REVIEW

Clin Transl Oncol (2007) 9:438-442
DOI 10.1007/s12094-007-0082-8

Management of gastric adenocarcinoma

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Abstract Gastric adenocarcinoma is the second most common cause of cancer death worldwide. The prognosis for patients with gastric adenocarcinoma depends on the stage of the disease at the time of diagnosis and treatment. Early gastric cancer, limited to the mucosa and submucosa, is best treated surgically and has a five-year survival rate of 70–95%. Surgical resection remains the primary curative treatment for localised disease. Despite this, the overall survival remains poor. The management of localised gastric adenocarcinoma is complex, and at present there is proven benefit of both preoperative chemotherapy and postoperative chemoradiotherapy. There is no standard regimen of chemotherapy for metastatic disease, although the regimen of ECF (epirubicin, cisplatin and fluorouracil) is the most used regimen, with a median survival of 7–9 months. With new regimens of chemotherapy, such as DCF (docetaxel, cisplatin and fluorouracil) or the combination of irinotecan, cisplatin and bevacizumab, the median survival has increased. Other new agents are under investigation.

Key words Gastric adenocarcinoma • ECF • DCF • D2 • Chemoradiotherapy

Khosravi Shahi P, Díaz Muñoz de la Espada VM, García Alfonso P et al (2007) Management of gastric adenocarcinoma. Clin Transl Oncol 9:438-442

Introduction

Adenocarcinoma of the stomach was the leading cause of cancer-related death worldwide throughout most of the 20th century. It now ranks second only to lung cancer, and an estimated 875 000 new cases are diagnosed annually worldwide [1]. Geographical differences are not fully understood; more than half of cases occur in China and Japan, but may be related to diets high in salted, smoked foods an low in fruit and vegetables. Other risk factors include male gender, *Helicobacter pylori* infection, pernicious anaemia, smoking, family history and chronic atrophic gastritis [2].

The incidence of gastric cancer has gradually decreased in western countries, nevertheless the incidence of proximal gastric and oesophagogastric junction adenocarcinomas has increased markedly since the mid-1980s [3, 4]. Proximal gastric tumours are more aggressive than distal tumours and more complex to treat [5]. The prognosis for gastric adenocarcinoma depends on the stage of the disease at the time of diagnosis and treatment [6–8]. Its prognosis is poor, except in Japan, where this tumour is endemic and more patients are diagnosed at an early stage, which is reflected by higher overall survival (OS) rates.

Complete surgical resection is the only proven, potentially curative treatment for gastric cancer. Despite this, the overall 5-year survival rate is between 15 and 35% in western countries [9]. Gastric adenocarcinoma recurs in regional and/or distant sites in up to 67% of patients after radical surgery. Therefore, adjuvant treatment after complete surgical resection is necessary in order to eradicate residual microscopic disease, and to improve results of surgery alone. The major treatment strategy during the last decades has been postoperative chemoradiotherapy. But new strategies in the management of localised gastric adenocarcinoma are intraperitoneal chemotherapy (ICh) and perioperative chemotherapy.

Untreated metastatic gastric cancer is associated with a median OS of only 3–4 months, but this can be increased to 8–10 months, associated with improved quality of life, with combination chemotherapy [10].

Localised gastric adenocarcinoma (M0)

The management of localised gastric cancer is complex, and surgical resection remains the primary curative treatment. Despite complete surgical resection, the overall 5-year survival rate remains poor [9]. Of patients that relapse after curative surgery, 87% have locoregional re-

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Received 28 December 2006 / Accepted 3 April 2007

Table 1 The results of chemoradiotherapy plus surgery for gastric adenocarcinoma

	Surgery only group	Chemoradiotherapy group	*p*
N	275 patients	281 patients	NS
Median age	59 years	60 years	NS
Median overall survival	27 months	36 months	0.005
Median relapse-free survival	19 months	30 months	<0.001
3-year survival rates	41%	50%	0.005

NS, non-statistically significant ($p>0.05$)

currence. The extent of the resection is determined by the adequacy of the resection margin, tumour location, the amount of remaining tissue and the planned method of reconstruction [11]. Subtotal gastrectomy is the standard surgical treatment for carcinoma of the proximal two-thirds of the stomach. And a distal gastrectomy is a reasonable option for an antral or pyloric carcinoma, but splenectomy and distal pancreatectomy is not recommended, except in selected cases.

The extent of lymphadenectomy is one of the most controversial topics in gastric cancer surgery. The Japanese developed an extensive classification system for the regional lymph nodes and a systematic method of dissection referred to now as the D2 resection [12]. Maruyama et al. [12] reported an improvement over this timespan in 5-year survival for resected patients from 44.3% to 61.6%. D2 lymph-node dissection entails the resection of all perigastric lymph nodes and some coeliac, splenic or splenic-hilar, hepatic artery and cardial lymph nodes, depending on the location of the tumour in the stomach [13]. However in western countries D1 lymph-node dissection (removal of all perigastric lymph nodes) is recommended, because of the results of two randomised studies, which compared D1 with D2 dissection. In a study conducted in the United Kingdom [14], similar five-year survival rates after D1 and D2 procedures were found: 35% and 33%, respectively; and 45% and 47%, respectively, in a trial in the Netherlands [15]. Both trials found significantly increased in-hospital mortality related to the distal pancreatectomy and splenectomy performed as part of the D2 procedure, therefore this procedure is not routinely recommended. A new approach in the surgical treatment of gastric cancer is video-assisted surgery (VAS). The study of Roig et al. [16] presented the initial results of the use of VAS in the curative intent treatment of gastric cancer. Mortality and morbidity of the study were 3.7% and 19%, respectively. There was a reduction in post-operative analgesia requirements and the mean hospital stay was 11 days. The authors concluded that gastric resection and related lymphadenectomy can be performed using VAS in a manner that is as safe as conventional surgery and, further, has considerable advantages.

The high rate of relapse after resection makes it important to consider adjuvant treatment for patients with gastric cancer. However, a meta-analysis reported by Hermans et al. [17] concluded that adjuvant chemotherapy did not add a survival benefit to surgery. A small but significant benefit of postoperative chemotherapy was found in two other meta-analyses, but these results have not changed standard clinical practice [18, 19]. Because of the high local and regional recurrence rates, regional radiation is an attractive possibility for adjuvant therapy. A randomised trial found clinically limited but statistically significant improvement ($p=0.009$) in survival after preoperative regional radiotherapy in patients with cancer of the gastric cardia [20]. Other small trials have suggested that survival is improved after intraoperative radiation [21], and after adjuvant radiation [22].

At present both preoperative chemotherapy and postoperative chemoradiotherapy have proven benefits. In the study of MacDonald et al. [23], chemoradiotherapy after surgery showed increased overall and progression-free survival (PFS) rates for the patients with high-risk gastric adenocarcinoma (stages IB-IVM0). Of the 556 patients, 275 were randomly assigned to surgery only and 281 to surgery plus chemoradiotherapy. Demographic factors were similar between the two groups. More than two thirds of the patients had stage T3 or T4 tumours, and 85% had nodal metastases. Only 10% of the patients underwent a D2 dissection, 36% had a D1 dissection and 54% had a D0 lymphadenectomy. With a median follow-up period of 5 years, the median duration of OS was 36 months in the chemoradiotherapy group and 27 months in the surgery-only group. The difference in OS was significant ($p=0.005$; Table 1).

The hazard ratio (HR) for relapse in the surgery-only group, as compared with the chemoradiotherapy group, was 1.52 (95% confidence interval [95%CI], 1.23–1.86; $p<0.001$). The median duration of PFS was 30 months in the chemoradiotherapy group and 19 months in the surgery-only group. The authors concluded that adjuvant treatment with fluorouracil plus leucovorin and radiation should be considered for all patients with high-risk gastric cancer. Nevertheless, this study has been criticised widely, because most patients (54%) had undergone suboptimal surgery (D0 dissection), which is less than a complete dissection of the N1 nodes.

The study conducted by Tormo Ferrero et al. [24] evaluated the acute toxicity of the combined treatment with chemoradiotherapy, according to the scheme of McDonald, in patients with gastric cancer after radical

Table 2 Pathological results of perioperative chemotherapy for resected gastroesophageal cancer (MAGIC trial)

Variable	Perioperative chemotherapy group	Surgery group
Tumour stage		
pT0	0%	0%
pT1	15.7%	8.3%
pT2	36.0%	28.5%
pT3	43.6%	54.9%
pT4	4.7%	8.3%
Median tumour size	3 cm	5 cm
Nodal status		
pN0 (0 node involved)	31.1%	26.9%
pN1 (<7 nodes involved)	53.3%	43.6%
pN2 (7–14 nodes involved)	14.1%	21.8%
pN3 (>14 nodes involved)	1.5%	7.7%

curative surgery. Grade 3 toxicity or higher appeared in 12% and grade 2 in 21%. Eight percent of patients needed to suspend treatment before the scheduled end date of treatment due to acute toxicity. The most frequent toxicity was gastrointestinal toxicity (detected in 79% of the patients). Therefore, combined chemoradiotherapy after radical curative surgery is a well tolerated treatment, with a low degree of acute toxicity, thus treatment compliance is not difficult.

The MAGIC trial reported by Cunningham et al. [25] showed that perioperative chemotherapy with a regimen of ECF (epirubicin 50 mg/m^2 body-surface area by intravenous bolus on day 1, cisplatin 60 mg/m^2 intravenously on day 1 and fluorouracil 200 mg/m^2 daily for 21 days by continuous intravenous infusion, every 21 days) decreased stage and tumour size of the resectable gastroesophageal cancer (Table 2), and significantly improved OS and PFS. This phase 3 trial included 503 patients (250 in the perioperative chemotherapy group and 253 in the surgery group). Chemotherapy consisted of three preoperative and three postoperative courses of ECF. The primary end-point was OS. With a median follow-up of four years, as compared with the surgery group, the perioperative chemotherapy group had a higher likelihood of OS (HR for death, 0.75; 95%CI, 0.60–0.93; p=0.009). The five-year survival rates were 36% in the chemotherapy group 23% in the surgery group. The HR for progression was 0.66 (95%CI, 0.53–0.81; p<0.001) in the perioperative chemotherapy group. Q1 An important limitation of this trial was that only 42% of patients in the chemotherapy group completed the whole protocol treatment with 6 courses of ECF.

Advanced or metastatic gastric adenocarcinoma (M1)

Advanced gastric adenocarcinoma patients have a poor prognosis, with a median survival time without treatment of 3–4 months [26–28]. However, treatment with chemotherapy has showed a significant improvement in both median survival (7.5–12 months 3–4 months) and quality of life. However, there is no clear standard chemotherapy regimen in metastatic gastric adenocarcinoma despite many regimens involving both a single agent and combinations being used, achieving response rates of 15–51%, and median survival ranging from 5.3 to 10.2 months.

The randomised trial reported by Webb et al. [29] and Waters et al. [30] compared ECF with the combination of FAMTX (fluorouracil, doxorubicin and methotrexate). ECF resulted in a significantly better overall response (OR) rate (46% 21%; p<0.00003), median survival (8.7 months *vs.* 6.1 months; p<0.0005) and 2-year survival (14% *vs.* 5%; p<0.03) compared with FAMTX. The toxicity profile also favoured ECF.

In the randomised trial reported by Ross et al. [31], in advanced oesophagogastric cancer the regimen of MCF (mitomycin C, cisplatin and fluorouracil) was compared with ECF. Five hundred and eighty patients were randomised to ECF or MCF. The OR rate (ECF 42.4% *vs.* MCF 44.1%), median survival (7 months for both arms) and 1-year survival (ECF 40% *vs.* MCF 32.7%) were similar between the two arms. The global quality-of-life scores favoured ECF at 3 and 6 months.

Therefore, on the basis of these trials, ECF is regarded as a standard regimen for metastatic disease in Europe, but in the USA the standard regimen is cisplatin in combination with continuous intravenous infusion of fluorouracil for 5 days (CF regimen).

A new option for therapy for untreated advanced gastric adenocarcinoma is the regimen of DCF (docetaxel, cisplatin and fluorouracil). The V325 study reported by Cutsem et al. [32] is a large randomised phase III trial that compared DCF with the CF regimen. The primary objective of this study was to demonstrate superiority in time-to-progression (TTP) for DCF over CF. This trial showed that DCF significantly improved TTP, OS and OR rate compared with CF, although with an increase in toxicities (Table 3). Interestingly, the higher incidence of toxicity seen with DCF did not appear to impact quality of life and clinical benefit, which were

Table 3 Toxicities of DCF vs. CF in V325 study

Toxicity	DCF		CF		*p*
	Grade 3–4	All grades	Grade 3–4	All grades	
Haematology					
Neutropenia	82%	95%	57%	83%	<0.05
Leukopenia	65%	96%	31%	81%	<0.05
Anaemia	18%	97%	26%	93%	NS
Thrombocytopenia	8%	25%	13%	39%	NS
Febrile neutropenia	0%	29%	0%	12%	NS
Non-haematologic					
Gastrointestinal	49%	93%	47%	91%	NS
Stomatitis	21%	59%	27%	60%	NS
Diarrhoea	19%	75%	8%	46%	<0.05
Nausea	14%	72%	17%	75%	NS
Vomiting	14%	61%	17%	71%	NS
Anorexia	10%	45%	9%	45%	NS
Neurosensory	8%	38%	3%	24%	<0.05

DCF, docetaxel, cisplatin and fluorouracil; *CF*, cisplatin and fluorouracil; *NS*, non-statistically significant ($p>0.05$)

significantly more favourable in the DCF arm. With a median follow-up of 13.6 months, the median TTP was 5.6 months (95%CI, 4.9–5.9) for DCF and 3.7 months (95%CI, 3.4–4.5) for CF; with a risk reduction of disease progression of 32% ($p<0.001$). The median OS was significantly longer for DCF *vs.* CF (9.2 months; 95% CI, 8.4–10.6; *vs.* 8.6 months; 95% CI, 7.2–9.5, respectively; $p<0.02$).

Based on the encouraging results of phase II studies, there is an emerging role for other new cytotoxic drugs in the treatment of advanced disease, including irinotecan, oxaliplatin [33], oral fluoropyrimidines (capecitabine) [34], paclitaxel [35], cetuximab and bevacizumab.

A phase II study has showed the benefit of regimens with irinotecan for advanced gastric cancer. This trial compared irinotecan-fluorouracil with irinotecan-cisplatin. The OR rate in the combination of irinotecan with 5-fluorouracil and folinic acid was 42.4%, with a complete response rate of 5.1%. Corresponding figures for the irinotecan/cisplatin arm were 32.1% and 1.8%, respectively. The median TTP was significantly longer for irinotecan-fluorouracil (6.5 months) *vs.* irinotecan-cisplatin (4.2 months; $p<0.0001$). The median survival times were 10.7 and 6.9 months, respectively ($p=0.0018$) [36].

A randomised multicentre phase III trial (REAL-2) [37, 38] with a two-by-two factorial design to compare the efficacy of capecitabine with 5-fluorouracil, and oxaliplatin with cisplatin in the ECF regimen, for patients with advanced oesophagogastric cancer, is currently under way. Preliminary results of this study indicate comparable activity for the substitution of the newer agents (oxaliplatin and capecitabine) with potentially less toxicity for oxaliplatin combination therapy (Table 4).

A recent phase II trial showed that the combination of bevacizumab with cisplatin and irinotecan can be safely given in patients with metastatic gastric or gastroesophageal junction adenocarcinoma, even with primary gastric tumours in place. With a median follow-up of 12.2 months, median TTP was 8.3 months (95%CI, 5.5–9.9), the OR rate was 65% (95%CI, 46–80%) and median survival was 12.3 months (95% CI, 11.3–17.2) [39].

Intraperitoneal chemotherapy for gastric adenocarcinoma

A new review article by Yu [40] evaluated the benefit of ICh for resected primary gastric cancer. An update on

Table 4 Results of REAL-2 Study

Variable	ECF	ECX	EOF	EOX
TN	249 patients	241 patients	235 patients	239 patients
OR	40.7%	46.4%	42.4%	47.9%
	–	$p=0.2$	$p=0.7$	$p=0.1$
PFS	6.2 months	6.7 months	6.5 months	7.0 months
OS	9.9 months	–	–	11.2 months
	–			$p=0.02$

ECF, epirubicin, cisplatin and fluorouracil; *ECX*, epirubicin, cisplatin and capecitabine; *EOF*, epirubicin, oxaliplatin and fluorouracil; *EOX*, epirubicin, oxaliplatin and capecitabine

Taegu's phase III trial of early postoperative ICh [41], with 248 patients with gastric cancer, showed that the overall 5-year survival rate was 61.1% and 10-year survival 55.8%. In this study patients were randomised intraoperatively after resection was complete to receive early postoperative ICh or not. All patients underwent D2 or more extended lymphadenectomy. In patients randomised to receive ICh, a 5-day course of ICh with mitomycin C and 5-fluorouracil was given through the catheters placed during the operation.

Survival distributions for ICh adjusted for stage showed statistically significant improvement, especially in patients with stage III gastric cancer (p=0.0288). The conclusions were that patients with serosa-positive gastric cancer are most likely to benefit from adjuvant ICh.

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