REVIEW

Chemotherapy of Oesophago-Gastric Cancer

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Oesophageal and gastric cancers are common tumors that represent a number of challenges for oncologists, gastroenterologists and surgeons. The prognosis remains poor with the majority of patients presenting with advanced disease. Combined chemotherapy and radiotherapy has demonstrated a survival benefit in patients with loco-regional oesophageal cancer compared to radiotherapy alone. In an interim analysis we have observed a 62% response rate using a chemoradiation regimen based on protracted venous infusion of 5-fluorouracil and cisplatin combined with radiotherapy in patients with inoperable oesophageal cancer. Improved outcomes with loco-regional disease has rekindled interest in preoperative therapy. In a trial comparing preoperative chemoradiation to surgery alone in patients with operable oesophageal adenocarcinoma, survival was improved with multimodality treatment. In addition, a study including both adeno- and squamous carcinomas demonstrated a trend towards improved survival. A complete pathological response to chemoradiation was associated with significantly improved survival. Gastric cancer is one of the most chemosensitive solid tumors of the gastrointestinal tract with the majority of patients being suitable for palliative chemotherapy. The ECF (epirubicin, cisplatin, protracted venous infusion 5-fluorouracil) regimen was developed in the Gastrointestinal unit of the Royal Marsden Hospital and first reported in 1991. In a prospective randomised trial including 274 patients ECF has been compared with the standard combination of 5-fluorouracil, adriamycin and methotrexate (FAMTX) in patients with previously untreated gastric cancer. Overall response rate, failure-free and overall survival were significantly improved with ECF. ECF also demonstrated improved quality of life and cost effectiveness when compared to the FAMTX regimen. ECF should now be regarded as the standard treatment for advanced oesophago-gastric cancer against which new therapies should be compared. In addition the Medical Research Council are conducting a trial randomising patients between surgery alone and perioperative chemotherapy using the ECF regimen in operable gastric cancer. (Pathology Oncology Research Vol 4, No 2, 87–95, 1998)

Key words: oesophagus, gastric, chemotherapy, chemoradiation

Introduction

Gastric cancer is the fourth most common tumor in western Europe and the second commonest worldwide. The overall incidence has been declining for the past 50 years although the pattern varies widely. The incidence is highest in Japan, China, South America and Eastern Europe. The decline in incidence of gastric cancer has been due to a decrease in lesions of the gastric body and antrum, whilst the incidence of adenocarcinomas of the proximal stomach and oesophagogastric junction is rising. The prognosis is poor with a 5-year survival of only 5-10% in most reported series in the west. This is due to the fact that approximately 80% of cases present with advanced disease; only tumors confined to the mucosa or submucosa have a cure rate above 80% with surgery.[1]

The association of gastric cancer with blood group A and dietary factors, particularly nitrites in food preservatives, is established. Evidence is now accumulating linking Helicobacter pylori to adenocarcinomas of the antrum, body and fundus of the stomach. It is postulated that atrophic gastritis induced by infection causes a reduction in intraluminal acid secretion and a bacterial overgrowth which produces increased nitrite formation. This association raises the possibility of further changes in the inci-

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dence and mortality of gastric cancer if programs of H. pylori eradication are successful.

Oesophageal cancer accounts for approximately 2% of cancer deaths in the United Kingdom annually. The incidence of oesophageal cancer varies widely according to gender, geographical region, racial origins and racial background. The annual age-adjusted incidence varies from 5 per 100,000 among Caucasian males in the United States to 18.7–26.5 per 100,000 in some regions in France, and >100 per 100,000 in China or the Caspian region of Iran. In most regions oesophageal cancer is 2–4 fold more frequent in males, whilst in China and Iran the gender difference is minimal. The prognosis is poor with a median survival of 10 months, and less than 5% of patients are cured. The poor overall survival, as with gastric cancer, reflects the high proportion of patients presenting with advanced disease. Fewer than 10% of patients have stage I disease confined to the mucosa or submucosa. In patients with stage I disease oesophagectomy results in 60–80% 5-year survival. However, in stages II and III disease oesophagectomy results in only 15% long term survivors.

Traditionally squamous carcinomas accounted for approximately 90% of oesophageal cancers, but the incidence of adenocarcinoma of the lower oesophagus has been rising, and now account for 20–40% of oesophageal cancers. The incidence of squamous oesophageal carcinoma is increased with cigarette smoking or alcohol consumption. In countries with the highest incidence of oesophageal cancer micronutrient deficiencies are common and thought to be etiologically important. Smoking and alcohol consumption are also etiologically important in oesophageal adenocarcinoma. Between 20–80% of adenocarcinomas arise from Barrett's oesophagus which is found in 8–20% of patients undergoing endoscopy for reflux.

The risk of developing cancer appears to be limited to patients with intestinal metaplasia, where there is a risk of progression to cancer within 5 years. Consequently screening endoscopy with biopsy every 1–2 years is recommended for patients with Barrett's oesophagus. In patients in whom dysplasia is detected the frequency of surveillance should be increased.

Chemotherapy and Radiotherapy for Oesophageal Cancer

Until 1990 standard therapy for localised oesophageal cancer was surgery and/or radiotherapy. The choice of therapeutic modality depended on site, stage and histopathology of the primary tumor. A further consideration is the patients' fitness for oesophagectomy. However, as already described the outcome from surgery is poor. Radiotherapy neither as single modality treatment, nor combined with surgical resection improves the prognosis.[2,3] Systemic chemotherapy either as single-agents or combination chemotherapy regimens have demonstrated efficacy in oesophageal cancer. The best results are observed with the use of cisplatin and 5-fluorouracil (5-FU) infusion. Several phase II studies have evaluated combination therapy with chemotherapy and radiotherapy. Poplin et al combining a 96-hour continuous infusion of 5-FU on days 1–4 and 29–32 and cisplatin on days 1 and 29 with radiotherapy on days 1 to 19 achieved a pathological complete response rate of 17% in patients with untreated loco-regional squamous oesophageal cancer.[4] Complete pathological responses were observed in 23% treated with concurrent cisplatin, vinblastine, 5-FU and radiotherapy over 21 days.[5] The median survival time in phase II studies is around 13 months, and the 2-year survival was approximately 25%, irrespective of whether patients underwent surgical resection or not.

The publication in 1992 of a randomised study involving 121 patients established the benefits of combined chemotherapy and radiotherapy compared to radiotherapy alone for patients with loco-regional oesophageal cancer. The median survival was 8.9 months for patients treated with radiation alone (6400 cGy) compared to 12.5 months in the patients treated with chemotherapy (5-FU 1000 mg/m^2 as a continuous infusion on days 1–4 and cisplatin 75 mg/m^2 on day 1 of each course every 28 days for 4 courses) and radiotherapy (5000 cGy).[6] Results from this study were updated in 1997 with an additional 69 non-randomised patients receiving combined modality therapy.[7] The median survival had improved to 14.1 months for patients randomised to the combined modality arm compared to 9.3 months for radiotherapy alone. Two-year survival figures are 36% compared to 10% and by 3 years all patients treated with radiotherapy alone had died whilst in the combined modality arm 30% were alive. This difference is maintained to 5 years with 27% of combined modality therapy patients alive.

The incidence of persistent disease and of first and overall relapses within the radiotherapy field are significantly less in patients randomised to combined chemotherapy and radiotherapy. This is despite the lower dose of radiation in the combined modality arm; 50 Gy over 5 weeks compared to 64 Gy over 6.5 weeks. This is compatible with the concept that chemotherapy may have been operating as a radiosensitiser. Furthermore, the incidence of distant metastases is significantly reduced with the addition of systemic chemotherapy consistent with independent cytotoxic effects reducing or eliminating micrometastases. Early result from the additional 69 non-randomised patients confirm the survival benefits of chemoradiation observed in the randomised study. However, there was an increase in the incidence of distant relapses compared to patients in the randomised

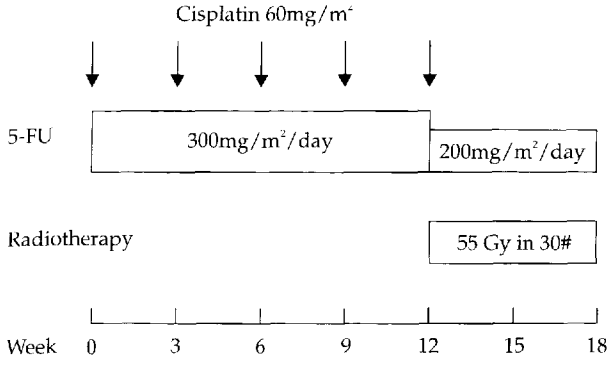

Figure 1. Cisplatin + PVI 5-FU + Radiotherapy

study. Possible explanations include higher tumor stage (26% v 8% T3), higher nodal stage (19% v 13% N1), and/or higher incidence of adenocarcinoma (20% v 15%) in the non-randomised chemoradiation patients as compared with the randomised group. The incidence of grade 3 toxicity was increased with combined modality therapy compared to radiation alone (25% v 10%) similarly there was an increase in grade 4 toxicity (8% v 2%).

The interim results of a randomised trial comparing radiotherapy alone to chemoradiation performed by the Eastern Cooperative Oncology Group (ECOG) demonstrate a similar survival benefit.[8] One hundred and eighteen patients were treated with 40 Gy alone or in combination with a 96-hour continuous infusion of 5-FU (1000 mg/m^2/day) on days 2-4 and 28-30 with bolus mitomycin C (10 mg/m^2) on day 2. The median survival was significantly improved in patients treated with combined modality therapy (14.9 months v 9.0 months; p=0.03). However, interpretation of this study is complicated by patients having the option of surgery after 40 Gy; those not proceeding to surgery received a further 20-26 Gy.

We have designed a chemoradiation regimen based on a protracted venous infusion (PVI) of 5-FU (300 mg/m^2/day) with cisplatin (60 mg/m^2) combined with 55 Gy of radiation. The use of PVI 5-FU permits a high dose intensity to be achieved with improved therapeutic ratio compared to bolus 5-FU regimens. In addition, there is experimental evidence that 5-FU based radiosensitisation is more effective when the exposure to 5-FU exceeds cycling time.

Twelve weeks of initial chemotherapy allows for downstaging of tumors prior to radiotherapy and 18 weeks total chemotherapy maximises micrometastatic control. The regimen is illustrated in *Figure 1*. A planned interim analysis of a phase II study evaluating this regimen in patients with inoperable oesophageal carcinoma has demonstrated a 58% response rate to the initial 12 weeks chemotherapy. The overall response rate to chemo-radiation is 62% (unpublished data).

Neoadjuvant Therapy for Operable Oesophageal Cancer

The improved outcomes for patients with loco-regional disease with combined modality therapy has rekindled interest in pre-operative therapy. There are now five randomised studies evaluating preoperative chemoradiation that have reported mature results *(Table 1)*. A Norwegian four arm randomised study included 187 patients.[9] The treatment regimens were surgery alone, or either cisplatin (20 mg/m^2 days 1–5) and bleomycin (5 mg/m^2 intramuscular injection days 1–5), or radiotherapy alone (35 Gy in 20 fractions), or cisplatin/bleomycin combined with radiotherapy followed by surgery. There was no survival advantage at 3 years for patients treated with preoperative chemoradiation (17%) compared to surgery alone. A French study randomised 104 patients to receive surgery alone or chemotherapy with cisplatin (100 mg/m^2 on days 1 and 21) and 5-FU (600 mg/m^2/day continuous infusion on days 2–5 and 22–25) with 20 Gy of radiation on days 8–19, followed by surgery.[10] Eighty-four patients proceeded to curative resection with an 8% postoperative mortality in both groups. There were no significant differences in survival. An European Organisation for Research and Treatment of Cancer (EORTC) trial randomised 297 patients to either surgery alone or 2 courses of cisplatin (80 mg/m^2) and concurrent radiotherapy (18.5 Gy) separated by a 2-week break followed by surgery.[11] Resection was curative in more patients treated with preoperative che-

***Table 1.* Survival in randomised studies comparing combined preoperative chemotherapy and radiotherapy to surgery alone**

Regimen	*Number of patients*	*Median survival (mths)*	*p*	*Reference*
cisplatin/bleomycin	50	8		9
radiotherapy	48	11		
cisplatin/bleomycin + radiotherapy	47	9		
surgery alone	41	8	NS	
cisplatin/5-FU + radiotherapy	41	10		10
surgery alone	45	10.5	<0.56	
cisplatin + radiotherapy	143	18.6		11
surgery alone	139	18.6	NS	
cisplatin/5-FU + radiotherapy	58	16		
surgery alone	55	11	<0.01	
cisplatin/vinblastine/5-FU + radiotherapy	50	13.7		13
surgery alone	50	17.5	<0.07	

NS = not significant

Table 2. **Survival in randomised studies comparing preoperative chemotherapy to surgery alone**

Regimen	*Number of patients*	*Median survival (mths)*	*p*	*Reference*
cisplatin/vindesine/bleomycin	19	9		14
surgery alone	20	9	NS	
cisplatin/5-FU	22	10		15
surgery alone	20	10	NS	
cisplatin/bleomycin	50	8		9
radiotherapy	48	11		
cisplatin/bleomycin + adiotherapy	47	9		
surgery alone	41	8	NS	
cisplatin/5-FU	74	16.8		16
surgery alone	73	13	<0.17	
cisplatin/etoposide	74	18.5		17
surgery alone	74	11	<0.002	
cisplatin/5-FU	202	16.1		18
surgery alone	221	16.8	NS	

NS = not significant

moradiation (81% v 67%; p=0.017). However, postoperative mortality was higher with preoperative therapy (12% v 4%; p=0.012). The time free of local disease was significantly longer in the multimodality treatment group (p=0.01) but there was no significant difference in the time to distant metastatasis (p=0.24). Overall, disease-free survival was significantly improved with preoperative chemoradiation (p=0.003) but this did not translate into an overall survival benefit. The median survival for both groups was 18.6 months. The failure of these trials to observe a survival benefit may be due to an inadequate total dose of radiation in the trial reported by Le Prise and insufficient chemotherapy in the EORTC trial.

In contrast a study evaluating preoperative chemoradiation in operable oesophageal adenocarcinoma demonstrated a survival benefit compared to patients treated with surgery alone (16 months v 11 months; p=0.01).[12] Patients received 2 courses of chemotherapy in weeks 1 and 6 (5-FU 15 mg/kg for 5 days and cisplatin 75 mg/m^2 on day 7) and 40 Gy radiation in 15 fractions commencing with the first cycle of chemotherapy. Chemoradiation is followed by surgery. At surgery 42% treated with chemoradiation had involved lymph nodes compared to 82% with surgery alone (p<0.001). Twenty-five per cent of patients achieved a pathological complete response with chemoradiation. The survival benefit was maintained to 3-years with 32% and 6% alive respectively. A further randomised study including patients with both adeno-and squamous carcinomas demonstrated a statistically non-significant trend in favour of chemoradiation after 3-years with 32% survival for patients treated with chemoradiation compared to 15% with surgery alone. However, a complete pathological response to preoperative chemoradiation was associated with significantly improved survival (p=0.006).[13]

In addition to the studies evaluating preoperative combined chemotherapy and radiotherapy there are six randomised studies evaluating preoperative chemotherapy compared to surgery *(Table 2)*. A study including 39 patients evaluated preoperative treatment with cisplatin (3 mg/kg or 120 mg/m^2 which ever was the less on day1), vindesine (3mg/m^2 on days 1,8,15, and 22 of the first 2 cycles) and bleomycin (10 U/m^2 loading dose on day 3 followed by an intravenous infusion of 10 U/m^2 over 24 hours for days 4-6).[14] Two cycles were administered preoperatively. Postoperatively patient randomised to preoperative chemotherapy received cisplatin every 6 weeks and vindesine every 2 weeks for 6 months. Overall survival was 9 months in both arms, although overall survival was significantly improved in responders compared to non-responders (20 v 6.2 months; p=0.008) and compared to surgery alone (20 v 8.6 months; p=0.05). A German study compared surgery alone to preoperative treatment with 3 cycles of 5-FU (1 g/m^2/day days 1-5) and cisplatin (20 mg/m^2/day days 1-5) followed by surgery in 77 patients.[15] Overall survival was 10 months in both arms and the trial was stopped early because of 2 toxic deaths with this regimen and increased postoperative morbidity and mortality in the combined arm. As stated above the four arm Scandinavian study evaluated preoperative chemotherapy in one of its arms.[9] Three-year survival was 3% with preoperative chemotherapy compared to 9% with surgery alone (not significant). A more recent study used a combination of cisplatin (100 mg/m^2 on day 1 and 22) and 5-FU (500 mg/m^2/day days 1-5 and 22–27) preoperatively compared to surgery alone in 147 patients.[16] Downstaging was evident from chemotherapy with curative resections possible in 67% of patients treated with preoperative chemotherapy compared to 35% in the surgery alone group (p=0.0003). T3 and T4 tumors were found in 67% and 91% of the chemotherapy and control groups respectively (p=0.0002), whilst N1 disease was observed in 70% compared to 88% (p=0.009). However, as with the earlier trials no significant survival benefit was observed (16.8 v 13 months; p=0.17). One further study reported final result at the 1997 meeting of the American Society of Clinical Oncology. The Rotterdam Esophageal Tumor Group randomised 160 patients between surgery alone and chemotherapy followed by surgery.[17] The chemotherapy regimen comprised cisplatin (80 mg/m^2 on day 1) and etoposide (100 mg intravenously on days 1 and 2; 200 mg/m^2 orally days 3 and 5). Clinical response was evaluated after 2 cycles of chemotherapy. Patients demonstrating a major response received another 2 cycles of chemotherapy preoperatively; non-responders underwent surgery after the second cycle. With median follow-up of 15 months

survival was significantly improved with the use of preoperative chemotherapy (18.5 months v 11 months; p=0.002). In contrast an intergroup study reporting interim results with 3 cycles of preoperative cisplatin (100 mg/m^2 on day 1) with 5-FU (1 g/m^2 as a 24 hour infusion on days 1-5) every 28 days have observed no survival benefit (16.1 months preoperative chemotherapy v 16.8 months surgery alone).[18] In conclusion, with adequate chemotherapy alone or in combination with radiotherapy there appears to be a survival advantage from preoperative treatment predominantly in those patients achieving a pathological complete response.

Chemotherapy for Advanced Oesophago-Gastric Cancer

Gastric cancer is one of the most chemosensitive solid tumors of the gastrointestinal tract with high response rates in phase II studies. The majority of patients will be suitable for palliative chemotherapy, with radiotherapy being reserved for the control of pain from bone metastases. Four randomised studies comparing chemotherapy regimens with best supportive care have been reported *(Table 3)*. The FEMTX regimen (5-FU, epirubicin, methotrexate) achieved an improvement in survival to 12.3 months compared to 3.1 months with best supportive care (p=0.0006).[19] A modified version of FAMTX (5-FU, adriamycin, methotrexate) resulted in a three-fold increase in median survival (10 v 3 months;p=0.001).[20] A study by Glimelius et al which included all gastrointestinal cancers using the ELF (etoposide, leucovorin, 5-FU) regimen demonstrated a survival benefit from immediate chemotherapy compared to best supportive care or chemotherapy on the emergence of symptoms (9 v 4 months; p<0.05).[21] Subgroup analysis confirmed the survival advantage from immediate chemotherapy in patients with primary gastric cancers (10 v 4 months; p<0.02). In addition, quality adjusted survival (improved/prolonged high quality of life without toxicity) was significantly better for group treated with immediate chemotherapy (7 v 2 months; p<0.05). The incremental cost per life year gained was approximately £10,000 and the incremental cost for a quality adjusted life was approximately £12,000. This cost analysis compares favourably with the cost of hydrochlorthiazide for hypertension ($23,500 per life year gained) and coronary artery bypass grafting (2 vessel plus angina) ($106,000 per life year gained).[22,23] A further study from the same group randomising patients between chemotherapy with the ELF regimen and best supportive care demonstrated an improved survival (8 v 5 months) although this did not achieve statistical significance.[24] However, 12 patients in the best supportive care arm received chemotherapy. After correction for pretreatment characteristics, chemotherapy was associated with increased survival (p=0.003). Moreover quality adjusted survival was improved with chemotherapy (6 v 2 months; p=0.03). Thus palliative chemotherapy should be offered to all patients maintaining good functional capacity (WHO performance status 0-2).

Table 3. **Survival in randomised studies comparing chemotherapy to best supportive care**

Regimen	*Number of patients*	*Median survival (months)* *Chemotherapy*	*BSC*	*p*	*References*
FEMTX	36	12.1	3.1	<0.001	19
FAMTX	40	10	3	<0.001	20
ELF	18	10	4	<0.02	21
ELF	61	8	5	0.12	18

Single Agent Activity

Objective response rates of up to 36% have been achieved with single agent epirubicin and the best response rate is 48% with high dose folinic acid modulated 5-FU *(Table 4)*.[19,20] Other agents demonstrating significant activity include doxorubicin, mitomycin C, PVI 5-FU, bolus 5-FU and cisplatin.[27-30] Two novel cytotoxic agents, Irinotecan, a topoisomerase I inhibitor, and docetaxel, a semi-synthetic taxane, have also demonstrated single agent activity.[31,32]

Few randomised studies compare single agents with combination chemotherapy. These trials are generally small with insufficient power to detect significant differences. One trial included 252 patients in a 4 way randomisation comparing a 5-day schedule of 5-FU to either FAMe (5-FU, doxorubicin, CCNU) or FAP (5-FU, doxorubicin, cisplatin) or FAMe alternating with triazinate.[33] None of the three combination regimens demonstrated a survival benefit compared to single agent 5-FU and all increased toxicity. The authors concluded that 5-FU should remain the standard treatment and combinations should be tested

Table 4. **Single Agent Activity of Cytotoxic Drugs in Advanced Gastric Cancer**

Drug	*No. of patients*	*Response (%)*	*Reference*
5-FU + high dose folinic acid	27	48	25
Epirubicin	22	36	24
PVI 5-FU	13	31	28
Mitomycin C	211	30	27
Doxorubicin	68	25	26
Bolus 5-FU	392	21	27
Cisplatin	129	19	29
Irinotecan	60	23	31
Taxotere	37	24	33

against 5-FU alone. A second randomised study including 295 evaluable patients determined the role of cisplatin in gastric cancer. Single agent 5-FU administered as 1 g/m^2 over 5 days was compared to the same 5-FU schedule combined with cisplatin (60 mg/m^2 i.v. every 3 weeks) and to FAM (5-FU, adriamycin, mitomycin C).[34] Response rates for the three groups were 26% v 51% v 25% respectively. The response rate was significantly higher with the cisplatin/5-FU combination than with the other two arms ($p<0.01$). Moreover, median time to progression was significantly greater with ciplatin/5-FU (21.8 weeks) than with FAM (12 weeks; $p<0.05$) or with 5-FU alone (9.1 weeks; $p<0.005$). However, the improvements in response rate and time to progression did not translate into a significant improvement in overall survival. Overall survival was 36.9 weeks for cisplatin/5-FU, 29.3 weeks for FAM and 30.6 weeks for 5-FU.

Combination Regimens

While FAM (5-FU, adriamycin and mitomycin C) with response rates of 22-40% in patients with gastric cancer was the most used regimen in gastric cancer, this has now be surpassed by other combinations.[35,36] In a randomised trial the FAMTX (5-FU, adriamycin, methotrexate) regimen demonstrated superior response rates (41% v 9%; $p<0.0001$) and survival (median 42 weeks v 29 weeks; $p=0.004$) when compared to FAM.[37] A superior response rate was also observed with the PELF regimen (cisplatin, epirubicin, leucovorin, 5-FU) compared to FAM (43% v 15%;$p=0.001$) but no survival benefit was detected (8.1 v 5.6 months).[38] In addition despite encouraging phase II results using EAP (etoposide, adriamycin and cisplatin), a randomised comparison with FAMTX revealed greater toxicity for EAP without a response or survival advantage.[39] This trial was stopped early due to 4 toxic deaths in the EAP arm. The inclusion of an anthracycline in the treatment of gastric cancer would appear to be important. A trial randomising patients to cisplatin with bolus 5-FU with or without epirubicin demonstrated an improvement in survival for the three drug combination with 1-year survival rates of 27% compared to 13% from cisplatin/5-FU.[40] The survival benefit of the three drug combination achieved statitistical significance for patients with recurrent disease ($p<0.01$) and for patients responding to chemotherapy ($p<0.05$). Preliminary results of a randomised trial comparing ELF (etoposide, leucovorin, 5-FU), FAMTX and cisplatin/bolus 5-FU demonstrated no difference in response rates or survival between the three regimens.[41] Furthermore, another recently reported randomised trial comparing FAMTX to FLEP (5-FU, leucovorin, epirubicin,cisplatin) has shown a higher response rate for FLEP but no survival advantage.[42] A phase II study reported a combination of cisplatin, epidoxorubicin, leucovorin and 5-FU (weekly PELF) administered for 8 consecutive weeks to 105 patients with advanced gastric cancer.[43] Patients with stable or responding continued with treatment for an additional 6 weeks. The overall response rate was 62% with 17% achieving complete response. The median survival was 11 months with 1- and 2-year survival rates of 42% and 5% respectively. The most common side effects were hematological with 21% developing grade 3/4 leukopenia and 12% grade 3/4 thrombocytopenia. Consequently 86% of patients required at least one treatment delay during the first 8 weeks, despite this regimen being administered in conjunction with granulocyte colony-stimulating factor. The findings of this phase II study must be interpreted with caution due to possible selection bias. Weekly PELF requires further evaluation in randomised studies to determine its role in the treatment of advanced gastric cancer.

The ECF regimen (epirubicin, cisplatin, protracted venous infusion 5-FU) was developed at the Royal Marsden Hospital and first reported in 1991.[44] The rationale for the three drugs was based on single agent activity and the synergy between 5-FU and cisplatin in experimental models.[25,29,30,45] An anthracycline was included because of the enhanced cytotoxicity afforded in combination with the other two drugs; epirubicin was selected instead of adriamycin because of it's lower toxicity. 5-Fluorouracil was given as a protracted venous infusion because of its improved therapeutic index compared to bolus 5-FU. Preliminary phase II results in 139 patients treated with ECF demonstrated a response rate of 71% with moderate toxicity.[46] A further expansion of these results with a total of 235 patients reported a response rate of 65% with 11% achieving complete responses.[47] Four further confirmatory trials from other groups have shown response rates ranging from 55-67% with the ECF regimen.[48-51]

A multicentre prospective randomised trial comparing ECF and FAMTX in advanced oesophago-gastric cancer was reported in 1997.[52] This study including 274 patients demonstrated superior response rates (45% v 21%; $p=0.0002$), failure-free survival (7.4 v 3.4 months; $p=0.00006$) and overall survival (8.9 v 5.7 months; $p=0.0009$) with ECF. In addition, there was improved global quality of life with ECF at 24 weeks. Toxicity is tolerable with both arms. The overall costs of ECF were marginally higher than FAMTX, but survival is improved resulting in an incremental cost of $975 per life year gained. This superiority was maintained when oesophageal and gastric primary sites were analysed separately. This study demonstrates that ECF should be regarded as the standard treatment in oesophago-gastric cancer against which new therapies should be compared. In addition, the Medical Research Council in conjunction with the British Stomach Cancer Group are conducting a trial randomising perioperative chemotherapy using the ECF regimen versus surgery alone in operable gastric cancer.

High-Dose Chemotherapy

In our phase II study of 235 patients treated with ECF, it was noted that there was a tail on the survival curve of 10% at 4 years. In addition long-term follow-up from the randomised study has demonstrated a significant increase in 2-year survival with ECF (unpublished data). One way to attempt to increase the proportion of long-term survivors is to use high dose chemotherapy as consolidation in patients who achieve a partial or complete remission. A similar approach is being used in other solid tumors for example breast and teratoma. Susuki et al reported the use of high dose etoposide and cisplatin achieving partial remission in 89% of the 9 assessable cases.[53] The lack of complete responses was probably due to the fact that patients were not cytoreduced with conventional chemotherapy prior to high dose therapy. A randomised study is under way in patients who achieve partial or complete remission at 12 weeks high dose carboplatin/etoposide with peripheral stem cell transplant to continuation of their initial treatment.

Conclusions

The benefits of palliative chemotherapy for advanced oesophago-gastric cancer have been established on the basis of randomised studies. On the basis of evidence from randomised trials we would recommend ECF to be the standard chemotherapy regimen and future comparisons should be made against this. The challenge remains to improve the outcome for patients with oesophago-gastric cancer. Two new drugs are demonstrating encouraging activity. Irinotecan is a topoisomerase I inhibitor that has achieved a response rate of 23% in 60 patients with untreated gastric cancer and a response rate of 16% in 45 patients who had received previous chemotherapy.[31,54] Docetaxel achieved a 24% response rate in 37 patients with advanced gastric cancer with a median duration of response of 7.5 months.[27] Further evidence for the activity of taxanes in oesophago-gastric cancer is a 67% complete pathologic response rate in a small phase II trial combining paclitaxel, carboplatin and PVI 5-FU with radiotherapy in patients with operable oesophageal cancer.[55]

A further challenge will be to integrate the oral 5-FU analogues, such as UFT and capecitabine, into treatment schedules for oesophago-gastric cancer. For those patients responding to conventional palliative chemotherapy the duration of response and survival may be increased by high dose chemotherapy. This remains an experimental therapy for patients with gastric cancer and should only be given within the randomised trial evaluating the benefit of this strategy.

Combined modality therapy with chemotherapy and radiotherapy for oesophageal cancer improves the outcome for patients with loco-regional disease alone. On the basis of current evidence the dose of chemotherapy (cisplatin and 5-FU) and of radiotherapy appear critical. In patients with potentially operable oesophageal carcinomas trials indicate a survival advantage in patients achieving a complete pathological response to preoperative chemoradiation. Further studies are required to define the role of preoperative chemoradiation in oesophageal cancer. In operable gastric cancer the role of neoadjuvant chemotherapy is under evaluation in the Medical Research Council Adjuvant Infusional Chemotherapy ('MAGIC') trial. The use of multimodality therapy in oesophago-gastric cancer emphasises the requirement for gastroenterologist, surgeon and oncologist to work closely together.

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