The role of oral fluoropyrimidines in the treatment of advanced gastric cancer

A. Pieters[1], S. Laurent[1], I. Dero[1], N. Van Damme[1], M. Peeters[1,2]

(1) Department of Gastroenterology, Digestive Oncology Unit, University Hospital Ghent, Belgium ; (2) Senior Clinical Investigator Research Foundation – Flanders (FWO).

Abstract

Although the incidence of gastric cancer is declining during the second half of the 20th century, it remains the second leading cause of cancer death worldwide.

The majority of patients with gastric cancer will require palliative treatment at some point in the course of their disease. Approximately 50% of patients already have advanced incurable disease at the time of initial presentation, and even those who undergo potentially curative resection have high rates of distant as well as local recurrence.

Chemotherapy in advanced gastric cancer demonstrated a significant survival benefit over best supportive care alone. Median overall survival increased from 3-5 to 8-12 months.

Today, a platinum based regimen is considered as first-line treatment in advanced gastric cancer. Different regimens are investigated and used in routine practice.

Similarly to fluorouracil, capecitabine is well tolerated in combination with a range of cytotoxic drugs. As a single agent, it has not undergone large scale randomised studies. S-1, another oral fluoropyrimidine, is a potential challenger to the role of capecitabine, but is lacking phase III data in Western population. (Acta gastroenterol. belg., **2008**, 71, **361-366**).

Introduction

Adenocarcinoma is the most common tumour of the stomach. It represents almost 90% of gastric cancers. Other histological types are less frequent and can be malignant or benign. Lymphomas (5%) and stromal tumours are the most important representatives of the former group. Their management is totally different from adenocarcinomas. This article will focus on the management of both diffuse and intestinal type adenocarcinoma.

Although the incidence of gastric cancer is declining during the second half of the 20th century, it remains the second leading cause of cancer death worldwide (1).

The incidence has a wide geographic variation. The high-risk countries include Central and South America, Japan, China, Russia and Eastern Europe. Western Europe and North America can be considered as low risk countries.

The incidence of gastric cancer in the European Union is 18.9/ 10^5 per year with a 1.5 times higher rate for males than females and with a peak incidence in the seventh decade (2). The incidence in Belgium (2003) is 14.9/ 10^5 per year for males and 8.4/ 10^5 per year for women (3).

Gastric cancer is a multi-factorial disease. Although the exact aetiology remains unknown, the interaction with environmental factors is striking. Studies in high-risk populations such as Japanese immigrants to the United States showed a significant reduction in cancer incidence after these people changed their dietary habits. Risk reduction becomes stronger in subsequent generations and reaches overall risk after three generations (4).

The known risk factors for gastric cancer are Helicobacter pylori infection, male sex, pernicious anaemia, smoking, high salt intake and Menetrier's disease. Increased incidence is also described in hereditary non-polyposis colon cancer.

Although the overall incidence of gastric adenocarcinoma is decreasing, an increase in carcinomas of the oesophagogastric junction is noticed. Especially in the developed countries, the increase is primarily related to Barrett's oesophagus (5). Also recently, Renehan *et al.* described that an increased body mass index is strongly associated with oesophageal adenocarcinoma, especially oesophagogastric junction adenocarcinoma. There is no correlation with the gastric adenocarcinomas (6).

The majority of patients in the Western world are diagnosed with advanced disease at presentation. Only 20 to 30% of patients are candidates for curative surgery. Consequently, the prognosis is poor, 5-year survival varies between 10% to 15%.

The mainstay of treatment in metastatic and/or inoperable patients is chemotherapy. This treatment results in survival and quality of life benefit compared with supportive care alone (7).

In this article the efficacy and tolerability of systemic treatment in advanced gastric cancer will be discussed. Old regimens will be critically evaluated against new therapeutic options.

Medical therapy in advanced gastric cancer

Chemotherapy in advanced gastric cancer demonstrated a significant survival benefit over best supportive care alone. Median overall survival increased from 3-5 to 8-12 months (7). Today, a platinum-based regimen is considered as first-line treatment in advanced gastric cancer. Different regimens are investigated and used in routine practice.

Correspondence to : Prof. Dr. Peeters Marc, Ghent University Hospital, Department of Gastroenterology, Digestive Oncology Unit, De Pintelaan 185 1K12IE, 9000 Ghent, Belgium. E-mail : marc.peeters@ugent.be

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Table 1. — **Comparison of CF and infused 5-FU**

Studies	Treatment arms	n	RR (%)	PFS (months)	OS (months)
Kim (8)	5-FU/cisplatin 5-FU/doxorubicin/mito C 5-FU	103 98 94	51 25 26	5.1 2.8 2.1	8.5 6.8 7.1
Atsushi (9)	5-FU 5-FU/cisplatin Uracil/tegafur/mitomycin	105 105 70	11 34 9	1.9 3.9 2.4	7.1 7.3 6
Vanhoefer (10)	Etoposide/leucovorin/5-FU 5-FU/cisplatin 5-FU/doxorubicin/methotrexate	132 134 133	9 20 12	3.3 4.1 3.3	7.2 7.2 6.7
Lutz (11)	5-FU 5-FU/ folinic acid 5-FU/folinic acid/cisplatin	33 48 46	6.1 25 45.7	1.9 4 6.1	7.1 8.9 9.7

CF : Cisplatin plus continuous infusion 5-Fluorouracil, RR : response rate, PFS : progression free survival, OS : overall survival.

Cisplatin plus continuous infusion 5-Fluorouracil (CF) was compared with infused 5-FU alone in four randomised trials (8-11). Although response rates (RR) and progression free survival (PFS) are improved with CF, no significant overall survival (OS) benefit was seen. Nevertheless, CF has long been accepted as the standard treatment option by regulatory authorities and cancer specialists. Table 1 summarises the results of these studies.

Epirubicin, cisplatin and continuous infusion 5-FU (ECF) is another standard treatment in advanced oesophagogastric cancer.

ECF was developed at the Royal Marsden Hospital (UK) based on the single agent activity of the three drugs in upper gastro-intestinal cancer and on the synergy between 5-FU and cisplatin in animal models. An anthracycline was added to enhance the efficacy of the combination. Epirubicin was preferred over doxorubicin because of its lower toxicity (12). Activity was demonstrated in two randomised trials involving 800 patients.

In one multi-centre study, 274 patients with advanced gastric cancer were randomised to FAMTX (5-fluorouracil plus doxorubicin and high dose methotrexate) or ECF. ECF showed superiority both for response (45% versus 21%) and OS (8.7 versus 6.1 months). ECF caused more alopecia and nausea while FAMTX was associated with more haematological toxicity and infections (13).

Another multi-centre study compared ECF (epirubicin 50 mg/m^2 every 3 weeks, cisplatin 60 mg/m^2 every 3 weeks and 5-FU 200 mg/m^2/d) to the combination of mitomycin, cisplatin and infusional 5-FU (MCF : mitomycin 7 mg/m^2 every 6 weeks, cisplatin 60 mg/m^2 every 3 weeks and 5-FU 300 mg/m^2/d). In this study 574 patients with chemo-naive advanced oesophagogastric cancer were randomised. No difference in response (42% versus 44%), OS (9.4 versus 8.7 months) and toxicity profile was reported. However, quality of life analysis was in favour of ECF (14).

The Cochrane meta-analysis demonstrated a statistically significant benefit in OS of 5-FU/Cisplatin/ anthracycline versus CF combinations with a weighted mean average survival gain of 2 months in favour of adding anthracycline (15).

ECF has emerged as a standard regimen in many parts of the world. However acceptance of this regimen is limited by the need for central venous access and an ambulatory continuous infusion pump.

Recently several large phase III trials investigated new combinations of 5-FU/oral fluoropyrimidines with platinum compounds, taxanes or topoisomerase I inhibitors. Table 2 describes the different oral fluoropyrimidines and their indications.

Van Cutsem *et al.* reported a phase III study which randomised patients to a 21-day cycle of docetaxel (75 mg/m^2 on day 1), cisplatin (75 mg/m^2 on day 1) and infusional 5-FU (750 mg/m^2 per day on days 1 to 5) or to the standard of cisplatin (100 mg/m^2 on day 1) and infusional 5-FU (every 4 weeks) (Table 3). There was an improved RR (37% versus 25%), PFS (5.6 versus 3.7 months) and OS (9.2 versus 8.6 months). Although DCF had more toxicity such as febrile neutropenia, quality of life and clinical benefit were increased with DCF. This might be the result of an anti-tumour activity of DCF (16).

Another phase III trial in advanced gastric cancer compared the effects of cisplatin (100 mg/m^2) plus 5-FU (1000 mg/m^2/d continuous infusion over 5 days every 4 weeks) (CF) with irinotecan (80 mg/m^2) and 5-FU (500 mg/m^2 over 2 h, followed by 5-FU 2000 mg/m^2 over 22 h weekly for 6 weeks) (IF) (Table 3). IF failed to demonstrate superiority over CF. No difference in either PFS (5.0 versus 4.2 months) or OS (9.0 versus 8.7 months). IF resulted in more grade 3/4 diarrhoea while CF resulted in more grade 3/4 neutropenia, stomatitis and nausea. Five toxic deaths were observed after CF versus one after IF (17). Personal experience with Folfiri in these patients showed efficacy with low toxicity. Today, irinotecan is not registered for this indication.

Table 2. — **Different oral fluoropyrimidines and indications**

Oral Fluoropyrimidine	Indication	Dose
Xeloda® (Capecitabine)	Adjuvant colon cancer stadium III	Twice daily 1250 mg/m² 14 days followed by 7 days rest - 6 months
	Metastatic colorectal cancer 1st line	Twice daily 1250 mg/m² 14 days followed by 7 days rest
	Advanced gastric cancer	Twice daily 1000 mg/m² 14 days followed by 7 days rest, with cisplatin
		Twice daily 625 mg/m² continue with epirubicin and cisplatin
UFT® (Tegafur, Uracil)	Metastatic colorectal cancer 1st line	Uracil 672 mg/m² and tegafur 300 mg/m² d1-d28
S-1 (Japan)	Advanced gastric cancer	Twice daily 40 mg/m² 28 days followed by 14 days rest OR Twice daily 40 mg/m² 21 days followed by 14 days rest with cisplatin

A phase III trial compared 5-FU (2600 mg/m^2 over 24 hours every 14 days), leucovorin (200 mg/m^2 every 14 days), oxaliplatin (85 mg/m^2 every 14 days) (FLO) with 5-FU (2000 mg/m^2 over 24 hours weekly), leucovorin (200 mg/m^2 weekly), cisplatin (50 mg/m^2 every 14 days) (FLP) (Table 3). There was no statistically significant difference between the two arms in terms of RR (34% versus 27%), PFS (5.7 versus 3.8 months) and OS (10.8 versus 8.7 months). FLO was associated with significantly less nausea and vomiting, fatigue, renal toxicity and alopecia. As expected more grade 3 and 4 sensory neuropathy (13% versus 3%) was seen with the oxaliplatin regimen (18).

Capecitabine in gastric cancer

More recent data suggest that capecitabine, an oral fluoropyrimidine, can be substituted to infusional 5-FU. Capecitabine is an oral fluoropyrimidine that is absorbed intact through the intestinal wall, and then converted to cytotoxic fluorouracil and its metabolites in three sequential enzymatic reactions. Compared with intravenously administered fluorouracil, capecitabine is more convenient for the patient, both in terms of the ease of administration as well as reduced time in the hospital. Moreover, metabolism of capecitabine occurs preferentially in tumour tissue, thereby reducing exposure of normal tissue to the drug (19).

Capecitabine is already used for colon and breast cancer. It is used as a first-line monotherapy in the treatment of metastatic colorectal cancer in most countries worldwide (including the EU and US) since 2000. It has also been approved by the European Medicines Agency and US FDA for the adjuvant treatment of colon cancer in March and June 2005, respectively. Capecitabine is licensed in metastatic breast cancer in combination with docetaxel in women whose disease has progressed following chemotherapy with an antracycline and as monotherapy in those resistant to antracyclines and taxanes. More recently, it has also been licensed for use in combination with lapatinib, in patients with advanced, HER2-positive breast cancer who have previously been treated with an antracycline, a taxane and traztuzumab. Capecitabine recently received approval in South Korea for the first-line treatment of patients with locally-advanced and metastatic pancreatic cancer, in combination with gemcitabine (20).

Two phase III trials have been performed to evaluate the role of capecitabine in advanced gastric cancer.

The UK National Cancer Research Institute (NCRI) REAL 2 trial (Table 3) randomised 1002 patients between four arms in order to evaluate the substitutions of oxaliplatin for cisplatin and capecitabine for infused 5-FU in the ECF regimen (21). It was a study using a 2 × 2 factorial design to three week cycles of epirubicin and cisplatin and either capecitabine (ECX) or infusional 5-FU (ECF), or epirubicin plus oxaliplatin and either capecitabine (EOX) or infusional 5-FU (EOF). The patients received eight cycles of treatment. Oral capecitabine (625 mg/m^2) was given twice daily throughout each cycle. Epirubicin (50 mg/m^2), cisplatin (60 mg/m^2) and oxaliplatin (130 mg/m^2) were administered intravenously once every 3 weeks, whereas infusional 5-FU (200 mg/m^2) was administered daily as a continuous infusion. The median follow-up period was 17.1 months.

The primary end point of this trial was a 2 × 2 comparison for non-inferiority of OS for both of these substitutions. The trial was able to reach this endpoint. There was no difference among the groups in terms of response rate (41%, 42%, 46% and 48% with ECF, EOF, ECX and EOX, respectively) and PFS (6.2, 6.5, 6.7 and 7.0 months with ECF, EOF, ECX and EOX, respectively). The authors concluded that the substitution of capecitabine for infusional 5-FU did not compromise the outcome.

However, when the 4 groups were compared separately, the OS in patients treated with EOX was modestly longer if compared to ECF (11.2 versus 9.9 months with EOX and ECF). Patients in both oxaliplatin-containing arms had significantly less grade 3 and 4 neutropenia, alopecia, thromboembolism and renal dysfunction. Otherwise they experienced significantly more peripheral neuropathy and diarrhoea. The authors concluded that EOX was better than ECF, but the costs of capecitabine and oxaliplatin are significantly higher than the combination 5-FU and cisplatin. Toxicity is not necessarily less.

Table 3. — **Recent phase III randomised controlled trials in advanced gastric cancer**

Studies	Treatment arms	n	RR (%)	PFS (months)	OS (months)
V325 (16)	Cisplatin/5-FU Docetaxel/ciplatin/5-FU	224 221	25 37	3.7 5.6	8.6 9.2
V306 (17)	Irinotecan/5-FU Cisplatin/5-FU	170 163	32 26	5.0 4.2	9.0 8.7
FLO (18)	5-FU/leucovorin/oxaliplatin 5-FU/leucovorin/cisplatin	112 108	34 27	5.7 3.8	10.8 8.7
REAL-2 (21)*	Epirubicin/cisplatin/5-FU (ECF) Epirubicin/oxaliplatin/5-FU (EOF) Epirubicin/cisplatin/capecita-bine (ECX) Epirubicin/oxaliplatin/capeci-tabine (EOX)	263 245 250 244	41 42 46 48	6.2 6.5 6.7 7.0	9.9 9.3 9.9 11.2
ML17032 (22)	Capecitabine/cisplatin Cisplatin/5-FU	160 156	41 29	5.6 5.0	10.7 9.5
JCOG 9912 (24)	5-FU irinotecan/cisplatin S-1	234 236 234	9 38 28	2.9 4.8 4.2	10.8 12.3 11.4
SPIRITS (25)	S-1 S-1/cisplatin	152 153	31 54	4.0 6.0	11.0 13.0

RR : response rate, PFS : progression free survival, OS : overall survival
* : 34% esophageal, 26% gastroesophageal junction and 40% stomach cancer patients.

Similar results were noted in a randomised trial comparing capecitabine plus cisplatin versus infusional 5-FU plus cisplatin (ML17032 trial) (22). Patients received oral capecitabine (1000 mg/m^2 twice daily on days 1-14) plus intravenous cisplatin (80 mg/m^2 on day 1), or continuous infusion fluorouracil (800 mg/m^2/day on days 1-5) plus intravenous cisplatin (80 mg/m^2 on day 1). The median number of treatment cycles was five for each group and the median follow up period was 22.1 months.

As for the REAL-2 study, this trial was powered to demonstrate non-inferiority. The PFS (5.6 versus 5.0 months, respectively) and the OS (10.7 versus 9.5 months, respectively) were comparable in both groups. Also no difference in incidence and severity of adverse effects was detected.

Although the conclusions of both studies are comparable, some important differences in the trial population should be remarked. First of all, the ML17032 trial only recruited advanced gastric cancer patients, whereas REAL-2 trial recruited patients with oesophageal, oesophagogastric junction as well as gastric cancer. Secondly, ML17032 recruited only patients with adenocarcinoma, whereas 10% of REAL-2 patients had squamous-cell histology. Nevertheless, the similarities in the efficacy results suggest that capecitabine in combination with platinum compounds is active in a broader group of patients rather than only those with gastric adenocarcinoma.

The results of both combination trials resulted in a successful application for the extension of the European license for capecitabine to advanced gastric cancer. As a single agent, it has not undergone large scale randomised studies and, therefore, should not be recommended routinely.

S-1 in gastric cancer

S-1, used mainly in Japan, is a recently marketed oral fluoropyrimidine. It is a combination of the 5-FU prodrug, tegafur, with two enzyme inhibitors ; 5-chloro-2.4-dihydropyrimidine and potassionoxonate. The first one inhibits 5-FU degradation by dipyrimidine dehydrogenase. Potassionoxonate reduces phosphorylation of 5-FU in the gastro-intestinal tract to reduce gastrointestinal toxicity (23).

The efficacy of S-1 was demonstrated in a phase III trial of 704 patients with unresectable or recurrent gastric adenocarinoma (24) (Table 3). Patients were randomly assigned to continuous infusion 5-FU (800 mg/m^2/d, day 1 to 5 every 4 weeks), S-1 alone (40 mg/m^2 day 1 to 28 every 6 weeks) or cisplatin (80 mg/m^2, day 1 every 4 weeks) plus irinotecan (70 mg/m^2, day 1 and 15). S-1 was not inferior to infusional 5-FU in terms of RR (28% versus 9%), PFS (4.2 versus 2.9 months) and OS (9.2 versus 7.2 months). There was a trend towards improved survival.

S-1 was associated with more grade 3 or 4 diarrhoea than 5-FU. Cisplatin-irinotecan did not show statistically significant superiority.

In the SPIRITS study a significant benefit was shown for combined S-1 (40 mg/m^2 twice daily 21 days followed by 14 days rest) plus cisplatin (60 mg/m^2 on day 8) over S-1 alone (40 mg/m^2 twice daily 28 days followed by 14 days rest) in terms of RR, PFS end OS (25) (Table 3). Unfortunately rates of grade 3 or 4 neutropenia, anaemia, nausea and anorexia were also significantly higher in the combination group.

The long OS seen in these Japanese studies can be explained by high use of second line chemotherapy and

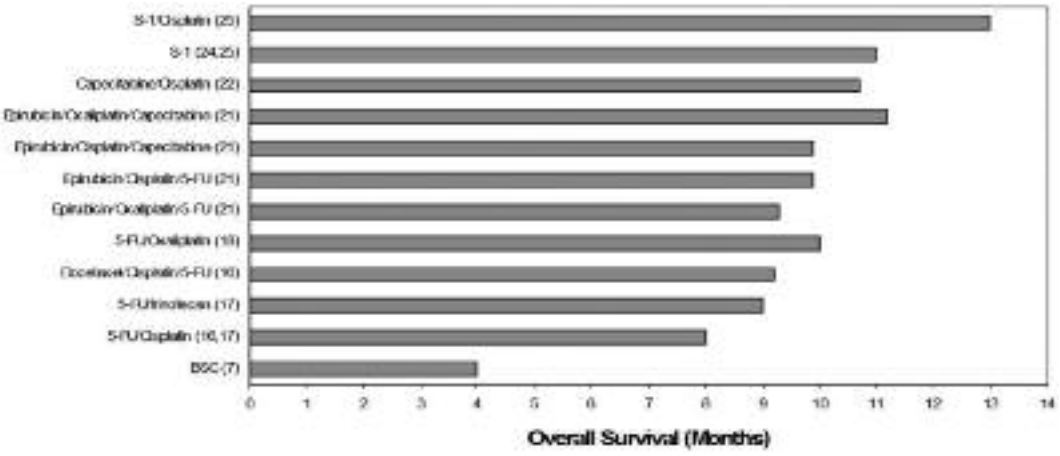

Fig. 1. — Overall survival with different regimens

small initial tumour burden. If these results can be reproduced in non-Asian populations, S-1 might be a very attractive therapeutic option, both as a single-agent and in combination. Figure 1 shows the overall survival regarding the different regimens.

S-1 will not only be an attractive option in advanced gastric cancer, but also in the adjuvant setting. Recently, a clear benefit was shown of S-1 monotherapy as postoperative adjuvant chemotherapy for stage II/III patients who underwent D2 dissection (26).

Conclusion

In phase III clinical trials in patients with advanced gastric or esophagogastric cancer, capecitabine has been shown to have similar efficacy to infused 5-FU in combination with a range of cytotoxic drugs. As a single agent, it has not undergone large scale randomised studies.

Capecitabine-based regimens were generally well tolerated and the adverse events are similar to those occurring fluorouracil-based regimens. Certainly, the use of oral chemotherapy agents avoids the burden of central venous access devices, which can reduce morbidity and improve quality of life.

Patients preference for oral over intravenous chemotherapy has been assessed in clinical trials in colorectal, but not gastric cancer (27-29). Patients prefer oral treatment if the toxicity is comparable (27,28) .

S-1 is a potential challenger to the role of capecitabine in advanced gastric cancer, but is lacking phase III data in Western populations.

More options became available for gastric cancer patients. Nevertheless, it is important to come to a personalized treatment based on patient profile, available drugs in a given country, side effects of a regimen and quality of life maintenance.

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