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REVIEW

# Current strategies in systemic treatment of gastric cancer and cancer of the gastroesophageal junction

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**Abstract** Gastric cancer is a major health issue and a leading cause of death worldwide. The results of standard therapy remain unsatisfactory mainly because of diagnosis at the late stage of disease. Innovative strategies such as neoadjuvant chemotherapy in locally advanced cancer have improved the outcome even in operable cases. Whether an adjuvant radiochemotherapy is of benefit after curative resection including systematic lymphadenectomy remains yet unclear. Some progress has been made in the palliative setting by introducing new substances. This review examines recent advances in the systemic treatment of gastric and gastroesophageal junction cancer.

**Keywords** Gastric cancer · Gastroesophageal junction cancer · Systemic therapy · Neoadjuvant chemotherapy · Adjuvant radiochemotherapy · Palliative chemotherapy · New chemotherapeutic agents

## Introduction

Gastric cancer remains to be an important health issue. It is second only to lung cancer as a leading cause of cancer deaths worldwide (Varadhachary and Ajani 2005). Whereas the incidence of gastric cancer has been steadily decreasing in western countries since 1940, it remains stable at a high level in countries of the Far East and of South and Central America (Crew and Neugut 2006).

For the past 20 years, a decline of distal gastric cancer is observed worldwide with a simultaneous significant rise of proximal cancers and those of the esophagogastric junction (Pera 2000). These proximal tumors usually present with a more advanced stage, a more aggressive histology and are associated with a worse prognosis (Sakaguchi et al. 1998; Maruyama et al. 1998; Hochwald et al. 2000; Kim et al. 2007). Nevertheless, they are locally treated in the same way and subsumed to "gastric cancer" in recent studies, as it is done in this review.

Radical surgery offers the only chance of cure, but less than half of the patients qualify for it at the time of diagnosis and even many of those who have been resected for cure will face recurrent disease.

Innovative strategies focus on neoadjuvant treatment to increase the chance for curative resection. In case of gastric cancer adjuvant treatment has gained attraction again by introducing radiochemotherapy. Systemic chemotherapy is the most effective treatment for metastatic gastric cancer. Several combination regimens have been shown to prolong survival and to improve quality of life compared to best supportive care (Pyrhonen et al. 1995; Glimelius et al. 1997). At present there is no internationally accepted standard for chemotherapy and a wide variety of new drugs are subject to trials in the palliative setting.

## Neoadjuvant treatment of gastric cancer

The results of surgery have reached a plateau of effectiveness. Even with extended surgery, including systematic

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lymphadenectomy, less than half of the patients with locally advanced gastric cancer achieve a microscopic tumor-free resection. In the German Gastric Cancer Study, which enrolled 1,999 patients, the R-0-resection rate was only 41.1% in UICC stage III (Roder et al. 1993). R-0-resection, however, is the most important treatment-related prognostic factor.

Neoadjuvant chemotherapy aims at "downstaging" of the tumor and at elimination of lymph node metastases. It focuses on stage III B and IV M0 patients as these are commonly considered not curatively resectable. In recent years also patients who might potentially be resected for cure, have been enrolled, as well. So far, there have been 19 published phase-II- and two large phase III-studies testing this concept.

## Efficacy of the treatment in terms of achieving R-0-resection

For analysis of the treatment efficacy, the mentioned studies have to be divided in those including only definitively irresectable patients, staged by laparotomy or laparoscopy, and those including potentially resectable patients. In 6 studies including a total of 264 definitely irresectable patients, most of them defined by laparotomy, R-0-resections were achieved in 14–45% (Wilke et al. 1989; Plukker et al. 1991; Lerner et al. 1992; Cascinu et al. 1998; Gallardo-Rincon et al. 2000; Cascinu et al. 2004). In a study of our group on patients staged either by laparotomy or by endoscopic ultrasound, computed tomography and, in case of conflicting results, surgical laparoscopy, we achieved a 52% R-0-resection rate among 25 patients of stage IIIB and IV M0 (Menges et al. 2003) (Table 1).

R-0-resection rates were consistently higher (41–76%) in phase-II-studies including potentially resectable patients (survey in Menges et al. 2003).

In 2006, a large randomized multicenter phase-III-trial—the MAGIC-study—was presented: 503 patients with UICC stage II and III resectable upper gastrointestinal cancers (in 74% gastric cancer, in 11% cancer of the esophagogastric junction), were randomized to receive either perioperative chemotherapy (three pre- and three postoperative cycles of Epirubicin, Cis-Platinum and 5-Fluorouracil (ECF) or surgery alone. Resection was considered curative in 79% under combination therapy versus in 69% of only operated patients ($P = 0.02$), 2-year survival rates were 50 and 41%, and 5-year-survival rates were 36 and 23% ($P = 0.009$), respectively (Cunningham et al. 2006) (Table 2). Thus, this "milestone" study definitely proved that neoadjuvant chemotherapy improves the outcome of patients with locally advanced gastric cancer, irrespective of the probability of curative resection.

This benefit did not have to be paid for by a higher morbidity or mortality: postoperative deaths were observed in 6% of patients in either group, postoperative complications were noted in exactly 46% of patients in either group, and even the average stay in hospital did not differ between the groups.

During the 2007 ASCO meeting Boigé et al. presented a multicenter phase-III-study on 224 patients with resectable adenocarcinoma of the lower esophagus and stomach. The patients were randomized to either receive two or three

**Table 1** Results of neoadjuvant chemotherapy in locally advanced gastric cancer (phase II)

| Source | Number of patients | Response rate (%) | R-0-resection rate (%) | Remarks |
|---|---|---|---|---|
| Wilke et al. (1989) | 34 | 70 | 44 | |
| Plukker et al. (1991) | 20 | N.r. | 40 | |
| Lerner et al. (1992) | 36 | 33 | 14 | Four chemotherapy-related deaths |
| Cascinu et al. (1998) | 32 | 47 | 41 | |
| Gallardo-Rincon et al. (2000) | 60 | 37 | 18 | |
| Cascinu et al. (2004) | 82 | 49 | 45 | |
| Menges et al. (2003) | 25 | 73 | 52 | |

*N. r.* Not reported

**Table 2** Results of neoadjuvant chemotherapy in potentially resectable gastric cancer (phase-III)

| Source | Number of patients | R-0-resection rate (%) | 2-year-survival-rate (%) | 5-year-survival-rate (%) |
|---|---|---|---|---|
| Cunningham et al. (2006) | 250 Preoperative chemotherapy | 79 | 50 | 36 |
| | 253 Surgery alone | 69 | 41 (n. s.) | 23 ($P = 0.009$) |
| | | | Three year-survival rate (%) | Five year-survival-rate (%) |
| Boigé et al. (2007) | 113 Preoperative chemotherapy | 84 | 48 | 38 |
| | 111 Surgery alone | 73 ($P = 0.04$) | 35 ($P = 0.02$) | 24 ($P = 0.02$) |

5-days cycles of preoperative chemotherapy (Cis-Platinum 100 mg/m$^2$ + 5-FU 800 mg/m$^2$) or surgery alone. Postoperative chemotherapy was recommended for responders or patients with stable disease and N+-stage and was applied in 50% of the cases. Perioperative chemotherapy was significantly superior to surgery alone in terms of 3- and 5-year disease free survival (40 and 34% vs. 25 and 20%) and 3- and 5-year overall survival (48 and 38% vs. 35 and 24%) respectively (Boigé et al. 2007).

Discussion

So far, there is no phase-III-study in *non-resectable* patients published. This is mainly due to the fact, that for ethical reasons a "control group" with non-resectable patients that are only operated on is not feasible.

Nevertheless, neoadjuvant chemotherapy in locally advanced gastric cancer is undoubtedly the treatment of choice for patients who are non-resectable for cure due to local reasons realizing a median survival of untreated patients of about 5–8 months.

The MAGIC trial serves as a milestone in terms of establishing neoadjuvant chemotherapy in (potentially) resectable patients (Cunningham et al. 2006). The only weak point of the study remains the fact that only about 40% of the patients received the full dosage of scheduled postoperative chemotherapy, mainly due to intolerance or toxicity reasons. On the other hand, this fact underlines the importance of the preoperative cytotoxic intervention.

The data of Boigé et al. suggest that similar results can be reached using a simpler chemotherapy regimen without Epirubicin. Even taking into account that the majority of patients in this study suffered from cancer of the esophagogastric junction (62% in the chemotherapy arm), the concept of neoadjuvant chemotherapy in potentially respectable patients is firmly supported (Boigé et al. 2007).

A persisting problem is the patients who do not respond to chemotherapy. According to clinical experience this applies to about one-third of patients treated with neoadjuvant chemotherapy. Chemotherapy response can be evaluated in patients with adenocarcinomas of the esophagogastric junction by a decrease of tumor glucose uptake values in positron emission tomography (PET) under therapy. By defining a decrease of at least 35% in tumor glucose standard uptake value (SUV) 2 weeks after the start of chemotherapy, Lordick et al. could demonstrate a good correlation of metabolic to clinical response. Recently, the MUNICON trial on 110 patients with adenocarcinoma of the esophagogastric junction prospectively confirmed the usefulness of early metabolic response evaluation by PET: those patients who responded to chemotherapy (49%) received further neoadjuvant chemotherapy for 12 weeks. The non-responders were taken off chemotherapy and proceeded to surgery. Median event-free survival was 29.7 months in responders as compared to 14.1 months in non-responders ($P = 0.002$) (Lordick et al. 2007). This might enable "tailoring" of treatment in future studies.

In any case a thorough staging to exclude distant metastases is mandatory. This staging procedure should include a diagnostic laparoscopy, because this way at least 20% of cases of peritoneal carcinosis or undetected small liver metastases will be revealed (Nakagawa et al. 2007; Feussner et al. 1999).

The ECF protocol can be recommended as a reference protocol in neoadjuvant treatment, bearing in mind that the continuous 5-FU application over up to 21 weeks complicates the handling and has prevented a worldwide spread of the protocol up to now. Data from the large REAL study in patients with stage IV gastric cancer suggest that the substitution of continuous infusional 5-FU by capecitabine results in response rates that are at least as good as the ECF regimen. Epirubicin, capecitabine and cisplatin constitute the standard arm in the neoadjuvant United Kingdom National Cancer Institute ST03 trial which investigates the effect of perioperative chemotherapy in gastric cancer with and without the anti-vascular endothelial growth factor antibody bevacizumab.

## Adjuvant treatment of gastric cancer

During the past 30 years there have been over 800 (!) studies published dealing with adjuvant chemotherapy of gastric cancer. Whereas until the late 1990s all the parties involved were agreed on the opinion that adjuvant therapy in gastric cancer is of no benefit, the situation has changed in two directions: on one hand four published meta-analyses in recent years with increasing numbers of enrolled patients (Earle and Maroun 1999; Mari et al. 2000; Panzini et al. 2002; Janunger et al. 2002) correspondingly supported a small but significant benefit of adjuvant chemotherapy in contrast to the first meta-analysis (Hermans et al. 1993). In their meta-analysis on 21 randomized studies Janunger and colleagues pointed out that the survival benefit is restricted to studies on Asian patients whereas in studies of the Western world no significant benefit was seen (Janunger et al. 2002).

Recently, Sakuramoto et al. presented a randomized phase-III-trial comparing S-1 (a mixture of fluoropyrimidin derivates) monotherapy versus surgery alone for patients with clinical stages II and III gastric cancer. The use of S-1 so far has essentially been limited to Japan. The study randomized 1,059 patients after D2-lymphadenectomy to S-1 (dosages of 80, 100, and 120 mg/day), 4 out of 6 weeks for 12 months versus surgery alone. The 3-year overall survival with chemotherapy was 80.5 versus 70.1%

($P = 0.0024$). Recurrence free survival also favored the S-1 arm with a 3-year recurrence free survival rate of 72.2% compared with 60.1% in the surgery alone arm ($P < 0.0001$). Toxicity was generally mild (Sakuramoto et al. 2007). In a similar way Nakajima and colleagues demonstrated a significant better overall survival under adjuvant chemotherapy with uracil-tegafur (UFT) in 190 patients with curatively resected T2 N1-2 gastric cancer, randomly assigned to surgery alone or to surgery and postoperative UFT 360 mg/m$^2$ daily for 16 months. After a median follow up of 6.2 years the hazard ratio for overall survival was 0.48 ($P = 0.017$) (Nakajima et al. 2007).

The Italian group for the study of digestive tract cancer (GISCAD) recently published a large randomized controlled trial comparing an intensive weekly chemotherapy protocol (PELF) versus a 6 month administration of a 5-day course of 5-FU and leukovorin in 397 gastric cancer patients in the adjuvant setting. The patients were at high risk for recurrence (pT3 N0 or pT2 and pT3 N1, 2, or 3). The authors did not find a difference between the groups according to relapse or 5-year survival rates (52 vs. 50%) (Cascinu et al. 2007). Furthermore, recent multicenter studies performed in European countries did not show a significant difference in disease-free or overall survival between resected patients and those treated additionally with adjuvant chemotherapy (Bouché et al. 2005; Nitti et al. 2006).

On the other hand a large randomized intergroup trial from the USA with 556 eligible patients of stages I B-IV M0 demonstrated a superiority of postoperative radiochemotherapy over surgery alone (Macdonald et al. 2001). There was a significant difference in time to progression (30 vs. 19 months) as well as in overall survival (36 vs. 27 months) in favor of the radiochemotherapy arm.

But several weak points of this study have to be addressed: despite the recommendation in the protocol only 10% of the patients received an extended D-2-lymphadenectomy and less than 50% underwent any systematic (D-1-) lymph node resection. The results of the radiochemotherapy arm were similar to those of the patients treated with extended lymphadenectomy alone in both of the European surgical studies (Bonenkamp et al. 1995; Cuschieri et al. 1999).

Further, the applied radiotherapy proved to be definitively toxic, only 64% of the patients finished this therapy regularly. Finally, the applied chemotherapy protocol (low dose 5-FU and leucovorin) was not an adequate chemotherapy for gastric cancer.

## Discussion

The benefit of adjuvant chemotherapy for resected gastric cancer is established for Asian patients. However, in the Western world postoperative chemotherapy in gastric cancer is still under discussion. Looking at the meta-analysis of Earle and Maroun you can calculate that 61% of the chemotherapy-treated patients will die from recurrence compared to 65% of the resected-only patients, resulting in a number needed-to-treat of 25 (Earle and Maroun 1999).

Adjuvant radiochemotherapy might be an established option in the future provided it will prove its effectiveness under "European" surgical conditions with systematic lymphadenectomy. Two small cooperative phase-II trials comparing a modern radiochemotherapy protocol with surgery alone have been presented meanwhile: 41 and 45 gastric cancer patients after D1 or D2-lymphadenectomy were randomized to adjuvant radiochemotherapy containing 5-FU/folinic acid, Cis-Platinum with or without additional Paclitaxel or to surgery alone. The calculated 2-year progression free survival rates were 64% for the triple and 61% for the quadruple chemotherapy regimen (Kollmannsberger et al. 2005).

At present, a general recommendation to perform adjuvant chemo- or radiochemotherapy outside of studies cannot be given. Decisions have to be made individually.

## Treatment of advanced and metastatic gastric cancer

Currently, platinum based combinations are the standard of treatment and have replaced protocols like FAMtx (5-FU, adriamycin, methotrexate). The combination of epirubicin (50 mg/m$^2$ every 3 weeks), cisplatin (60 mg/m$^2$ every 3 weeks) and infusional 5-FU (200 mg/m$^2$ continously daily) (ECF) is the best investigated regimen. In two large phase III studies comparing ECF with FAMtx and MCF, ECF proved to be superior to FAMtx (median survival of 8.9 vs. 5.7 months; and MCF (9.4 vs. 8.7 months, respectively) (Webb et al. 1997; Ross et al. 2002). But in many countries ECF has not been accepted as a standard therapy due to the need of continuous infusion of 5-FU over 21 days. At present, in Germany PLF (biweekly cisplatin 50 mg/m$^2$, and weekly leucovorin/5-FU 500/2,000 mg/m$^2$ as continuous infusion) is the most frequently used regimen, despite the fact that there has been no phase-III-data so far (Lutz et al. 2007).

A number of promising new drugs have been studied in the first line therapy of patients with advanced gastric cancer that broaden the therapeutic options in the future.

### Taxanes

The two taxanes in clinical use are paclitaxel and docetaxel. When used as single agents in the treatment of advanced gastric cancer, response rates between 5 and 24% have been reported. Multiple taxane-containing combination regimens have been studied, and it is not clear whether any is

superior to the others, since few randomized trials have been carried out. (Kollmannsberger et al. 2000; Bouche et al. 2003; Thuss-Patience et al. 2005).

The superiority of adding docetaxel to cisplatin and 5-FU compared to cisplatin and 5-FU alone was shown in a multinational trial that randomly assigned 457 patients with chemotherapy-naive advanced gastric cancer to 21-day cycles of cisplatin plus infusional 5-FU and docetaxel versus 28-day cycles of cisplatin plus infusional 5-FU alone (Van Cutsem et al. 2006).

The addition of docetaxel resulted in a significantly higher response rate (37 vs. 25%), as well as longer time to tumor progression (5.6 vs. 3.7 months) and 2-year survival (18 vs. 9%). However, severe neutropenia (grades 3 and 4) occurred in 84% of the DCF treated patients and 14% of patients had neutropenic infections. In 12.5% of DCF cycles G-CSF was given to prevent complications (Van Cutsem et al. 2006).

Taxanes are presently the most expensive cytotoxic drugs in the treatment of advanced gastric cancer. Prevention of severe neutropenia with G-CSF will lead to further increase of treatment costs. Split dose regimens with weekly instead of 3 weekly administration result in much less severe hematologic toxicities and infectious complications while maintaining similar efficacy (Lorenzen et al. 2007).

## Irinotecan

Irinotecan is a water-soluble semisynthetic derivative of camptothecin. In a published phase II-study with irinotecan monotherapy, a response rate of 20% was achieved Ajani et al. 2002).

The combination with cisplatin is of particular interest because the two drugs show considerable synergy in vitro. Cisplatin causes platinum–DNA cross-links that must be removed by excision-repair. This process requires DNA synthesis, which in turn needs uncoiling of DNA, which is facilitated by topoisomerase 1. In a study with 38 patients irinotecan (65 mg/m$^2$, day 1) and cisplatin (30 mg/m$^2$ day 1, weekly for 4 weeks) a response rate of 58% and a median survival of 9 months were reported (Pozzo et al. 2001). In another phase II-study that compared irinotecan (80 mg/m$^2$, day 1, weekly for 6 weeks), leucovorin (500 mg/m$^2$, day 1) and 5-FU (2,000 mg/m$^2$ continued day 1) to cisplatin (100 mg/m$^2$, day 1) and 5-FU (1,000 mg/m$^2$, day 1–5, every 4 weeks, FUP) the overall response rate in irinotecan treated patients was 40%, the progression free and overall survival was 6.5 and 10.7 months These results were the basis for a large phase III trial investigating this combination. The overall response rate was 32% for the IF regimen compared to 26% for the FUP therapy. The overall survival was 9.0 months compared to 8.7 months for the two different regimens, respectively. The toxicity profile favored the irinotecan containing therapy (Dank et al. 2005).

In a meta-analysis, the comparison of irinotecan versus non-irinotecan-based regimens (mainly 5-FU/cisplatin) resulted in a nonstatistically significant trend toward better survival with irinotecan (HR for death 0.88) (Wagner et al. 2006). However, there were no trials comparing irinotecan-based regimens to other more active three-drug regimens (such as ECF).

## Oxaliplatin

Oxaliplatin combinations, which have been extensively studied in colorectal cancer, are also active in the treatment of gastric cancer.

A variety of different regimens have been studied, all of which are associated with response rates in the range of 40–67%, with median survival durations between 9 and 15 months.

At least two trials have directly compared oxaliplatin-based versus cisplatin-containing regimens (including ECF) both of which suggest at least comparable efficacy and a different toxicity profile.

The substitution of oxaliplatin for cisplatin in combination with epirubicin and a fluoropyrimidine was investigated in the REAL-2 trial, a randomized phase III comparison of ECF, ECX, EOF (epirubicin, oxaliplatin, infusional 5-FU), and EOX (epirubicin, oxaliplatin, capecitabine) (Cunningham et al. 2006). In a preliminary report, response rates in the two oxaliplatin-containing arms were comparable to those achieved with the two cisplatin-based regimens, and there were no significant differences in median survival in this comparison. However, when the four groups were considered separately, median survival in patients treated with EOX was modestly longer when compared to ECF (median 11.2 vs. 9.9 months, hazard ratio 0.80, 95% CI 0.66–0.97). Patients in both oxaliplatin-containing arms had significantly less grade 3 to 4 neutropenia, alopecia, thromboembolism, and renal dysfunction, although they had significantly more peripheral neuropathy and diarrhea. The authors concluded that EOX was more efficacious than ECF.

Similar outcomes with the substitution of oxaliplatin for cisplatin were also found in a randomized phase III trial comparing the FLO regimen (infusional 5-FU, leucovorin and oxaliplatin) (Table 3) versus FLP (5-FU, leucovorin and cisplatin) (Al-Batran et al. 2008). In a preliminary report, there were no statistically significant differences between the two arms in terms of response rates of 34 and 25%, respectively, or time to progression (the primary endpoint) of 5.7 and 3.8 months, respectively. From a toxicity standpoint, FLO was associated with significantly less

**Table 3** Phase III studies of 1st line combination chemotherapy in advanced gastric cancer

| Source | Medication | Patients | Response rate (%) | Median survival (months) |
|---|---|---|---|---|
| Webb et al. (1997) | ECF | 111 | 45 | 8.9 |
| | FAMTX | 108 | 21 | 5.7 |
| Ross et al. (2002) | ECF | 289 | 40 | 9.4 |
| | MCF | 284 | 44 | 8.7 |
| Dank et al. (2005) | IF | 170 | 32 | 9.0 |
| | FUP | 163 | 26 | 8.7 |
| Kang et al. (2006) | XP | 160 | 41 | 10.5 |
| | CF | 156 | 29 | 9.3 |
| van Cutsem et al. (2006) | DCF | 221 | 37 | 9.2 |
| | FUP | 224 | 25 | 8.6 |
| Cunningham et al. (2008) | ECF | 249 | 41 | 9.9 |
| | EOX | 239 | 48 | 11.2 |
| | ECX | 241 | 46 | 9.9 |
| | EOF | 235 | 42 | 9.3 |
| Al-Batran et al. (2008) | FLO | 112 | 34 | 10.6 |
| | FUP | 108 | 35 | 8.7 |
| Narahara et al. (2007) | S1 | 150 | 31 | 11.0 |
| | S1/cisplatin | 158 | 54 | 13.0 |
| Boku et al. (2007) | 5-FU | 234 | 9 | 10.8 |
| | S1 | 234 | 28 | 11.4 |
| | Iri/cisplatin | 236 | 38 | 12.3 |

nausea and vomiting, fatigue, renal toxicity and alopecia, but more grade 3 or 4 sensory neuropathy (13 vs. 3%, respectively).

Taken together, these data show that oxaliplatin combinations are as least as effective as cisplatin and has a more favorable toxicity profile than cisplatin.

## Capecitabine

Epirubicin, Cis-Platinum and 5-Fluorouracil (ECF) requires central venous access and an ambulatory infusion pump. More recent data suggest that capecitabine, an orally active fluoropyrimidine, can be substituted for infusional 5-FU, improving the convenience of combination regimens that utilize this drug (Kim et al. 2002; Sumpter et al. 2003).

The efficacy of regimens substituting capecitabine for infusional 5-FU was directly studied in the REAL-2 trial, a randomized phase III study in which 1,002 patients with advanced gastric cancer were assigned, using a 2 × 2 factorial design, to 3 week cycles of epirubicin (50 mg/m$^2$) and cisplatin (60 mg/m$^2$) and either capecitabine (625 mg/m$^2$ twice daily, ECX) or infusional 5-FU (200 mg/m$^2$ daily, ECF), or epirubicin (50 mg/m$^2$) plus oxaliplatin (130 mg/m$^2$) and either capecitabine (same doses as above, EOX) or infusional 5-FU (same doses as above, EOF) (Cunningham et al. 2006). There were no significant differences among the groups in terms of objective response rate (41, 42, 46, and 48% with ECF, EOF, ECX, and EOX, respectively). There was a statistically insignificant trend towards improved overall survival when outcomes of both capecitabine-containing arms were combined and compared to both 5-FU-containing arms (hazard ratio for death 0.86, 95% CI 0.8–0.99). The substitution of capecitabine for infusional 5-FU did not compromise outcomes.

Similar results were noted in a randomized trial comparing 21-day cycles of capecitabine (1,000 mg/m$^2$ twice daily for 14 days) plus cisplatin (80 mg/m$^2$ day 1) versus infusional 5-FU (800 mg/m$^2$ per day, days 1–5) plus the same dose of cisplatin (Kang et al. 2006). As with the REAL-2 study, this trial was also powered to demonstrate noninferiority. The median progression free survival (5.6 vs. 5.0 months, respectively) and overall survival durations (10.5 vs. 9.3 months, respectively) were comparable in both groups, as was the incidence and severity of adverse effects.

Taken together, these studies suggest that the substitution of capecitabine for infusional 5-FU in these regimens is at least equivalent in terms of efficacy. While the use of capecitabine allows patients to avoid infusion pumps and a central venous catheter, the cost of capecitabine is significantly higher than 5-FU. Furthermore, the toxicity profile with capecitabine is different. In the REAL-2 trial, patients receiving ECX had a higher rate of grade 3 or 4 neutropenia compared to ECF (51.5 vs. 41.7%), while the EOX group had a significantly lower rate (27.6%). Despite these

differences, the rates of febrile neutropenia were not significantly different between the arms. The incidence of grade 3 or 4 hand-foot syndrome was higher with ECX compared to both ECF and EOX (10.3 vs. 4.3 and 3.1%, respectively).

### S-1

S-1 is a fourth generation fluoropyrimidine, an oral formulation of the following components in a 1:0.4:1 ratio: Tegafur (ftorafur), the prodrug for cytotoxic 5-FU 5-chloro-2,4-dihydroxypyridine, an inhibitor of dihydropyrimidine dehydrogenase (DPD), which prevents its degradation in the gastrointestinal tract, thus prolonging its half-life. Potassium oxonate, a specific inhibitor of one of the enzymes, orotate phosphoribosyl transferase, which phosphorylates 5-FU in the intestine. Phoshorylated 5-FU is thought to be mainly responsible for treatment-related diarrhea.

S-1 plus cisplatin is highly active in Asian patients. Ftorafur is metabolized differently in Western and Asian populations on account of polymorphic differences in the CYP2A6 gene; as a result, the maximally tolerated dose (MTD) differs.

Preliminary results of a large three-armed randomized phase III trial with 704 Japanese patients with advanced gastric cancer comparing the combination of cisplatin (80 mg/m$^2$, day 1) and irinotecan (70 mg/m$^2$, day 1 and day 15, q4w) with continuous infusion 5-FU (800 mg/m$^2$/day, day 1–day 5, q4w) and S-1 (40 mg/m$^2$, bid, day 1–day 28, q6w) showed no inferiority of S-1 to 5-FU with a 1 year survival rate of 47% compared to 52.5 (irinotecan/cisplatin) and 44% (5-FU) respectively (Boku et al. 2007).

Western experience with combined S-1 plus cisplatin for advanced gastric cancer is limited but also promising (Ajani et al. 2006; Lenz et al. 2007). In a multicenter phase II trial in which 72 patients received S-1 (25 mg/m$^2$ twice daily on day 1 through day 21) and cisplatin (75 mg/m$^2$ on day 1) every 28 days, the objective response rate was 55%, and the median duration of response was >5 months. The safety profile was favorable; the most frequent grade 3 or 4 toxicities were fatigue/asthenia (24%), emesis (17%), nausea (15%), diarrhea (13%) and neutropenia (19%).

### Targeted agents

Elevated serum and tumor levels of vascular endothelial growth factor (VEGF) and elevated expression of the epithelial growth factor receptor are associated with a poor prognosis in patients with gastric cancer (Kopp et al. 2002; Fondevila et al. 2004). These data, in conjunction with the demonstrated benefit of adding the anti-VEGF or anti-EGFR monoclonal antibodies bevacizumab to chemotherapy in metastatic colorectal cancer, provided the rationale for studies of targeted therapies in advanced gastric cancer.

In a phase II study of bevacizumab (15 mg/kg on day 1) in combination with cisplatin (30 mg/m$^2$ days 1 and 8 of every 21-day cycle) and irinotecan (65 mg/m$^2$ on days 1 and 8) in 47 patients with advanced gastric or gastroesophageal junction adenocarcinoma (Shah et al. 2006) the response rate was 65 and median survival was 12.3 months. However, among the toxicities that were likely related to the addition of bevacizumab were two gastric perforations (and one near-perforation), and 1 myocardial infarction, 13 patients with grade 3 hypertension, and grade 3 to 4 thromboembolic events in 25% of treated patients.

In another phase II trial, 38 patients with metastatic gastric cancer were treated with FOLFIRI plus cetuximab (400 mg/m$^2$ initially, then 250 mg/m$^2$ weekly). The overall response rate was 44%. Treatment was reasonably well tolerated with the exception that 42% experienced grade 3 or 4 neutropenia (Pinto et al. 2007).

Erlotinib, an orally active inhibitor of the EGFR tyrosine kinase appears to be active against adenocarcinomas involving the gastroesophageal junction (GEJ), but not the distal stomach (Dragovich et al. 2006). The reason for the apparent differential sensitivity of GEJ and gastric carcinomas to EGFR blockade using erelotinib is unclear. Others have reported a lack of activity for a related agent, gefitinib, in patients with distal gastric cancer (Doi et al. 2003).

## Discussion

Combination chemotherapy for advanced gastric cancer regimens provides higher response rates and modestly longer durations of disease control and survival. However, even new combination regimens including docetaxel or oxaplatin or capecitabine achieve in randomized studies only median survival durations of less than 1 year.

Epirubicin, Cis-Platinum and 5-Fluorouracil (ECF) is accepted as a standard regimen in many parts of the world. This regimen requires insertion of a central venous access and an ambulatory infusion pump. A number of phase III studies suggest that antitumor efficacy of oral fluoropyrimidines (capecitabine or S-1) is comparable to infusional 5-FU. The substitution of infusional 5-FU increase the convenience for patients. In addition, substances as oxaliplatin and irinotecan have shown similar efficacy as cisplatin in combination with 5-FU, however, these substances have a more favorable toxicity profile. Patients receiving cisplatin may have more nausea, vomiting, and renal insufficiency, while those receiving oxaliplatin have more sensory neuropathy and those receiving irinotecan have diarrhea and alopecia. Docetaxel shows similar efficacy but has the least favorable toxicity profile.

The poor long-term outcome (median survival 9–11 months) strongly argues for investigation of novel treatment strategies, particularly using targeted agents.

**Conflict of interest statement** This review was created completely independent of any pharmaceutical company or any commercial interest. Both authors certify that there are no conflicts of interest.

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