Review article

Adjuvant chemotherapy for gastric cancer: a comprehensive review

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Abstract

The role of adjuvant chemotherapy in gastric cancer has been studied extensively over the past three decades in an attempt to further improve the prognosis of patients with gastric cancer who have undergone curative surgery. To date, no definitive conclusions have been drawn from randomized clinical trials of adjuvant chemotherapy for gastric cancer, because few studies have shown a significant positive impact on survival as compared with surgery alone. The negative results of most previous clinical studies do not necessarily mean that the adjuvant chemotherapy approach to treatment of gastric cancer does not work. Recent published reports of meta-analyses concerning adjuvant chemotherapy of gastric cancer revealed small but clear survival advantages for adjuvant therapy over surgery alone. The positive data from meta-analyses suggests that there are potential survival advantages of adjuvant chemotherapy, but this must be proven in the future by well-designed clinical trials that compare adjuvant chemotherapy with surgery alone, in which sufficient numbers of patients are enrolled and effective chemotherapeutic regimens with appropriate dose intensity are employed. Newly developed anticancer agents and/or newer therapeutic combinations or strategies (neoadjuvant chemotherapy, chemoradiotherapy, intraperitoneal chemotherapy) have the potential to benefit high-risk patients.

Key words Adjuvant chemotherapy · Gastric cancer · Chemoimmunotherapy

Introduction

A gradual increase in overall survival after curative surgery for advanced gastric cancer has recently been reported [1]. Even after curative surgery, however, especially in the advanced stages of gastric cancer, re-

currences are often experienced [2], as a result of which tremendous efforts have been made over the past three decades to further improve the clinical outcomes of gastric cancer with postoperative adjuvant chemotherapy, both in Japan and Western countries [3]. To date, worldwide, no definitive conclusions concerning the efficacy of adjuvant chemotherapy for gastric cancer have been reached. A few reports from Western countries support the survival benefits of adjuvant chemotherapy for gastric cancer, whereas Japanese reports suggest favorable results in limited subsets of patients treated [3,4]. These differences may stem from several differences between Japan and Western countries in the methodologies employed in clinical trials as an adjuvant setting. Many factors may interfere with the interpretation of the data, as follows [5,6]. (1) The details of surgery and pathology for curative resection of advanced gastric cancer seem to differ. While most Japanese surgeons perform quite a uniform extended lymph node dissection (D2 or D3) and radical gastrectomy with a sufficiently free margin from the tumor, many patients in Western countries undergo less than the recommended (D1) lymph node dissection [7]. Thus, the residual tumor burden seems to differ, even in potentially curative cases, between Japan and Western countries. Furthermore, pathological evaluation of the dissected lymph nodes is often inadequate in Western countries. (2) Worldwide, the staging systems employed have been different, such that comparisons of survival results of surgery with or without adjuvant chemotherapy in the past have been confused [5]. Moreover, because the staging systems for gastric cancer have changed a number of times over the decades, it has often been difficult to establish exactly which staging system was involved. (3) Previous Japanese clinical trials for adjuvant chemotherapy enrolled patients at all stages of the disease, had inadequate sample sizes, and often lacked surgery alone as a control arm [8]. (4) The initiation of postoperative chemotherapy varies widely

[9]. In Japan, postoperative treatment for gastric cancer patients begins immediately after surgery, whereas in Western countries, treatment often starts 4 to 6 weeks after surgery, and this factor may have an influence on the efficacy of adjuvant chemotherapy. (5) Chemotherapy regimens and the dose intensity employed vary between centers and countries. Most Japanese adjuvant chemotherapy regimens include mitomycin C (MMC) with an oral 5-fluorouracil (5-FU) analogue, while Western countries have been using nitrosurea-, MMC-, and doxorubicin-containing regimens in combination with intravenous 5-FU [3,4].

As mentioned above, there have been several differences in the methodologies of adjuvant chemotherapy between Japan and Western countries. Thus, for this article, we have reviewed reports of adjuvant chemotherapy for gastric cancer from Japan and Western countries separately.

Japanese postoperative adjuvant chemotherapy trials

Adjuvant chemotherapy vs surgery alone

In Japan, the National Hospital Cooperative Cancer Chemotherapy Study Group conducted multi-center

clinical trials of postoperative adjuvant chemotherapy for gastric cancer from 1959 to 1978 [10,11]. In eight trials, several regimens containing MMC, Triethylene Thiophosphoramidate (thio-TEPA), or MMC combined with 5-FU were tested, but no significant survival advantages were found over surgery alone. Table 1 lists studies of postoperative adjuvant chemotherapy comparing the treatment arm to a surgery-alone arm [12–20]. Adjuvant MMC has been used as a moderate dose delivery medium over the long term (0.08 mg/kg, twice a week for 5 weeks) [12,13]. There was no prolongation in overall survival, but significant benefits were seen in stages II or III by subset analysis. The combination of the three drugs, MMC, 5-FU, and cytosine arabinoside (MFC) produced a favorable result [14]. Although there was no significant survival difference among all patients tested, MFC therapy revealed a significant survival benefit in the subset of stages II and III patients. Based on the previous results, Nakajima et al. [16] conducted a subsequent clinical trial in which patients with curative surgery were randomized to receive either MFC plus oral 5-FU, MFC plus tegafur (FT), or surgery alone. Although they did not achieve a significant survival benefit in the treated group, there was a 17% difference in the 5-year survival rates between the MFC + FT and control groups. The MFC + FT regimen was superior to

Table 1. Adjuvant chemotherapy for gastric cancer: Japanese studies (chemotherapy vs surgery alone [control])

Author (year)	No. of patients	Treatment	Percent survival/years	P value	Suggested data
Imanage [12] (1977)	242 283	A: MMC B: Control	68/5 54/5	NS	Stage II, III A > B
Nakajima [13] (1978)	207 223	A: MMC B: Control	52/5 44/5	NS	Stage III A > B
Nakajima [14] (1980)	42 40 38	A: MMC B: MMC/5-FU/Ara C C: Control	64.3/5 66.9/5 56.0/5	NS 0.05	S + B > C
Ochiai [15] (1983)	49 49 40	A: MMC/5-FU/Ara C + FT B: MMC/5-FU/Ara C + FT + BCG C: Control	36/5 18/5 31/5	0.05	
Nakajima [16] (1984)	81 83 79	A: MMC/5-FU/Ara C + 5-FU B: MMC/5-FU/Ara C + FT C: Control	68.4/5 62.5/5 51.4/5	NS	Stage III 56.1% P < 0.05 5.3%
Yamamura [17] (1986)	32 33 34	A: MMC/5-FU B: MMC/5-FU/OK-432 C: Control	53.1/5 66.7/5 58.8/5	NS	
Maehara [18] (1990)	137 118	A: MMC/5-FU/PSK B: Control	56.9/15 45.7/15	0.03	
Fujii [19] (1994)	70 72 34	A: MMC/5-FU (6 months) B: MMC/5-FU (12 months) C: Control	51.5/5 72.2/5 56.1/5	NS	
Nakajima [20] (1999)	285 288	A: MMC/5-FU + UFT B: Control	82.9/5 85.8/5	NS	

NS, Not significant; MMC, Mitomycin C; 5-FU, 5-fluorouracil; Ara C, cytosine-arabioside; FT, tegafur; BCG, Bacillus Calmette-Guerin; PSK, protein-bound polysaccharide; UFT, tegafur-uracil

the control in the subsets of stages I to III patients. Ochiai et al. [15] found a significant survival advantage among patients treated postoperatively with MFC + FT and Bacillus Calmette-Guerin (BCG) over surgery alone. We also found a significant survival improvement in patients treated with MMC + 5FU combined with protein-bound polysaccharide (PSK), a potent immunomodulator, when compared with a surgery alone group [18]. More recently, Nakajima et al. [20] reported the results of a phase III clinical trial of adjuvant chemotherapy after curative gastrectomy for macroscopically serosa-negative gastric cancer. In their study, 579 patients were allocated randomly to adjuvant chemotherapy with MMC + UFT or no further treatment. Although there was no survival benefit with the adjuvant therapy for patients with macroscopically serosa-negative gastric cancer after curative surgery, subset analysis showed a better survival rate among the chemotherapy group in T2 patients (83.0% vs 76.9%). They concluded that patients with T1 cancer could be excluded from future trials, because curative surgery alone yielded a very high survival rate, and there seemed to be no need for adjuvant therapy.

Chemotherapy vs chemotherapy

In Japan since the 1980s, most clinical trials of postoperative adjuvant chemotherapy for gastric cancer have

consisted of chemotherapy treatment arms without a surgery alone control arm. As a result of early trials conducted in Japan in the 1970s, MMC with or without 5-FU is now regarded as a standard regimen for postoperative adjuvant chemotherapy, because subset analyses of trials often indicated superior survival curves for the treatment groups compared with surgery alone in stage II or III patients. Table 2 shows a summary of Japanese clinical trials of postoperative adjuvant chemotherapy without a surgery-alone control arm [21–28]. Inokuchi et al. [21] investigated the effect of MMC plus FT in comparison to MMC alone. There was no significant survival advantage in the MMC plus FT group. When subset analysis was conducted, however, patients with stage III disease who received a high dose of MMC survived longer than those who received a moderate dose of MMC ($P = 0.036$). Similarly, the combination of MMC plus FT was evaluated in a prospective randomized control trial by Hattori et al. [22]. A total of 2873 patients were randomized to MMC alone, FT alone, or MMC plus FT. There were no significant differences in the 5-year survival rates among the three treatment arms, except for subset analyses showing the superiority of the FT or MMC + FT groups over the MMC-only group in stage III. We compared the effect of MMC plus UFT, with MMC plus FT in patients with resected stage IV gastric cancer [24]. Although the number of patients was small, MMC + UFT had significant survival benefit, with a 5-year survival rate of 23%, vs 13% for MMC

Table 2. Adjuvant chemotherapy for gastric cancer in Japan

Author (year)	No. of patients	Treatment	Percent survival/years	<i>P</i> value	Suggested data
Inokuchi [21] (1984)	582	A: MMC (md)	46.7/5	NS	Stage III A < B; <i>P</i> < 0.05
	463	B: MMC (md) + FT	47.3/5		
	386	A: MMC (hd)	54.6/5	NS	
	374	B: MMC (hd) + FT	56.1/5		
Hattori [22] (1986)	925	A: MMC	52.1/5	NS	Stage III A < B; <i>P</i> < 0.001, A < C; <i>P</i> < 0.02
	965	B: MMC + FT	54.1/5		
	983	C: FT	53.4/5		
Nakazato [23] (1986)	81	A: MMC + 5-FU	—	NS	n(+) ps(+) A < B
	90	B: MMC + HCFU	—		
Maehara [24] (1990)	24	A: MMC + FT	13/5	0.045	
	22	B: MMC + UFT	23/5		
Kubota [25] (1994)	163	A: MMC + FT	—	NS	Curative A < B; <i>P</i> < 0.05
	162	B: MMC + FT + MMC	—		
Arima [26] (1994)	117	A: MMC + FT	39/5	NS	Curative A < B; <i>P</i> < 0.05
	113	B: MMC + UFT	55/5		
Nakajima [27] (1994)	155	A: MMC/5-FU/Ara C + 5-FU	70.8/5	NS	
	155	B: MMC/5-FU/Ara C + UFT	66.7/5		
	156	C: MMC/5-FU + UFT	62.5/5		
Danno [28] (2001)	707	A: MMC (hd) + UFT (hd)	57.9/5	NS	n(+) ps(−) A > B
	703	B: MMC (ld) + UFT (ld)	53.7/5		

NS, Not significant; HCFU, carmofur; md, moderate dose; hd, high dose; ld, low dose; n, node; ps, serosal invasion

+ FT, which was considered an encouraging finding. Arima et al. [26] also examined the clinical efficacy of MMC + UFT vs MMC + FT in resected gastric cancer and found similar results. Danno et al. [28] recently reported the results of a large randomized control trial investigating the correlation between efficacy and dose intensity of postoperative adjuvant chemotherapy with MMC and UFT. A total of 1410 patients were allocated to a low-dose group (MMC, 8mg/m² on the day of surgery and UFT, 300mg/day for 6 months) and a high-dose group (MMC, 8mg/m² on the day of surgery and at 4, 10, 16, 22 weeks after surgery and UFT, 600mg/day for 6 months). The disease-free survival rate of the patients in the high-dose group was significantly higher than that of those in the low-dose group, although the differences in overall survival rates were not significant. The survival rates of patients with positive nodes without serosal invasion: n(+) and ps(-), were significantly higher in the high-dose group than in the low-dose group. These reports suggest that adjuvant chemotherapy with fluoropyrimidines should be carefully designed to achieve an effective dose intensity of 5-FU in the blood.

Chemoimmunotherapy

The results of adjuvant chemoimmunotherapy trials in Japan reported since 1984 are summarized in Table 3

[29–37]. Immunostimulators, such as PSK and OK-432, have been widely used in Japan during the past two decades. In an early study reported in 1984, Fujimoto et al. [29] and Niimoto et al. [30] evaluated the effectiveness of schizophyllan or levamisole, respectively, in addition to MMC plus FT. They found no significant survival advantage for chemoimmunotherapy, except for stage III patients. Koyama et al. [31] published the results of a randomized clinical study comparing FT and FT plus *Nocardia rubra* cell wall skeleton. In that study, the survival rate was significantly higher in the chemoimmunotherapy group. Niimoto et al. [32] investigated the effect of PSK with adjuvant chemotherapy for gastric cancer. PSK, a protein-bound polysaccharide (β -D glucan) extracted from the mycelia of *Criolus versicolor* of the Basidiomycetes, is known to induce interleukin (IL)-1, IL-6, and IL-8, as well as tumor necrosis factor and macrophage chemotactic factor. A total of 579 patients were randomized to either MMC + PSK, MMC + FT, or MMC + FT + PSK groups. The difference in 5-year survival rates among the three arms was significant. We also observed a survival advantage at 15 years in treated patients who received MMC + FT + PSK [18]. In particular, adjuvant chemoimmunotherapy was effective in patients with ps(+) / n(-) or ps(-) / n(+). In 1994, Nakazato et al. [35] published the final results of a randomized control trial performed to examine the efficacy of PSK in gastric cancer when com-

Table 3. Adjuvant chemoimmunotherapy for gastric cancer in Japan

Author (year)	No. of patients	Treatment	Percent survival/years	P value	Suggested data
Fujimoto [29] (1984)	169 157	A: MMC + FT B: MMC + FT + schizophyllan	55/3 55/3	NS	Stage III A < B; P = 0.08
Niimoto [30] (1984)	77 78	A: MMC + FT B: MMC + FT + LV	75/2 80/2	NS	Stage III A < B; P < 0.01
Koyama [31] (1986)	98 115	A: FT B: FT + N-CWS	60.2/5 73.2/5	<0.05	
Niimoto [32] (1988)	189 199 191	A: MMC + PSK B: MMC + FT C: MMC + FT + PSK	64.1/5 58.5/5 71.5/5	<0.05	
Hattori [33] (1990)	1357 1426 1363 1338	A: MMC + FT B: MMC + FT + PSK C: MMC + FT + PCB D: MMC + FT	62.6/3 71.6/3 68.7/3 69.1/3	NS	
Maehara [18] (1990)	137 118	A: MMC + FT + PSK B: Control	56.9/15 47.5/15	<0.035	
Niimoto [34] (1990)	45 51	A: MMC + FT B: MMC + FT + Bestatin	37.6/7 56.5/7	NS	ps(+) A < B; P < 0.05
Nakazato [35] (1994)	129 124	A: MMC + 5-FU B: MMC + 5-FU + PSK	60/5 73/5	P = 0.044	
Sugimachi [36] (1997)	100 96	A: MMC + UFT (md) + PSK B: MMC + UFT (hd) + PSK	58.6/5 69.4/5	<0.05	

NS, Not significant; LV, Leucovorin; N-CWS, *Nocardia rubra*; PCB, picibanil (OK-432)

bined with postoperative adjuvant chemotherapy of MMC + 5FU. This trial was carefully designed, focusing on the category of patients with positive purified protein derivative of tuberculin (PPD) skin test, T2 or T3 tumors, and pathologically proven curative surgery. The overall 5-year survival rates were 73.0% for the PSK arm and 60.0% for the control arm, with a significant difference. We recently demonstrated the impact of dose intensity of UFT combined with MMC + PSK on the survival of patients with curative surgery [36]. Patients prescribed higher doses of UFT survived for significantly longer, with a lower peritoneal recurrence rate. This result demonstrated that dose intensity is crucial in adjuvant chemotherapy for patients with gastric cancer for achieving a decrease in the recurrence rate and an improvement in the survival rate.

Western postoperative adjuvant chemotherapy trials

The results of Western studies published since 1980 are summarized in Table 4 [37–52]. There were few studies that demonstrated survival benefits of postoperative adjuvant chemotherapy over surgery alone. The 5-year survival rates for surgery alone ranged from 20% to 40%. In these patients, it is questionable whether or not curative surgery had been conducted, and it seems to be difficult to achieve positive results with postoperative adjuvant chemotherapy in these patients with a poor prognosis. In 1983, Alcobendas et al. [39] reported on a trial that compared treatment with MMC to observation alone after surgery. Although there was a significant survival advantage for treatment with MMC, the number of patients was very small and the follow-up

Table 4. Adjuvant chemotherapy for gastric cancer: Western trials

Author (year)	No. of patients	Treatment	Percent survival/years	<i>P</i> value	Suggested data
Hugier [37] (1980)	27 26	A: 5-FU/VBL/CPA B: Control	18/5 18/5	NS	
Douglass [38] (1982)	71 71	A: 5-FU/Me-CCNU B: Control	45/5 32/5	<i>P</i> = 0.06	
Alcobendas [39] (1983)	33 37	A: MMC B: Control	79/5 38/5	<i>P</i> < 0.001	
Higgins [40] (1983)	156 156	A: 5-FU/Me-CCNU B: Control	38/5 39/5	NS	
Engstrom [41] (1985)	91 89	A: 5-FU/Me-CCNU B: Control	57/2 57/2	NS	
Schlag [42] (1987)	42 53	A: 5-FU/BCNU B: Control	57/5 43/5	NS	
Allum [43] (1989)	141 140 130	A: MMC/5-FU B: MMC/5-FU/CMFV C: Control	11/5 17/5 12/5	NS	
Coombes [44] (1990)	133 148	A: FAM B: Control	45/5 35/5	NS	T3,4 A > B (<i>P</i> = 0.04)
Krook [45] (1991)	61 64	A: 5-FU/ADM B: Control	32/5 33/5	NS	
Grau [46] (1993)	68 66	A: MMC B: Control	41/5 26/5	<0.025	
MacDonald [47] (1995)	93 100	A: FAM B: Control	37/5 32/5	NS	
Lise [48] (1995)	155 159	A: FAM B: Control	43/5 40/5	NS	
Neri [49] (1996)	48 55	A: 5-FU/Epi/FA B: Control	13/3 25/3	<0.01	
Tsavaris [50] (1996)	42 42	A: FEM B: Control	— —	NS	
Grau [51] (1998)	45 40	A: MMC B: MMC + FT	44/5 67/5	<i>P</i> = 0.04	
Cirera [52] (1999)	76 72	A: MMC + FT B: Control	56/5 36/5	<i>P</i> = 0.04	

NS, Not significant; VBL, vinblastine; CPA, cyclophosphamide; Me-CCNU, smustine; BCNU, carmustine; CMFV, cyclophosphamide, methotrexate, 5FU, vincristine; FAM, 5FU + ADM + MMC; ADM, doxorubicin; Epi, epirubicin; FA, folinic acid; FEM, 5FU + Epi + MMC

was too short to allow for definitive conclusions. In 1993, Grau et al. [46] reported on 134 patients randomized to receive either MMC or no treatment after gastrectomy. In accordance with the earlier study, survival was significantly better in the MMC group compared with the nontreatment group. Grau et al. [51] reported their results for 85 patients who were randomized to receive either MMC plus FT or MMC alone. An improved 5-year survival rate was demonstrated for the MMC plus FT group. Coombes et al. [44] studied the effect of 5-FU, Adriamycin, and MMC (FAM) in a prospective randomized adjuvant trial of 281 patients with curative resection who were allocated to FAM treatment or no treatment. Although there was no significant difference in disease-free or overall survival, subgroup analysis revealed better survival rates for the T3-T4 treated patients. In another adjuvant chemotherapy trial, reported by Neri et al. [49], 103 node-positive patients who underwent curative gastric resection were randomized to either observation or to administration of combination chemotherapy with epirubicin, 5-FU, and folinic acid for 7 months; a survival advantage was found for patients receiving the chemotherapy. Cirera et al. [52] reported significantly better overall and disease-free survivals in a group of resected stage III gastric cancer patients who were treated with MMC 20mg/m² and oral FT 400mg daily for 3 months when compared with surgery alone. These studies suggested the potential benefits of adjuvant chemotherapy for resected gastric cancer.

Meta-analysis

In general, meta-analysis is a way of providing the highest level of statistical evidence among pooled data derived from several clinical trials, and is, thus, most reliable.

In 1993, Hermans and colleagues [53] published the results of a meta-analysis of 11 randomized trials reported between 1980 and 1991, in which postoperative adjuvant chemotherapy for gastric cancer was compared with surgery alone. As a result of the analysis, they found no definitive improvement in the survival of patients who received postoperative adjuvant chemotherapy (odds ratio, 0.88; 95% confidence interval [CI], 0.78–1.08). Pignon et al. [54] criticized the results of this meta-analysis for its choice of trials. In response, Hermans and Bonenkamp [55] published an update of their analysis, with the odds ratio (OR) being significant (OR, 0.82; 95% CI, 0.68–0.97) in 1994. Nakajima et al. [56] suggested a significant survival benefit for MMC-based adjuvant chemotherapy compared with surgery alone as a result of the meta-analysis of six randomized trials that included 1177 gastric cancer patients who underwent curative surgery (OR, 0.63; 95% CI, 0.51–0.79). Recently, Earle and Maroun [57] evaluated the

effect of adjuvant chemotherapy in gastric cancer by the meta-analysis of 13 randomized control trials performed in non-Asian countries. They found a significant survival benefit for patients with adjuvant chemotherapy over patients with surgery alone, with an OR of 0.80 (95% CI, 0.66–0.97). Subgroup analyses indicated a trend towards a larger magnitude of the effect when analysis was restricted to trials in which at least two-thirds of the patients had node-positive disease. Mari et al. [58] presented the results of a meta-analysis of 20 randomized trials with a surgery-alone control arm. They also demonstrated the survival impact of adjuvant chemotherapy on curative surgery for gastric cancer, with an OR of 0.82 (95% CI, 0.75–0.89). They suggested a trend of favorable results in 5-FU-based regimens, and of unfavorable results in adriamycin-including regimens.

These meta-analysis results suggest that a possible survival advantage of adjuvant chemotherapy after curative surgery for gastric cancer may be proven by a well designed clinical trial comparing adjuvant chemotherapy with observation alone following curative surgery, in which a sufficient number of patients is enrolled and effective chemotherapeutic regimens with sufficient dose intensity are employed.

Ongoing studies and future prospects

In general, with the systemic treatment regimens available in the past, no major decrease in recurrence rates has been shown. The efficacy of treatment with routine postoperative systemic chemotherapy remains unproved. Several new approaches are currently undergoing intensive studies.

Early Japanese trials enrolled patients at all stages of disease and yielded inadequate samples, which may account for the nonsignificant results. Early-stage gastric cancer could be cured by surgery alone. By contrast, late stage cancer resulted in an excessive residual tumor burden, even after surgery. Subset analyses of past trials indicated that adjuvant chemotherapy may show a survival advantage for moderately locally advanced gastric cancer, such as stages II or III. Thus, early- or late-stage gastric cancers might be excluded from clinical trials in an adjuvant setting. The National Surgical Adjuvant Study (NSAS)-gastric cancer (GC) trial was designed, based on subset analysis of the results of Nakajima et al. [20], which contained the agent UFT [59]. In the NSAS-GC trial, patients with pathologically proven curative surgery for gastric cancer with negative serosal invasion (t2) and positive nodes (n1 or n2) are divided into two groups: UFT treatment (360mg/m² for 16 months) and surgery alone, and the survival and toxicity profiles of the groups will be compared.

Chemotherapy plus concurrent radiation has recently attracted much attention in the United States. An inter-

group 116 trial was conducted to test the hypothesis that postoperative chemoradiation therapy would decrease the risk of recurrence and, thereby, increase the cure rate for patients with resected gastric cancer [60]. This trial included 556 patients with stages Ib–IV gastric cancer, who were divided into 275 patients receiving surgery alone (control) and 281 patients treated with 5-FU plus leucovorin (LV) and irradiation (4500cGy) [61]. A significant prolongation of the median survival was noted, with 35 months for the treatment group and 28 months for the control. Analysis of the failure pattern in the study suggested that adjuvant chemoradiation suppressed locoregional relapse. These results indicated that 5-FU + LV + radiation is a candidate for a standard adjuvant treatment regimen for locally advanced gastric cancer, but lymph node dissection was inadequate for enrolled patients with D1 of 36% and D2 of 10%. Surgical treatment with D2 dissection could decrease the need for radiation.

One of the new approaches taken in an attempt to improve the survival of patients undergoing curative gastrectomy is the use of preoperative (neoadjuvant) systemic chemotherapy. The goal of these treatment plans is to allow an early attack on systemic micrometastatic disease and, by downstaging the primary tumor, to increase the percentage of patients who are able to undergo curative resection. A number of phase II trials have been performed to investigate the potential of preoperative chemotherapy to influence the outcome for patients with gastric cancer [62–64]. A positive impact on prognosis was claimed. Lowy et al. [65] analyzed three phase II studies and showed response rates of 24%–38% and a rate of curative resection of 73%. With multivariate analyses, they demonstrated that the effect of neoadjuvant chemotherapy was the only prognostic factor. Recently, a small-scale phase III trial was reported by Kang et al. [66], using neoadjuvant chemotherapy followed by surgery vs surgery alone for locally advanced gastric cancer. While the curative resection rate was significantly higher and the postoperative stage was significantly lower for the neoadjuvant group, there was no significant difference in overall survival. Thus, this approach, although promising, requires definitive random phase III trials with a higher statistical power before a firm conclusion can be reached. Preoperative chemoradiation using continuous 5-FU (300mg/m²) with 45Gy for potentially resectable gastric cancer has been conducted in an attempt to improve locoregional control and overall survival [67]. Preliminary results showed an overall median survival of 34 months and disease-specific survival greater than 60% at 4 years, with a high rate of tumor downstaging, and without significant preoperative toxicity.

Another approach is the delivery of chemotherapy directly to the peritoneal space [9]. The rationale for the use of this administration route is based on the finding

that more than half of the recurrence sites after curative surgery are in the peritoneal space. The rates of peritoneal recurrence in both treatment and control arms have seemed to be similar in adjuvant intravenous therapy studies. The pharmacokinetic advantages of intraperitoneal (IP) chemotherapy have been well described. Drug concentrations within the peritoneal cavity are from severalfold to one to two logs higher than the concentrations that can be achieved by oral or intravenous administration. IP chemotherapy has also been shown to be capable of treating both peritoneal and liver micrometastasis in a rat model [68]. In the clinical setting, Hagiwara et al. [69] reported a significant improvement in 3-year survival (69% vs 27%, surgery alone) in patients treated with IP administration of carbon-absorbed MMC at surgery. An Austrian randomized multicenter trial, however, could not determine any improvement in survival, and found an increased rate of postoperative complications with the same drug [70]. Schiessel et al. [71] and Sautner et al. [72] performed IP cisplatin treatment and concluded that IP cisplatin had no significant impact on recurrence. More recently, Sugarbaker and Yonemura [73] reviewed the clinical results of several IP studies reported for gastric cancer with peritoneal seeding. Although not all those treated were in an adjuvant setting, these investigators stressed the value of an aggressive surgical approach, including gastrectomy with peritonectomy, to eliminate all visible implants, combined with perioperative IP chemotherapy, for selected patients.

Future trials may evaluate the use of recently developed new cytotoxic agents, such as TS-1 [74–76], irinotecan [77], paclitaxel [78], and docetaxel, [80] either alone or in combination (Fig. 1). Among these, the oral 5-FU prodrug, TS-1, FT-gimstat-otastat potassium, has shown significant activity in the treatment of advanced gastric cancer, with response rates of 49%. In addition, the response rate to TS-1 is further enhanced, to more than 70%, by combination with cisplatin [80]. This drug has been developed to increase the antitumor effect by inhibiting dihydropyrimidine dehydrogenase (DPD) activity, with gimstat, and also to decrease the

Fig. 1. Possible combinations of anticancer drugs for adjuvant chemotherapy

adverse effect by protecting the gastrointestinal tract, with otastat potassium, thus resulting in a pharmacokinetic profile similar to that of continuous venous 5-FU infusion and with less toxicity and improved patient quality of life [81]. A recent report demonstrated both survival and toxicity advantages for continuous infusion over bolus infusion of 5-FU [82]. Because orally administered agents have pharmacokinetics that approximate those of continuous infusion without the patient inconvenience and morbidity associated with indwelling catheters and infusion pumps, oral preparations of fluoropyrimidines have several advantages when employed in an adjuvant setting and are now attracting considerable attention from oncologists worldwide [81]. Several clinical trials of adjuvant chemotherapy using such oral fluoropyrimidines in Japan have so far failed, however, to show a firm survival advantage for gastric cancer. This could be attributable to the low-dose intensity of the chemotherapy. Danno et al. [28] and Sugimachi et al. [37] demonstrated significant survival advantages by giving higher doses of UFT (600mg/day) compared with lower doses of UFT (300–400mg/day), although the hematological and/or gastrointestinal toxicities increased in the higher-dose of UFT group. In patients with advanced colorectal cancer, a clear relationship between the 5-FU plasma level and efficacy has been noted [83]. With appropriate doses of fluoropyrimidines, an effective 5-FU plasma level, resulting in improved patient survival, can be achieved. Because TS-1 has a more nearly ideal profile with regard to both the increase of antitumor effects and the decrease of adverse effects compared with UFT, TS-1 could be a potential candidate for future adjuvant chemotherapy for gastric cancer. A pilot study of TS-1 in an adjuvant setting is now underway to evaluate the feasibility of this drug as an adjuvant chemotherapeutic agent.

Irinotecan, an inhibitor of DNA topoisomerase I, is also a unique and attractive agent, developed in Japan, and it has been investigated in combination with cisplatin. Boku et al. [84] reported that the response rate of patients treated with irinotecan and cisplatin without prior chemotherapy was 59%, with a median survival time of 11 months. Severe side effects of the combination were also noted, so that the feasibility of the use of this combination chemotherapy as an adjuvant treatment must be evaluated in future trials. Paclitaxel and docetaxel, novel taxoids which act as mitotic spindle poisons and induce a mitotic block, have potent antineoplastic activities. These taxoids, when combined with cisplatin and/or 5-FU, showed response rates of more than 50%, and could be attractive tools in an adjuvant setting for gastric cancer [85,86].

To date, no definitive conclusion has yet been drawn from randomized clinical trials of adjuvant chemo-

therapy for gastric cancer, because few studies have shown a significant positive impact on survival as compared with surgery alone. The negative results of most previous clinical studies do not necessarily mean that the adjuvant chemotherapy approach to gastric cancer treatment is not working. The positive data from meta-analyses may suggest potential survival advantages of adjuvant chemotherapy, but these must be proven in future by well designed clinical trials comparing adjuvant chemotherapy vs surgery alone, in which sufficient numbers of patients are enrolled and effective chemotherapeutic regimens with appropriate dose intensity are employed.

Newly developed anticancer agents and/or newer therapeutic combinations or strategies (neoadjuvant chemotherapy, chemoradiotherapy, intraperitoneal chemotherapy) have the potential to benefit high-risk patients.

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