European Review for Medical and Pharmacological Sciences 2010; 14: 309-314

Chemotherapy for locally advanced and metastatic gastric cancer: state of the art and future perspectives

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Abstract. – Despite a decline in the incidence in Western countries, gastric cancer is still the second most common cause of cancer-related death worldwide. Many advances have been made in diagnosis and treatment of gastric cancer in the last decades but the prognosis for gastric cancer patients remains disappointing, especially in more advanced stages. The poor outcome associated with surgical resection with curative intent has generated intensive investigation of combined modality treatment approaches including systemic chemotherapy and radiotherapy to prevent recurrences and improve survival. In this setting the use of perioperative chemotherapy or postoperative chemoradiotherapy has demonstrated to give survival benefits. In advanced disease, major improvements of the last years are represented by the introduction of oral fluoropyrimidines and drugs such as docetaxel or irinotecan and the demonstration of efficacy of the anti-HER2 agent trastuzumab.

Key Words:

Gastric cancer, Adjuvant chemotherapy, Cisplatin, 5-FU, Trastuzumab, Docetaxel, Irinotecan.

Introduction

Despite its incidence in Europe and North America has declined over the last three decades, gastric cancer is still one of the most common cause of cancer-related deaths worldwide, representing a challenging problem for oncologists, with an estimated 755,000 new cases diagnosed annually around the world[1]. Surgery remains the mainstay of any curative treatment for gastric cancer, however patients with locally advanced disease show high rates of loco-regional or distant recurrence even after potentially curative resections. In the past few years, important advances have been made in the adjuvant setting where survival benefits have been demonstrated with the use postoperative chemoradiotherapy and perioperative chemotherapy. In advanced disease, patients prognosis remains very poor and the primary goal of systemic chemotherapy is palliation. In this setting, major improvements are represented by the introduction in clinical practice of oral fluoropyrimidines, as capecitabine and S-1, and the use of new chemotherapy agents, such as docetaxel and irinotecan. Even more recent is the demonstration that trastuzumab added to chemotherapy can improve overall survival of HER 2 positive gastric cancer patients.

Adjuvant Treatment

The role of adjuvant chemotherapy in gastric cancer has been extensively studied in the past three decades, often with disappointing results. Meta-analyses of clinical trials in this setting have shown only a small benefit deriving from adjuvant chemotherapy on overall survival, with risk of death reduction by 12-18%[2-5]. Hovewer, no clear conclusions could be drawn from these meta-analyses that showed methodological limits, included small clinical trials and analyzed older chemotherapy regimens, used before the introduction of cisplatin in the treatment of gastric cancer. More recently, four clinical trials have evaluated the role of cisplatin-based chemotherapy regimens in the adjuvant treatment of gastric cancer. In a study by GOIRC (Gruppo Oncologico Italiano di Ricerca) 258 patients with adenocarcinoma of the stomach, were randomized to receive surgery alone or surgery followed by four cycles of PELF (cisplatin, epirubicin, leucovorin and 5-FU). In this study adjuvant chemotherapy did not improve disease-free survival (HR of recurrence= 0.92, 95% CI= 0.66-1.27) or overall

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survival (HR of death= 0.90, 95% CI= 0.64-1.26)[6]. A French Federation Francophone de Cancerologie Digestive (FFCD) study on adjuvant chemotherapy, randomized 260 gastric cancer patients to postoperative chemotherapy, with 5-FU and cisplatin, or surgery alone. Also this study failed to demonstrate a benefit in terms of survival for adjuvant chemotherapy[7]. Similar results were obtained from an ITMO group study comparing surgery alone with adjuvant EAP (etoposide, adryamicin, cisplatin) chemotherapy[8] and from a GISCAD study comparing postoperative chemotherapy with 5-FU versus weekly PELF regimen[9].

The efficacy of adjuvant chemoradiotherapy after gastric cancer resection was evaluated in a large phase III trial, the US Intergroup 0116, which randomized 556 patients who underwent surgery for gastric or esophageal gastric cancer junction to postoperative chemoradiation or observation[10]. In this study the use of adjuvant chemoradiotherapy compared to surgery alone resulted in a statistically significant improvement in median overall survival (35 versus 26 months, HR= 1.31, 95% CI= 1.08-1.61) and disease-free survival (30 versus 19 months, HR= 1.52, 95% CI= 1.25-1.85). The treatment was particularly effective in improving local control, lowering the incidence of local relapse (from 29% to 19%). Hovewer, quality of surgical treatment in the study was poor, with only 10% of patients receiving D2 lymph node resection and more than half (54%) who underwent D0 resection. These observation suggest the possibility that chemoradiotherapy could be a reasonable option for patients with resected gastric cancer in case of inadequate surgery.

Peri-Operative Treatment

The disappointing results emerging from studies on adjuvant chemotherapy in gastric cancer patients has led to evaluate the role of more aggressive approaches, such as perioperative treatments. Recently, two important trials have shown that perioperative treatment could improve clinical outcome in gastric cancer patients. The MAGIC (Medical Council Adjuvant Gastric Infusional Chemotherapy) trial randomised 504 patients with resectable stomach, lower esophagus or esophageal-gastric junction adenocarcinoma to receive surgery alone or perioperative chemotherapy with three cycles of epirubicin-cisplatin-5-fluorouracil (ECF) given preoperatively and postoperatively[11]. Patients receiving perioperative chemotherapy had a significantly better overall survival, with a 36% survival rate at 5 years compared to 23% in patients treated with surgery only (Table I). Perioperative chemotherapy showed significant results also in tumor downsizing, 3 cm in chemotherapy group versus 5 cm in surgery alone group (p<0.001), and improved R0 resection rate, 79% versus 70% (p=0.03).

These results have been confirmed by a French trial (ACCORD07-FFCD 9703) that evaluated another chemotherapy regimen with 5-fluorouracil and cisplatin[12]. Two hundred and twenty-four patients were randomized to surgery alone or surgery and perioperative chemotherapy (2-3 neoadjuvant cycles and 3-4 postoperative cycles). Perioperative chemotherapy improved R0 resection rates (84% versus 73%, p=0.04) and 5-years disease-free survival (34% versus 21%) and overall survival (38% versus 24%) rates. The magnitude of these benefits is similar to what observed in MAGIC trials, (a 13% higher rate of survival after 5 years). In both these studies, in the chemotherapy arm about 85% of patients completed their neoadjuvant treatment while less than 50% received the planned adjuvant part of systemic therapy, maybe due to decreased tolerance to chemotherapy observed after gastrectomy.

The MAGIC and FFCD-9703 trials are the first studies to demonstrate survival advantage with perioperative chemotherapy in gastric and esophago-gastric junction cancer. Based on these data, perioperative chemotherapy with ECF or 5-

Table I. Perioperative chemotherapy trials.

Trial	Number of patients	Chemotherapy regimen	Hazard Ratio for disease-free survival	Hazard Ratio for overall survival	5 years overall survival rate (%)
MAGIC	504	ECF	0.66 (0.53-0.81)	0.75 (0.60-0.93)	36 vs 23
FFCD 9703	224	5FU, CDDP	0.63 (0.46-0.86)	0.69 (0.50-0.95)	38 vs 24

FU and cisplatin should be considered for stage II-IV M0 gastric cancer patients.

Advanced Gastric Cancer Treatment

Despite a remarkably improvement in the diagnosis and treatment of gastric cancer, approximately two thirds of patients presents unresectable advanced disease at the time of diagnosis, with a median survival of less than 9 months. Advanced or recurrent gastric cancer is still incurable, but the role of chemotherapy in this group of patients remains crucial for symptoms palliation and improved survival. During the past two decades, various randomized trials have been carried out for metastatic gastric cancer. Some of these trials demonstrated that a 5-fluorouracil (5-FU)-based regimen provided superior survival in patients with advanced gastric cancer when compared with the best supportive care[13-15]. Moreover, randomized trials comparing monotherapy with combination regimens consistently showed increased response rates in favour of combination regimens, whereas similar survival rates were usually found[16]. When compared with best supportive care, a consistent survival benefit[3-9] months) of combination chemotherapy has been demonstrated in advanced gastric cancer[13-15].

One of the first multidrug regimen used in advanced gastric cancer was the combination of 5-FU, doxorubicin and mitomycin (FAM), which achieved a response rate of more than 40% . In addition, it was also well tolerated, producing only moderate bone marrow suppression[17,18]. However, a randomized three-arm trial performed by the NCCTG including 305 patients with advanced gastric and pancreatic cancer, comparing the FAM regimen with 5-FU as single agent and 5-FU plus doxorubicin, was not able to show a significant survival difference among patients treated with these regimens, although higher response rates were observed in patients receiving combination chemotherapy compared with 5-FU alone[19]. Subsequently, a further randomized trial performed by EORTC compared FAM regimen with FAMTX (5-FU, adriamicyn and methotrexate): FAMTX showed significantly superior response rate and improved overall survival and became the reference regimen in this setting[20].

In the past several years, several randomized studies compared FAMTX vs various combination schedules, in order to identify the optimal regimen in advanced gastric cancer (Table II).

The results of these trials showed that, although in many studies response rates for platinum containing regimens were significantly better than for regimens without platinum, usually this did not translate in an improved median survival. However the Webb trial comparing FAMTX and ECF (epirubicin, cisplatin, 5-FU) suggested that ECF may be considered superior over FAMTX in terms of both response rate (45% vs 21%) and median survival (8.9 vs 5.7 months)[21]. These impressive results were con-

Table II. Randomized phase III trial in advanced gastric cancer.

Author (years)	N° pts	Treatment	Response rate (%)	Median survival	*p*
Kelsen et al (1992)	30	FAMTX	33	30 weeks	NS
	30	EAP	20	29 weeks	
				37 weeks	
Cocconi et al (1994)	52	FAM	15	5.6 months	NS
	85	PELF	43	8.1 months	
Webb et al (1997)	130	FAMTX	21	5.8 months	0.0009
	126	ECF	45	8.9 months	
Vanhoefer et al (2000)	134	FUP	20	7.2 months	NS
	132	ELF	9	7.2 months	
	133	FAMTX	12	6.7 months	
Ross et al (2002)	289	ECF	42	9.4 months	NS
	285	MCF	44	8.7 months	
Cocconi et al (2003)	200	PELF	98	7.7 months	NS
		FAMTX	97	6.9 months	

FAMTX: 5-FU, doxorubicin, methotrexate; FAM: 5-FU, doxorubicin, mitomycin C; ELF: etoposide, leucovorin, 5-FU; EAP: etoposide, doxorubicin, cisplatin; PELF: cisplatin, epirubicin, leucovorin, 5-FU; ECF: epirubicin, cisplatin, 5-FU; FUP: infusional 5-FU, cisplatin; MCF: mitomycin C, cisplatin, 5-FU; NS: not significant.

Table III. Ongoing phase III clinical trials in advanced gastric cancer patients[26].

Protocol IDs	Title	Design	Status	Trial description
AVF4200g	A study of bevacizumab in combination with capecitabine and cisplatin as first-line therapy in patients with advanced gastric cancer	Phase III, Randomized	Closed	**Arm 1:** capecitabine/cisplatin plus bevacizumab **Arm 2:** capecitabine/cisplatin plus placebo
BO18255	ToGA study – A study of herceptin (trastuzumab) in combination with chemotherapy compared with chemotherapy alone in patients with HER2-positive advanced gastric cancer	Phase III, Randomized	Closed	**Arm 1:** herceptin in combination with a fluoropyrimidine and cisplatin **Arm 2:** chemotherapy alone
104578	Lapatinib in combination with weekly paclitaxel in patients with ErbB2 amplified advanced gastric cancer	Phase III, Randomized	Active	**Arm 1:** lapatinib plus paclitaxel **Arm 2:** only paclitaxel
EGF110656	LOGiC – Lapatinib optimization study in ErbB2 (HER2) positive gastric cancer: A phase III global, blinded study designed to evaluate clinical endpoints and safety of chemotherapy plus lapatinib	Phase III, Randomized	Active	**Arm 1:** capecitabine/oxaliplatin plus lapatinib **Arm 2:** capecitabine/oxaliplatin alone
CCR3024	REAL 3 Version 1.3: Trial of the efficacy of epirubicin, oxaliplatin and capecitabine (EOX) with or without panitumumab in previously untreated advanced oesophago-gastric cancer	Phase III, Randomized	Active	**Arm 1:** EOX **Arm 2:** EOX + panitumumab
ML22367	A study of avastin (bevacizumab) in combination with xeloda (capecitabine) and cisplatin as first-line therapy for advanced gastric cancer	Phase III, Randomized	Active	**Arm 1:** capecitabine/cisplatin plus bevacizumab **Arm 2:** capecitabine/cisplatin alone
EMR 200048-052	Erbitux in combination with xeloda and cisplatin in advanced esophago-gastric cancer	Phase III, Randomized	Active	**Arm 1:** capecitabine plus cetuximab **Arm 2:** capecitabine alone
CRAD001R 2301	Safety and efficacy of RAD001 (everolimus) monotherapy plus best supportive care in patients with advanced gastric cancer (AGC)	Phase III	Active	This study is designed to assess the safety and efficacy of RAD001 monotherapy in patients with advanced gastric cancer which has progressed after one or two lines of prior chemotherapy

firmed by other subsequent studies, and the Authors regarded the ECF regimen as the standard of care and the reference treatment for oesophagogastric cancer patients with good performance status.

Recently developed new agents, such as capecitabine, docetaxel, paclitaxel, irinotecan, S-1, and oxaliplatin may have potentials that will break through this status. Newer-generation regimens with these agents are now being investigated in randomized trials throughout the world. Promising results were achieved with a regimen of docetaxel, cisplatin and 5-FU (DCF). In fact, the phase III trial V325, comparing CF (cisplatin and 5-FU) VS DCF regimen, showed that DCF was superior in term of time to progression, response rate and overall survival. Based on results from this study, FDA (Food and Drugs Administration) approved DCF for the treatment of patients with advanced gastric cancer[22]. New drugs combination were also tested in a large, randomized, phase III study, the REAL-2 trial. The results of this study demonstrated the non inferiority of EOX (epirubicin, oxaliplatin, capecitabine)

regimen vs ECF, with a remarkable safety advantage[23]. Recent data also emerged on the use of irinotecan in advanced gastric cancer, in particular in combination with 5-FU and leucovorin (FOLFIRI), with acceptable response rates and overall survival time[24]. The use of biological agents may represent a further step towards the improvement of advanced gastric cancer treatment. At the present time, the role of biologic agents, including epidermal growth factor receptor (EGFR) and human epidermal growth factor receptor (HER)-2-targeted monoclonal antibodies, tyrosine kinase inhibitors (TKIs) and angiogenesis inhibitors is the subject of ongoing clinical trials. During the recent ASCO meeting, a randomized phase III trial aiming to determine the efficacy of trastuzumab in combination with chemotherapy (5-fluorouracil or capecitabine and cisplatin) versus chemotherapy alone in patients with HER-2 positive gastric cancer was presented. The results showed that trastuzumab plus chemotherapy is superior to chemoterapy alone, with a median overall survival significantly improved in the experimental arm (13.5 vs 11.1 months, respectively)[25].

In the tables we reported several ongoing clinical trials regarding treatment for advanced gastric cancer (Table III).

In conclusion, substantial progress has been made in the treatment of advanced gastric cancer, but the rates of cure are still poor compared to other tumor sites. Future applications of newer cytotoxic drugs, targeted therapies and integration of molecular determinants of tumor behaviour, prognosis and response to therapy may help to improve on current standard treatments and facilitate the delivery of more tailored therapeutic interventions.

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