically significant ($P = .14$). The 5-year survival in the chemotherapy plus surgery group was 91.2% versus 86.1% in patients who had surgery alone ($P = .13$). Fewer patients who received the combination of chemotherapy plus surgery experienced cancer recurrence (7.1%) than did patients who received surgery alone (13.8%). Because there was no relapse-free or OS benefit with this adjuvant chemotherapy regimen in patients with macroscopically serosa-negative gastric cancer after curative resection, and there were no remarkable differences in modes of cancer recurrence between the arms, the investigators concluded that adjuvant chemotherapy with this regimen is not recommended for this patient population in clinical practice.

Nakajima et al[10] conducted a randomized, phase III trial (JCOG-8801) in patients with T1 and T2 gastric tumors, who were either observed or received chemotherapy following resection to assess the survival benefit of adjuvant chemotherapy after curative gastrectomy for macroscopically serosa-negative gastric cancer. Patients who were randomly assigned to the chemotherapy group received MMC 1.4 mg/m^2 and 5-FU 166.7 mg/m^2 twice weekly for 3 weeks and oral uracil-tegafur (UFT) 300 mg daily for 18 months following surgery. At the median follow-up time of 72 months, 5-year survival was 82.9% for the observation group versus 85.8% for patients receiving chemotherapy. This difference in survival was not significant (log-rank test, $P = .17$; hazard ratio, 0.738; 95% confidence interval, 0.498–1.093). Toxic effects were generally mild. For patients with T1 (mucosal or submucosal) gastric tumors, 5-year survival was 94.9% in the observation group and 92.0% in the chemotherapy-treated group. Survival for T2 (muscularis propria or subserosa) was 76.9% and 83.0% for the observation and chemotherapy treated groups, respectively; the differences observed between the two groups were not statistically significant. The respective cancer recurrence rate was 13.7% versus 10.1% of the observation and chemotherapy-treated groups. Death from cancer occurred in 0.4% versus 1.0% of the observation and chemotherapy groups, respectively. The investigators concluded that there was no survival benefit with this adjuvant chemotherapy regimen for patients with macroscopically serosa-negative gastric cancer (T1 and T2) after surgery. They also recommended that T1 cancer patients be excluded

Table 2 Japanese Studies of Adjuvant Chemotherapy Versus Surgery Alone in Patients With Resected Gastric Cancer

Study/Trial	Target Patients	Treatment	No. of Patients	5-Year Survival (%)	*P* Value
Nashimoto et al/JCOG-9206-1[9]	T1-T2	5-FU plus MMC plus cytarabine followed by oral 5-FU	127	91.2	.13
	T1-T2	Observation	123	86.1	
Nakajima et al/JCOG-8801[10]	T1-T2	5-FU plus MMC followed by UFT	288	85.8	.17
	T1-T2	Observation	285	82.9	
JCOG 9206-2	T3-T4	5-FU plus cisplatin followed by UFT	135	*	*
	T3-T4	Observation	133	*	

Abbreviations: 5-FU, 5-fluorouracil; JCOG, Japan Clinical Oncology Group; MMC, mitomycin-C; UFT, uracil-tegafur.
*Not yet available: data will be available in 2005.

from future trials because surgery alone resulted in a good survival rate.

Results of a randomized phase III clinical trial evaluating patients with T3 and T4 gastric tumors in Japan will be available in 2005. This ongoing study has enrolled 133 patients who are being observed post-surgery and 135 patients who are receiving 5-FU plus cisplatin followed by UFT.

Another phase III study of adjuvant chemotherapy for gastric cancer in Japan (Adjuvant Chemotherapy Trial of S-1 for Gastric Cancer [ACTS-GC])[11] began accruing patients with stage II, IIIA, or IIIB gastric cancer in October 2001. Anticipated accrual is 1,000 patients (500 patients per arm), and the primary objective is to assess OS. Expected 5-year survival of the control arm compared with the test arm is 70% versus 78%, respectively. There are 108 institutions involved in the study, 825 patients have been accrued, and the expected final accrual was completed in the third quarter of 2004. Table 2 summarizes the results of these studies.

Adjuvant Therapy for Resected Gastric Cancer in the United States

The development of adjuvant chemotherapy for gastric cancer in the West was not based on combinations with MMC, but rather 5-FU. While sometimes showing a survival benefit compared with surgery alone, these 5-FU–containing regimens have been criticized for lack of regimen standardization as adjuvant chemotherapy.

Macdonald et al[12] conducted the randomized, multicenter, phase III intergroup INT-0116 study that evaluated survival at 3 and 5 years following adjuvant chemoradiotherapy (chemoRT) in patients with adenocarcinoma of the stomach or gastroesophageal junction after curative resection. A total of 556 patients were enrolled in the trial; 275 patients were randomly assigned to receive surgery only, and 281 patients received surgery plus chemoRT. Patient tumor stage was 1 (n = 14), 2 (n = 74), 3 (n = 175), and 4 (n = 18). Of the 552 patients whose surgical records were reviewed, 10% had undergone a formal D2 lymph node dissection, 36% a D1 dissection, and most patients (54%) a D0 dissection. Adjuvant chemotherapy consisted of 5-FU 425 mg/m^2 plus leucovorin 20 mg/m^2 per day, for 5 days, followed by 4,500 cGy of radiation therapy (RT) (180 cGy/day), given 5 days per week for 5 weeks. Modified doses of 5-FU and leucovorin were given on the first 4 and the last 3 days of RT. One month after the completion of RT, two 5-day cycles of 5-FU (at 425 mg/m^2/day) plus leucovorin (20 mg/m^2/day) were given 1 month apart. The median 5-year survival was 36 months in patients who received chemoRT plus surgery versus 27 months in patients who received surgery alone. The 3-year survival rates were 50% versus 41% in the chemoRT plus surgery groups and surgery-only groups, respectively. The median duration of relapse-free survival was significantly longer in patients who received chemoRT plus surgery versus those receiving surgery only (30 *v* 19 months; $P < .001$, log-rank test). Relapses were reported in 64% of patients who received surgery only versus 43% of patients who received surgery plus chemoRT. The investigators concluded that local-regional RT plus fluoropyrimidine-based chemotherapy as adjuvant treatment significantly improves OS and relapse-free survival in patients with gastric cancer. This study also showed that the most frequently performed lymph node dissection in the United States was a D0 lymphadenectomy.

Table 3 Comparison of Results of INT-0116 and JCOG-9501[16]

	INT-0116	JCOG-9501
Surgery (%)	D0: 54 D1: 36 D2: 10	D2: 50 D3: 50
Adjuvant therapy	CT: 5-FU and LV RT: 45 Gy	None
No. of patients	281 (CT arm)	523
Tumor location (%)	Antrum: 53 Gastric body: 24 Cardia: 21 Multiple lesions: 2	Lower-third: 41 Middle-third: 39 Upper-third: 19
pT stage (1:2:3:4)	1: 14 pts 2: 74 pts 3: 175 pts 4: 18 pts	1: 23 pts 2: 257 pts 3: 230 pts 4: 13 pts
Survival (%)	3-yr: 50 5-yr: 42	5-yr: 71.4

Abbreviations: CT, chemotherapy; 5-FU, 5-fluorouracil; LV, leucovorin; pT, pathologic tumor stage; RT, radiation therapy; pts, patients.

Future Directions

Individualizing chemotherapy in various types of cancers has recently received much focused interest. In gastric cancer, individualized chemotherapy is based on subgroups of patients who are evaluated through molecular targeting that includes the use of the epidermal growth factor and vascular endothelial growth factor receptors. Recent studies have confirmed that: (1) the use of cDNA microarray analysis to detect expression files of cancer tissues improves the understanding of molecular changes during the development of gastric cancers, and (2) the expression of the S100A11 gene was useful to distinguish lymph node metastases of gastric cancers.[13–15] The evaluation of individual genetic information may prompt the future development of more personalized adjuvant chemotherapy regimens.

Discussion

In the United States, adjuvant chemoRT is considered a standard treatment and is based largely on the results of INT-0116, whereas in Japan the use of adjuvant therapy is the standard. Sasako[16] compared the results of INT-0116 with those of JCOG-9501 (Table 3).[16] INT-0116 showed a survival advantage with chemoRT plus surgery in patients with gastric cancer following curative resection; however, the 3-year survival rate in INT-0116 was only 50% which, when compared with Japanese studies, is lower than the 3-year