Anti-Cancer Drugs, 2, pp. 433–445

Review paper

Adjuvant treatment for gastric cancer

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In spite of progress made in surgical techniques and intensive care, only a slight improvement in the therapeutic control of gastric carcinoma has been achieved in the last 20 years. In this paper we present a review of controlled clinical trials on adjuvant chemotherapy and chemo-immunotherapy for gastric cancer and this topic is discussed in the light of our experience and that of the Gastrointestinal Group of the European Organization for Research and Treatment of Cancer. The results of adjuvant therapy are less satisfactory in Western countries than in Japan. The efficacy of the 5-fluorouracil + adriamycin + mitomycin C regimen in advanced gastric cancer has not been confirmed in an adjuvant setting. The therapeutic benefit reported in Japanese studies may be due to a chemotherapy started intraoperatively or during the immediate postoperative period and should also be considered in the light of a standardized surgical treatment. The new therapeutic trends, using recent chemotherapeutic associations tested in Phase I and II clinical trials or combining traditional chemotherapy with different types of immunostimulators, are discussed. Only when large-scale clinical studies have been made will it be possible to confirm their therapeutic efficacy.

Key words: Adjuvant chemotherapy, chemo-immunotherapy, immunotherapy, stomach neoplasms.

Introduction

Epidemiological data show a significant spontaneous reduction in mortality from gastric cancer in Western countries, probably as a consequence of ill-defined environmental changes.[1–4] Yet, in the last decades only a slight improvement has been achieved in the therapeutic control of the disease. The only possibility of cure lies in surgery. After curative surgery, survival in Western countries is only 40% for stage II and 20% for stage III patients.[5–7] In Japan, where the incidence of stomach cancer is still very high, these figures are, respectively, 70 and 40%; this is probably the combined effect of mass early detection and standardized surgery.[8,9]

Patterns of relapse after 'curative' surgery show a high frequency of distant metastases calling for a systemic adjuvant treatment, but also a high incidence of recurrences in the gastric bed,[10–18] showing the need for effective locoregional control of the tumor.[19] To achieve this, 'adequate' surgery is probably the most important factor. Adjuvant external radiotherapy has been used only sporadically in clinical trials due to alleged technical difficulties,[20,21] while intraoperative radiotherapy has only recently been introduced and is not yet widely available.[22–29]

The first attempts at multimodal treatment using chemotherapy were made in the 1940s, but the series included a large percentage of patients with residual disease after surgery.[30–34] In the 1970s the idea of 'minimal residual disease' was introduced for gastric carcinoma,[35] as well as for other forms of neoplasia.[36,37] Meanwhile, experimental studies demonstrated the efficacy of systemic treatment as a preventive measure against metastases after removal of the primary tumor.[38] This prompted an increase in the number of proposals for adjuvant therapy protocols based either on drugs active in advanced disease, or on chemo-immunotherapy.

Now adjuvant chemotherapy is widely used, although any positive effect it may have has not

Supported in part by a grant from Regione Veneto (39550/6100).

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yet been demonstrated by clinical trials. In Japan the benefit of adjuvant chemotherapy is usually taken for granted so most clinical trials are run without a control arm. We review here the results of clinical studies on adjuvant therapy for gastric cancer and discuss future possibilities in the light of our experience and that of the Gastrointestinal (GI) Group of the European Organization for Research and Treatment of Cancer (EORTC).

The importance of adequate surgery

Resection is still the only available therapeutic option for most solid tumors, including gastric cancer. Adequate treatment of the primary tumor appears to be related both to the stage of disease and the extent of surgery. Patients who relapse after gastrectomy for carcinoma can present distant metastases but in 26–83% of cases locoregional recurrences also occur.[10–18] This indicates that when surgery is performed, some patients already have disseminated disease, but in some, residual disease is left in the gastric bed. On the other hand, if tumor spread is only locoregional, 'adequate' surgery can encompass the entire tumor and be 'curative'.

The concept of 'radical' surgery for solid tumors entails: resection of the organ bearing the tumor, disease-free margins, en-bloc resection of organs 'adhering' to the neoplasia and en-bloc locoregional lymphadenectomy. In gastric cancer, few authors agree on the extent of the latter, due to the difficulty of making an accurate intraoperative evaluation of lymph node involvement.[39–44] Standardized lymphadenectomy, used for other solid tumors, would be preferable.[8,9,45–49] However, as yet there is no agreement as to the degree of standardization (R1, R2 or R3).[8,50–54] Randomized studies comparing R1 with R2 have either failed to show any difference[53] or are still ongoing.[55] Japanese authors maintain that extended lymphadenectomy is an essential means for achieving good results in the surgical treatment of gastric cancer and sustain that the excision of N2 lymph nodes (R2) is 'adequate' from an oncological viewpoint and should be adopted as a standard method.[8,9,46,49,56] A retrospective analysis of the quality of surgery in the EORTC protocol N. 40813 indicated that R2 lymphadenectomy may provide a good compromise between adequacy of surgery and the number of surgical complications,[57] also in Western countries.

Adjuvant chemotherapy

Although gastric carcinoma is less sensitive to chemotherapy than other tumors, such as breast cancer and lymphoma, it responds better to chemotherapy than all the other gastrointestinal tumor types. The first randomized controlled clinical studies on adjuvant chemotherapy, made in the 1960s, used monochemotherapy regimes (Table 1). In two subsequent studies thio-thepa was proposed with different modalities of administration (intraportal, intraperitoneal, intravenous), at different doses.[30,32,58,59] In both studies, about 35% of the patients had undergone palliative resection. In none of these studies was a significant difference observed between the survival of treated patients and controls (Table 1). However, in the first part of the Veteran's Administration Surgical Oncology Group (VASOG) study (1965)[30] an improvement in survival was observed in a subgroup of patients who underwent total gastrectomy ($p < 0.035$). However, this was a limited subgroup, and these results were not confirmed in the second part of the study (1977)[59] after a median follow-up of 14 years. Moreover, the postoperative mortality of treated patients was significantly ($p < 0.01$) higher than that of controls (23% vs 9%).

In another VASOG study,[33,59] which utilized fluorodeoxyuridine (FUDR) for monochemotherapy, no significant survival differences at 3 and 6 years were found between treated patients and controls. About 40% of patients, however, had undergone palliative resection.

In the mid-1970s polychemotherapy was found to give better results than monochemotherapy for advanced gastric cancer, and polychemotherapy protocols were then utilized for adjuvant treatment (Table 1). Huguier *et al.*[60] found no difference between operated patients treated with a new regimen (5-FU + vinblastine + cyclophosphamide), and controls with curative surgery alone. As encouraging results were obtained in advanced gastric carcinoma by associating 5-fluorouracil (5-FU) and nitrosurea,[61] this regimen was proposed in four controlled clinical trials[14,18,62,63] started in the 1980s (Table 1). Results reported were, however, contradictory. In VASOG, Eastern Cooperative Oncology Group (ECOG) and German studies, no significant differences were found either for 2–3.5- or 6.5-year survivals or disease-free intervals, while the Gastrointestinal Tumor Study Group (GITSG) found a significant difference ($p = 0.03$) between the 5-year survival of treated patients (47%) and that of controls (33%). The

Table 1. Adjuvant chemotherapy: Western countries experience

Trial	No. of patients	Survival (%)	Survival (y)	Comments	Reference
Thio-thepa	195	18.0	5	NS. Palliative surgery in 33%. Postoperative mortality higher in treated patients (23% vs 9%; $p < 0.01$).	30, 59
Control	250	20.0	5		
Thio-thepa	142	22.0	5	NS	32, 58
Control	135	24.0	5		
FUDR	217	16.6	5	NS. Palliative surgery in 39%.	33, 59
Control	241	15.4	5		
5-FU + CPA + VBL	27	16.0	5	NS. Small number of patients.	60
Control	26	18.0	5		
Me-CCNU + 5-FU	71	47.0	5	$p = 0.03$	14
Control	71	33.0	5		
Me-CCNU + 5-FU	66	37.8	3.5	NS	62
Control	68	38.9	3.5		
Me-CCNU + 5-FU	91	57.0	2	NS	63
Control	89	57.0	2		
BCNU + 5-FU	42	57.0	6.5	NS	18
Control	53	43.0	6.5		
Me-CCNU + 5-FU + ADR	31	29.0	5	NS. Small number of patients.	66
Control	35	37.0	5		
Me-CCNU + 5-FU	169	30.0	5	NS. Severe toxicity in 50%	67
5-FU + Me-CCNU + ADR		30.0	5		
5-FU + ADR	59	52.0	4	NS.	68
Control	61	51.0	4		
MMC	33	30.0	2	$p < 0.001$. Small number of patients and short follow-up.	69
Control	37	76.0	2		
5-FU + MMC	141	12.0	8	NS. Mean follow-up 100 months. Palliative surgery in 30%.	70, 71
5-FU + MMC + IND	140	11.0	8		
Control	130	15.0	8		
FAM	180	No data		No data	7
Control					
FAM	300	No data		No data	84
Control					
FAM	133	45.7	5	NS. T3-T4: higher survival in treated patients (41.4% vs 22.8%; $p = 0.04$).	85, 86
Control	148	35.4	5		
FAM2	153	40.0	5	NS. Adequate surgery major prognostic factor ($p < 0.01$).	93
Control	159	40.0	5		

FUDR, fluorodeoxyuridine; 5-FU, 5-fluorouracil; CPA, cyclophosphamide; VBL, vinblastina; Me-CCNU, semustine; BCNU, carmustine; ADR, adriamycin; MMC, mitomycin C; IND, cyclophosphamide + 5-FU + vincristina + methotrexate (MTX); FAM, 5-FU + ADR + MMC; FAM2, 5-FU + ADR + MMC (high doses). NS, not significant.

discrepancies between findings reported for survival of patients not submitted to chemotherapy and recurrences in treated patients and controls[18] probably depend on the different staging criteria used in the four studies for the selection of gastric cancer patients and on differences in follow-up systems used. In all these studies, moreover, the overall numbers of randomized patients were limited. It is important to stress the recent finding of long-term toxicity induced by nitrosurea in adjuvant therapy, with 12% of patients developing leukemia.[64] Data on survival and toxicity confirm that 5-FU + nitrosurea should 'not be recommended as standard postoperative therapy'.[65]

In two subsequent studies made in Spain[66] and in the USA,[67] adriamycin (ADR) was added to

5-FU + nitrosurea (Table 1). In the GITSG study,[67] which had no control arm, no significant differences were found between ADR+ and ADR− patients, and 50% of all patients presented severe toxicity. Nor were findings from the Estrada trial significant,[66] although only a small number of patients were studied. The North Central Cancer Therapy Group (NCCTG) used combined 5-FU + ADR in a randomized study of 120 patients,[68] but failed to demonstrate statistically significant differences between treated patients and controls after a median follow-up of 4 years (Table 1).

Following significant findings reported by Japanese authors (Table 2), mitomycin C (MMC) was utilized in controlled clinical studies, both as monochemotherapy and in association with other drugs. In a controlled clinical study of 70 patients who underwent radical surgery, Alcobendas *et al.*[69] found a statistically significant survival difference ($p < 0.001$) at 2 years between the treated patients and controls (70% and 30% survival, respectively) (Table 1). The drawbacks of this trial were that T4 patients were excluded from the study, the series was small and the follow-up short. Nor were findings confirmed in a recently completed randomized study made by the British Stomach Cancer Group (BSCG) on 411 patients[70,71] with a 100 month follow-up (Table 1). In this study, however, unlike that of Alcobendas *et al.*, 30% of patients had positive resection margins, residual disease or distant metastases.

Of the polychemotherapy protocols for the treatment of advanced gastric carcinoma proposed between 1974 and 1980, the most effective was FAM (5-FU + ADR + MMC), first attempted by McDonald *et al*,[72] who reported response percentages ranging from 42 to 45, with acceptable levels of toxicity. Subsequent studies on advanced gastric cancer have confirmed the efficacy of this therapeutic regimen, reporting responses ranging from 17 to 55% (mean 33%) in 453 patients.[72–83] FAM was therefore proposed in a number of controlled clinical studies (Table 1), but the results of two, made in the USA, on 180 and 300 patients, respectively, are not yet available.[7,84] In a study completed in 1990 by the International Collaborative Cancer Group (ICCG),[85,86] no statistically significant difference was found in the survival and disease-free interval between treated patients and controls. These authors, however, maintain that there is a trend in favor of the treated patients (45.7% vs 35.4% at 5 years) and that in T3–T4 patients there is a statistically significant survival difference (41.4% vs 22.8%, $p < 0.04$). However, analysis of subgroups can be misleading,[87] and these results should be re-evaluated in future studies.

A 60% response rate in patients with advanced gastric carcinoma was reported with FAM2, a modified version of the original FAM made by increasing drug doses and reducing the interval between cycles.[88] FAM2 was therefore proposed for adjuvant therapy in a controlled clinical study (40813) by the GI group of the EORTC.[89–91] The study, completed in August 1989, included 312 evaluable patients who had undergone radical surgery for gastric tumors (stages II and III according to the Union Internationale Contre le Cancer (UICC), 1978) at 28 institutions in eight countries in Europe.[92] Even though a higher rate of recurrence was found in the control arm, no statistically significant difference was found ($p = 0.65$) between treated patients and controls (mean follow-up 4 years).[93,94] Nor was any difference found when patients were analysed by stage of disease.

Japanese experience

In Japan, the drug most frequently used since 1960 has been MMC, alone or combined with other drugs and/or immunostimulators.[31,95] Among the earlier trials reported in the literature (Table 2), Imanaga's study analyses the results from about 2000 patients randomized over 10 years at 19 different centers.[96] Patients were divided into four treatment groups, each with a control arm. Surgery was palliative in 35% of cases. Only in the group treated with medium dose MMC, was a significant survival difference observed at 8 years between treated patients and controls (73.6% vs 53.9%). When only stage II patients were considered, the difference was even greater (75% vs 42%). In the remaining three groups, MMC (different doses) alone or combined with cyclophosphamide or with cytosine-arabinoside failed to show any advantage with respect to controls.

Another four randomized clinical studies[97–100] utilized MMC combined with i.v. or oral fluoropyrimidine (5-FU) and in two studies also with cytosine-arabinoside (Table 2). Only one study had a control arm. None demonstrated statistically significant differences in the overall survivals between treated patients and controls. However, when particular subgroups are considered, such as patients with positive lymph nodes (n+) or with a tumor involving the serosa (ps+), treated patients have a better survival than controls. Importantly, any advantage of adjuvant therapy found in Japanese trials should be considered in the

Table 2. Adjuvant chemotherapy: Japanese experience

Trial	No. of patients	Survival (%)	Survival (y)	Comments	Reference
MMC (md)	242	63.6	8	NA. Palliative surgery in 35%.	96
Control	283	53.9	8		
MMC (hd)	255	58.5	8	NS. Palliative surgery in 35%.	96
Control	265	56.9	8		
MMC + CPA	146			NS. Palliative surgery in 35%	96
MMC	135				
Control	152				
MMC (md)	197	73.5	3	NS. Palliative surgery in 35%.	96
MMC + 5-FU + AraC	208	68.9	3		
Control	217	68.5	3		
MMC (hd)	1045	46.7	5	NS. Palliative surgery in 25%.	97
MMC (md) + FT		47.3	5		
MMC (hd)	760	54.6	5	NS. Stage III: FT(−) 39.7%, FT(+) 48.7%	97
MMC (hd) + FT		56.1	5	($p < 0.05$); n(+) ps(+): FT(−) 27.%, FT(+) 35.8% ($p < 0.05$). Palliative surgery in 25%.	
MFC + F1	73	68.4	5	NS. Stage III: MFC 56.1%, MFIC 44.7%, control	98
MF1C + F1	76	62.5	5	35.3% ($p < 0.05$).	
Control	74	51.4	5		
MMC (A)	925	52.1	5	NS. Stage III: MMC 34.2%, MMC + FT 50.4%,	99
MMC + FT (B)	965	54.1	5	FT 41.4% (B vs A: $p < 0.001$, C vs A: $p < 0.017$).	
FT (C)	983	53.4	5		
MFC + F1		78.2	3	NS.	100
MFC + F1	507	76.4	3		
MF + UFT		70.1	3		

MMC, mitomycin C; CPA, cyclophosphamide; 5-FU, 5-fluorouracil; AraC, cytosine-arabinoside; MFC = MMC + 5-FU + AraC; FT, Fl, ftorafur, 5-FU oral; MFIC, MMC + FT + AraC; MF, MMC + 5-Fu; UFT, combined drug of uracil and tegafur.
md, medium dose; hd, high dose.
n(+), positive lymph nodes; ps(+), serosa involvement.
NA, not available; NS, not significant.

light of the fact that it is given to patients with minimal residual disease due to early diagnosis and adequate surgery. Moreover, in several Japanese studies MMC is given in the early postoperative period when the burden of residual tumors should be minimal.[101] However, adjuvant chemotherapy is at present used in Japan on a routine basis on the assumption that it is beneficial.

Chemoimmunotherapy

The first studies on immunotherapy for cancer were made in the late 1960s, when it was discovered that melanoma and leukemia in infants regressed following Bacille Calmette-Guerin (BCG) treatment.[102,103] Afterwards, a non-randomized study was made of 121 resected colorectal patients treated with adjuvant BCG, and it was found that their disease-free intervals and survivals were better than those of historic controls.[104] The findings, however, were not confirmed in controlled clinical studies,[105–107] and so this immunostimulator was no longer used. Like patients with other types of neoplasia, patients with gastric carcinoma have a depressed cell-mediated response proportional to the disease stage.[108] However, contradictory results have been reported following the use of different immunostimulators.

The first randomized studies on chemoimmunotherapy were made in Japan in the 1980s (Table 3). Different types of immunostimulators have been used: bacterial extracts from *Schizophyllum commune*,[109] *Nocardia rubra*,[110,111] and *Streptococcus piogenes*;[112–114] extracts from funguses, such as *Streptomyces olivoreticuli*[115] and *Coriolus versicolor*;[114,116–119] and chemicals, such as levamisole[117,120,121] and polyadenylic-polyuridylic acid.[122,123]

In six controlled clinical studies, five in Japan[109,110,114–116] and one in Europe,[113] different

Table 3. Adjuvant chemoimmunotherapy in gastric cancer

Trial	No. of patients	Survival (%)	Survival (y)	Comments	Reference
MMC + FT	169	55	3	NS. Palliative surgery in 33%.	109
MMC + FT + SPG	157	55	3	Stage III: SPG(−) 50%, SPG(+) 63% ($p < 0.08$). Palliative surgery: SPG(−) 0%, SPG(+) 57% ($p < 0.002$).	
MFC + FT	90	80	2	NS. Palliative surgery: N-CWS(−) 26.9%, N-CWS(+)	110
MFC + FT + N-CWS	97	80	2	65.3% ($p < 0.01$).	
FT	98	60.2	5	$p < 0.05$. Stage III and IV: N-CWS(−) 28.8%, N-CWS(+)	111
FT + N-CWS	115	73.2	5	52.4% ($p < 0.002$).	
MFC or FME + PCB	74	44.6	5	$p < 0.05$. Only patients with subtotal gastrectomies.	112
Control	64	23.4	5		
MFC	53	45	4.5	NS	113
MFC + PCB				T2-T3: treated patients 45%, controls 30% ($p < 0.05$).	
Control	34	29	4.5		
MMC + FT	1357	62.6	3	NS	114
MMC + FT + PSK	1426	71.6	3		
MMC + FT + PCB	1363	68.7	3		
MMC + FT + PSK + PCB	1338	69.1	3		
MMC + PSK	49	46.4	3	NS. Some patients palliative surgery.	116
MMC + FT	28	46.1	3	Stage III: PSK + FT 100%, FT 44.4%, PSK 34%.	
MMC + PSK + FT	33	62.0	3		
MMC + PSK	189	64.1	5	$p < 0.05$	118
MMC + FT	199	58.5	5		
MMC + PSK + FT	191	71.7	5		
MMC + FT + PSK	137	56.9	15	$p < 0.035$. PSK + FT: ps(−)n(+) and ps(+)n(−)	119
Control	118	45.7	15	$p < 0.05$; ps(+)n(+) and ps(−)n(−) NS.	
MMC + FT	45	37.6	7	NS.	115
MMC + FT + BEST	51	56.5	7	ps(+): BEST(−) 13.3%, BEST(+) 48.3% ($p < 0.05$).	
MMC + FT + PSK	47	47.6	5	NS. n(+)ps(+): LMS(−) 13.8%, LMS(+) 40% ($p < 0.05$).	117
MMC + FT + PSK + LMS	46	44.9	5		
MMC + FT	77	75	2	NS. Some patients palliative surgery.	120
MMC + FT + LMS	78	80	2	Stage III: LMS(−) 45%, LMS(+) 95% ($p < 0.01$).	
5-FU + Me-CCNU	75	50	5	NS.	121
5-FU + Me-CCNU + LMS	69	50	5		
Control	69	50	5		
5-FU + ADR + placebo	116	59	4.5	OS: $p < 0.05$; DFI: $p < 0.02$.	122
5-FU + ADR + Poly(AU)	108	86	4.5		
5-FU + ADR	104	45.5	5	OS: $p < 0.003$; DFI: $p < 0.001$.	123
5-FU + ADR + Poly(AU)	100	74.8	5		

MMC, mitomycin C; FT, FT-207, tegafur, ftorafur, 5-FU oral; SPG, Schizophyllan (extract from *Schizophyllum* commune); MFC, MMC + 5-FU + AraC; N-CWS, *Nocardia rubra* cell wall skeleton; FME, FT + Me-CCNU; PCB, picibanil, OK-432, extract from *Streptococcus piogenes*; PSK, extract from *Coriolus versicolor*; BEST, bestatin, extract from *Streptomyces olivoreticuli*; LMS, levamisole; ADR, adriamycin; Poly (AU), polyadenylic-polyuridylic acid.
n(+), positive lymph nodes; ps(+), serosa involvement.
OS, overall survival; DFI, disease-free interval.

immunostimulators (PSK, Picibanil, Bestatine, N-CWS, SPG) have been used; MMC, with or without fluoropyrimidine, was the main chemotherapeutic agent (Table 3). No significant benefit was found for overall survival, although the survival of stage III patients and those submitted to non-curative procedures was improved. In most of these studies, no 'surgery alone' control arm was used. However, four randomized studies made in Japan[111,112,118,119] using similar regimens demonstrated statistically significant differences between treated patients and controls (Table 3).

The contradictory results reported by authors using similar chemotherapeutic regimens may be linked to differences in: criteria for patient selection, size of series, and follow-up. Unequivocal results are, on the other hand, reported in two recent studies[122,123] using polyadenylic-polyuridylic acid (Polv-AU) as immunostimulator and 5-FU and ADR as chemotherapeutic drugs. In both studies a significant improvement was observed in survival and disease-free interval of patients treated with the immunostimulator (Table 3).

In the three studies made using adjuvant levamisole for gastric cancer,[117,120,121] findings have been disappointing. The Italian Gastrointestinal Tumor Study Group (IGTSG) study failed to demonstrate any difference between the survivals of controls and treated patients, while in the two Japanese studies, chemoimmunotherapy was only effective in patients with stage III tumors.

Future trends

In recent years, new therapeutic combinations have been proposed in an attempt to improve upon results reported for drugs used in adjuvant chemotherapy for advanced gastric cancer. The more effective drugs used in monochemotherapy (cisplatin, epirubicin and methotrexate) have been associated with traditional drugs (5-FU, MMC and ADR) in new therapeutic regimens (Table 4). In Phase II and III studies the more promising results have been obtained with FAMTX (5-FU, ADR and methotrexate), with response percentages of about 45,[124,125] FP (5-FU and cisplatin) with response percentages of about 45,[127–129] and EAP (etoposide, ADR and cisplatin) with response percentages of about 47.[130–132]

In three controlled clinical studies on advanced gastric carcinoma,[139–141] these new therapeutic regimens have been compared with each other and also with FAM (Table 5). In one study of 60 patients,[140] response percentages with FAMTX were higher than with EAP, although the difference was not statistically significant. FAMTX, however, had a lower toxicity ($p < 0.05$). Another study (166 patients), made to compare 5-FU alone, FAM and FP[141] has not yet revealed any significant differences in overall survival, but the response percentages of patients treated with FP were higher ($p < 0.05$). In the third study, made on 212 patients, 102 of which could be evaluated,[139] FAMTX was significantly better than FAM, both for the number of objective

Table 4. Advanced gastric cancer recent Phase II trials

Drug	No. of patients	CR/PR (%)	Reference
FAMTX	30	63	124
	71	33	125
FEM	39	33	126
FP	18	55	127
	56	41	128
	31	45	129
EAP	29	45	130
	145	57	131
	28	43	132
EMP	22	32	133
	25	48	134
FEC	52	37	135
	38	82	136
FAM + FA	19	53	137
	19	47	138

FAMTX, 5-FU + adriamycin + methotrexate; FEM, 5-FU + epirubicin + MMC; FP, 5-FU + cisplatin; EAP, etoposide + adriamycin + cisplatin; EMP, etoposide + cisplatin; FEC, 5-FU + epirubicin + cisplatin; FAM + FA, 5-FU + adriamycin + mitomycin + folinic acid.
CR, complete response; PR, partial response.

Table 5. Recent randomized studies on chemotherapy in advanced gastric cancer

Drug	No. of patients	CR	PR	Responses (%)	Reference
FAM	67/105	0	6	6 (9)	139
FAMTX	55/107	5	20	25 (45)	
FAMTX	30	3	6	9 (31)	140
EAP	30	0	6	6 (21)	
5-FU	54/ 98	0	14	14 (26)	141
FAM	57/107	1	13	14 (25)	
FP	55/103	2	25	27 (49)	

FAM, 5-FU + adriamycin + mitomycin; FAMTX, 5-FU + adriamycin + methotrexate; EAP, etoposide + adriamycin + cisplatin; FP, 5-FU + cisplatin.
CR, Complete response; PR, partial response.

Table 6. EORTC 40905

Stratification according to the UICC staging system (1987)		
Stage IB Stage II Stage IIIA Stage IIIB	RANDOM	No further treatment FAMTX

FAMTX regimen

Drug	(mg/m²)	Days				
		1	2	3	4	15
MTX	(1500)	X				
5-FU	(1500)	X				
ADM	(30)					X
Leucoverin	(15/6h)		X	X	X	

Recycle from day 29 for 6 cycles

responses (25 vs 6), and for the median survival (40 vs 29 weeks), with an almost identical toxicity.

FAMTX has therefore been proposed in the new study (40905) of adjuvant chemotherapy begun by the GI Group of the EORTC in 1991. The protocol (Table 6) plans a 6-month period of systemic chemotherapy with FAMTX and leucoverin, a standardization of surgery with R2 lymphadenectomy, and calls for large-scale patient recruitment. Moreover, in order to improve local control of the disease, optional use of intraoperative radiotherapy is provided; results with the latter have been promising both in Japan[22–24,28] and in Western countries.[25–29]

The contribution made by immunotherapy in the treatment of tumors has increased in recent years due to the utilization of biological response modifiers. For some neoplasms, such as melanoma and renal carcinoma, immunotherapy with interleukin-2 (IL-2) is now the main approach for the advanced forms, giving results that are comparable to, or even better than, those achieved with traditional chemotherapy.[142–145] Recently, unexpected findings were made with adjuvant levamisole in the treatment of resectable carcinoma of the colorectum,[146,147] and immunostimulators have now been reproposed in anticancer therapy. Immunotherapy may therefore be an important complement, or even an alternative, to conventional treatment in gastric carcinoma. In Phase II clinical studies conventional doses of gamma-interferon do not appear to be effective in the treatment of advanced gastric carcinoma.[148] However, in theory it should be active for this neoplasia. In fact, it has been demonstrated[149] that the surgical treatment of gastrointestinal tumors is followed by an important if temporary depression of the antitumoral lymphocytotoxic activity of some cells (NK and LAK cells). Moreover, it has been observed that the administration of alpha-interferon in the preoperative period can prevent depressed NK cell activity.[149] Therefore the utilization of interferon, both alone and associated with traditional chemotherapeutic drugs, should be tested in larger trials. In a recent work[150] on 32 patients with advanced stomach cancer, the 5-FU + alpha-2A-interferon combination demonstrated a 34% objective response including two complete responses.

Modifiers of biological responses (IL-2 with or without LAK cells and TIL cells) seem to have little effect on gastric cancer and gastrointestinal tumors in general.[151–153] Moreover, one of the reasons limiting the future use of these drugs is the toxicity of IL-2 when administered systemically.[142,145,154] Greater attention should therefore be paid to the attempt to utilize these substances intraperitoneally, thus limiting the collateral systemic effects and allowing the direct activation of many macrophages present in the peritoneal site.[155,156] Monoclonal antibodies have been used, so far, as a diagnostic tool. Anti-CEA and anti-CA-19-9 monoclonal antibodies have a low specificity of about 40%.[157–159] In recent times, monoclonal antibodies against the p21 product of the *ras* oncogene on gastric cancer cells have been used to identify neoplastic cells obtained during endoscopic brushing[158]; because of their high specificity (100% of cases), they might also be used in the future as carriers of anti-tumoral drugs.

Conclusions

Results with adjuvant chemotherapy in Western countries are not satisfactory. Only in the GITSG study with nitrosurea were statistically significant results obtained in the survival and disease-free interval, but these were not confirmed in subsequent studies that utilized the same therapeutic regimen. The promising results with FAM in advanced gastric cancer have not been confirmed in trials on adjuvant chemotherapy made in the late 1980s, and for this reason this therapeutic regimen cannot be advocated as routine treatment in gastric cancer. The therapeutic benefit reported in Japanese studies may be due to the fact that chemotherapy is started during the immediate postoperative

period or intraoperatively, and their results should also be considered in the light of the earlier diagnosis obtained through mass screening, and an extended and standardized surgical treatment. Moreover, the benefits from adjuvant chemotherapy in the Japanese studies are often observed only in patient subgroups. It must be borne in mind that subgroup evaluation has an important drawback as subgroups are retrospectively selected, causing a less casual stratification, which can distort statistical results. In Western countries, however, new clinical trials must utilize better defined and standardized surgical criteria.

New therapeutic trends now hinge upon the use of recent chemotherapeutic associations tested in Phase I and II clinical trials (FAMTX, EAP, FP, etc.) or, as reported by Japanese authors, by combining traditional chemotherapy with different types of immunostimulators. Only when large-scale clinical studies have been made will it be possible to confirm their therapeutic efficacy. Adoptive immunotherapy, so far used almost exclusively in experimental trials, is another therapeutic trend that also calls for further clinical studies.

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(Received 28 August 1991; accepted 2 September 1991)