REVIEW ARTICLE

Drugs 2008; 68 (3): 299-317
0012-6667/08/0003-0299/$53.45/0

Locally Advanced and Metastatic Gastric Cancer

Current Management and New Treatment Developments

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Abstract

The management of gastric cancer remains a challenge. In recent years, the most important advances have been achieved in the adjuvant setting for patients with locally advanced disease, where significant survival benefits have been demonstrated for both perioperative chemotherapy and adjuvant chemoradiotherapy. These findings have changed the standard of care for patients with resectable disease.

In the setting of metastatic gastric cancer, the development of new cytotoxic regimens must consider the balance between efficacy and toxicity in patients

whose overall prognosis is poor. Major advances in recent years include the development of orally administered fluoropyrimidine analogues, which can be used in place of intravenous fluorouracil, and the addition of newer agents such as oxaliplatin and docetaxel, which have demonstrated efficacy in patients with advanced disease. Targeted therapies have had a major impact on the management of certain malignancies, and while their evaluation in the treatment of advanced gastric cancer remains early, it is likely that these agents will continue to be developed and studied in combination with chemotherapy.

This article reviews recent advances in the use of chemotherapy for advanced gastric cancer. Targeted therapies, their mechanisms of action and emerging data supporting their use in gastric cancer are also discussed. The two randomized phase III trials supporting adjuvant therapy for locally advanced, resectable gastric cancer are discussed in detail, together with strategies for future trials in this area. Overall, there remains optimism that further incremental gains will be achieved with future studies combining chemotherapy, radiotherapy and targeted therapies, both in the adjuvant and metastatic disease settings.

Gastric cancer is a common malignancy that, despite considerable research effort, remains difficult to treat and carries a poor prognosis. The National Cancer Institute SEER (Surveillance Epidemiology and End Results) database projected over 11 000 deaths from gastric cancer in the US for 2007 alone, despite having one of the lowest incidence rates in the world.[1] There is a large geographical variation in incidence rates. In Eastern Asia, 46 per 100 000 males and 21 per 100 000 females develop gastric cancer, compared with world figures of 22 (male) and 10 (female) per 100 000. Gastric cancer is the second most common cause of cancer-related death in the world (after lung cancer), and globally 700 000 deaths annually are attributed to the disease.[2] Even those initially treated with curative intent have a 60% chance of developing loco-regional or distant metastatic disease,[3] and the median survival with metastatic disease is generally <12 months.[4]

Gastric cancer is diagnosed at a late stage in up to 80% of patients and may present with symptoms such as asthenia, early satiety, nausea, dysphagia and weight loss. The disease is almost always advanced by the time any clinical signs become apparent, such as hepatomegaly, an enlarged stomach, or the eponymous Sister Mary Joseph nodule or Virchow's node (palpable umbilical or left supraclavicular metastatic nodal deposits, respectively). Common sites of metastasis from gastric cancer include loco-regional lymph nodes, the liver and the peritoneum.

There are a number of possible causative factors for the development of gastric cancer, including dietary (e.g. smoked meats, pickled vegetables, salted fish), which may contribute to the striking regional variations in incidence. *Helicobacter pylori* infection, chronic gastritis, pernicious anaemia and previous gastric surgery have also been implicated in its development.[5] Genetic predisposition may be a contributing factor in a small percentage of individuals. For example, the germline mutations associated with hereditary non-polyposis colon cancer (HNPCC),[6,7] and mutations in the gene for E-cadherin are known genetic associations.[8,9]

The most common histological subtype is adenocarcinoma, occurring in 90–95% of patients. Adenocarcinomas have been classified by Lauren[10] into intestinal-type and diffuse-type. Intestinal-type is associated with chronic atrophic gastritis, a glandular structure, sharp margins and minimal invasiveness, while diffuse-type is associated with irregular margins, poor differentiation, and invasion of large areas of the stomach often producing linitis plastica or 'leather bottle' stomach.[10] Lymphomas and gastrointestinal stromal tumours also occur in the stom-

ach, but are not covered in this review. Of interest, in recent years, there has been a change in the location of the primary tumour in the stomach, with an increase in the incidence of more proximally (gastric cardia) located tumours and a decrease in the incidence of distally located tumours.[5] Postulated reasons for this include changing patterns of diet and a decreased incidence of *H. pylori* infection.[11,12]

Perhaps of some encouragement is the slight decline in mortality rates by 3.1% over the years 1994–2003.[1] While effective *H. pylori* treatment is thought to be a contributing factor, it does not entirely explain the decline in mortality. This discussion focuses primarily on chemotherapeutic but also other interventional strategies that have contributed in part to this improvement in mortality rates. The review also discusses novel therapies, already at the forefront in other malignancies, which have shown promise in metastatic gastric cancer.

1. Commonly Used Chemotherapy Regimens

There is no true 'gold standard' regimen in the treatment of advanced gastric cancer. A Cochrane meta-analysis of randomized phase II and III trials in advanced gastric cancer[13,14] concluded that chemotherapy produced an overall survival benefit over best supportive care (hazard ratio [HR] 0.39) and that combination chemotherapy was more effective than single-agent treatment (HR 0.85). A significant survival benefit was seen for regimens that included fluorouracil (5-FU), anthracyclines and cisplatin.

To date, therefore, the most commonly used chemotherapy regimen for advanced disease is a doublet or triplet regimen based on 5-FU, with cisplatin and/or an anthracycline. The meta-analysis also showed that delivering 5-FU as a continuous intravenous infusion rather than in bolus form reduces the rate of toxic deaths.[14] It should be noted that the meta-analysis has been met with some controversy with respect to the benefits of triplet (including anthracyclines) over non-anthracycline regimens utilizing cisplatin and 5-FU only, and differing opinions mean that both doublet and triplet combinations continue to be used worldwide with no true 'reference' standard.[15]

1.1 Epirubicin, Cisplatin plus Fluorouracil (ECF) and Other Combinations

The ECF regimen consists of epirubicin (an anthracycline) and cisplatin (a platinum agent) given on day 1, and 5-FU (an antimetabolite) given as a 21-day continuous intravenous infusion. It is a commonly used regimen for the treatment of advanced gastric cancer in some countries including Australia and the UK, where it is considered 'standard' therapy.[4] However, to date, it has not been as widely used as a reference standard in the US over doublet therapy with cisplatin and 5-FU.[16,17] Two randomized phase III trials have demonstrated superiority of ECF over alternative chemotherapy combinations. The first compared ECF with FAMTX (5-FU, doxorubicin and methotrexate) and demonstrated superior response rate (45% vs 21%; $p = 0.0002$) and median overall survival (8.9 vs 5.7 months; $p = 0.0009$).[18] The second compared ECF with MCF (mitomycin, cisplatin and 5-FU), and while response rate and overall survival were similar, quality of life was superior in those treated with ECF.[19]

Other chemotherapy combinations have also been evaluated. A three-arm, randomized, phase III trial compared FAMTX, ELF (etoposide, folinic acid [leucovorin] and 5-FU) and CF (5-FU and cisplatin), and found no significant differences between the three regimens, with median survivals ranging from 6.7 to 7.2 months.[20] Another randomized study compared ECF with EEC (etoposide, epirubicin and cisplatin) and found no significant differences in response rates or survival.[21] Given that the median overall survival with ECF chemotherapy is <10 months, improvements in systemic therapy are clearly needed, and over the last decade newer and potentially more active chemotherapeutic agents have been evaluated in the setting of advanced gastric cancer (table I).

Table I. Efficacy of newer chemotherapy agents in advanced gastric cancer (selected phase II and III trials)

Study	No. of patients	Treatment arms	Response rate	TTP or PFS	Median survival
Oxaliplatin					
Al-Batran[22]	220	FLO vs FLP	34% vs 27%	5.7 vs 3.8 mo (p = 0.08)	NA
Cunningham (REAL-2)[23]	964	ECF vs EOF vs ECX vs EOX[a]	EOX: 47.9% vs 40.7–46.4% (p = NS)	EOX: 7 vs 6.2–6.7 mo (PFS) [p = NS]	Oxaliplatin arms: 10.4 vs 10.0 mo (p = NS)
Docetaxel					
Elsaid[24]	64	DCF (carboplatin) vs ECF	66.7% vs 44.1%	NA	12.4 vs 8.7 mo (p = 0.0005)
Van Cutsem et al. (TAX325)[25]	445	DCF (cisplatin) vs CF	37% vs 25% (p = 0.01)	5.6 vs 3.7 mo (p < 0.001)	9.2 vs 8.6 mo (p = 0.02)
Paclitaxel					
Murad et al.[26]	31	Paclitaxel + 5-FU	65%	9 mo (PFS)	12 mo
Kollmannsberger et al.[27]	45	Paclitaxel + 5-FU + folinic acid + cisplatin	51%	9 mo (PFS)	14 mo
Honecker et al.[28]	29	Paclitaxel + 5-FU + folinic acid + cisplatin	48%	8 mo (PFS)	11 mo
Irinotecan					
Bouche et al.[29]	134	5-FU + folinic acid + irinotecan vs 5-FU + folinic acid vs 5-FU + folinic acid + cisplatin	40% vs 13% vs 27%	6.9 vs 3.2 vs 4.9 mo (PFS)	11.3 vs 6.8 vs 9.5 mo
Moehler et al.[30]	114	ILF vs ELF	43% vs 24%	4.5 vs 2.3 mo (PFS)	10.8 vs 8.3 mo
Pozzo et al.[31]	115	Irinotecan + 5-FU + folinic acid vs irinotecan + cisplatin	42.4% vs 32.1%	6.5 vs 4.2 mo (p < 0.0001)	10.7 vs 6.9 mo
Dank (V306)[32]	337	5-FU + folinic acid + irinotecan vs CF	NA	5.0 vs 4.2 mo (p = 0.088)	HR 1.08 (p = NS)
Capecitabine					
Cunningham (REAL-2)[23]	964	ECF vs EOF vs ECX vs EOX[a]	EOX: 47.9% vs 40.7–42.4%	EOX: 7 vs 6.2–6.7 mo (PFS)	Capecitabine arms: 10.9 vs 9.6 mo (HR 0.89)
Kang (ML07132)[33]	316	XP vs FP[a]	41% vs 29% (p = 0.03)	5.6 vs 5.0 mo (PFS) [p = 0.08]	10.5 vs 9.3 mo (HR 0.85)

a Powered for equivalence.

5-FU = fluorouracil; **CF** = cisplatin plus 5-FU; **DCF** = docetaxel, carboplatin or cisplatin, 5-FU; **ECF** = epirubicin, cisplatin, 5-FU; **ECX** = epirubicin, cisplatin, capecitabine; **ELF** = etoposide, folinic acid, 5-FU; **EOF** = epirubicin, oxaliplatin, 5-FU; **EOX** = epirubicin, oxaliplatin, capecitabine; **FLO** = 5-FU, folinic acid, oxaliplatin; **FLP** = 5-FU, folinic acid, cisplatin; **FP** = 5-FU plus cisplatin; **HR** = hazard ratio; **ILF** = irinotecan, 5-FU, folinic acid; **NA** = not available; **PFS** = progression-free survival; **TTP** = time to progression; **XP** = capecitabine, cisplatin.

1.2 Taxanes

Taxanes are naturally-derived chemotherapeutic agents derived from the bark of yew trees, which prevent microtubule depolymerization during mitosis. This process disrupts mitosis of cells and hence causes cell cycle arrest. Both paclitaxel and docetaxel have demonstrated clinical activity in metastatic gastric cancer. Toxicities include myelosuppression, peripheral neuropathy and hypersensitivity reactions.

Given the promising results observed in preclinical and early phase studies, both as a single agent and in combination treatment, docetaxel has been evaluated in a small number of phase III studies. A small Egyptian phase III study of 64 patients compared DCF (docetaxel, carboplatin and 5-FU)

with ECF and found an overall response rate of 66.7% for DCF versus 44.1% for ECF and median survival of 12.4 versus 8.7 months ($p = 0.0005$).[24] However, because of the small number of patients in the study, these results must be viewed with caution.

A large international phase III trial reported in 2006 (TAX325 study) has shown encouraging results with a docetaxel-based regimen.[25] This study of 445 previously untreated patients compared DCF (docetaxel, cisplatin and 5-FU) with CF (cisplatin and 5-FU). Time to progression was 5.6 months (DCF) versus 3.7 months (CF) [$p < 0.001$], and median overall survival was 9.2 versus 8.6 months ($p = 0.02$). At 1 year, 40% versus 32% of patients were alive, and at 2 years 18% in the DCF arm were still alive. Toxicity was higher in the DCF arm, which needs to be carefully considered given its impact on a patient's quality of life and survival. Chemotherapy delays were necessary in 64% of patients in the DCF arm, the most common reason being lethargy. Patients in both arms of the trial experienced a high incidence of grade 3 and 4 toxicities (46% for DCF and 42% for CF). Neutropenia was significant: 82% grade 3–4 neutropenia for DCF versus 57% for CF. There was a 29% incidence of febrile neutropenia and neutropenic infection for DCF, and 12% for CF. Even with the use of secondary granulocyte colony-stimulating factor prophylaxis, the rate of neutropenic infection was 12%. Grade 3 or 4 gastrointestinal toxicities were seen in nearly 50% of patients in both arms. Despite the high incidence of toxicities, quality of life, as measured by global health status questionnaire, was found to be significantly better with DCF, as was time to deterioration of Karnofsky performance status. While the results with DCF are encouraging, it should be noted that the improvement in median survival is small (18–20 days) and this needs to be balanced against the significant toxicity associated with this regimen. A statistically significant benefit does not always translate to a meaningful clinical benefit, and the balance between efficacy and toxicity, as well as failure to actually improve quality of life, has been discussed in recent publications.[34,35]

Paclitaxel has thus far been examined only in phase II studies, both as monotherapy and in combination with other agents. Paclitaxel, cisplatin and 5-FU in various combinations have been studied in a number of phase II trials,[27,28,36,37] where response rates of about 50% and median survival times up to 14 months have been observed. Similarly to docetaxel, myelosuppression (particularly neutropenia) is the major dose-limiting toxicity. Further studies including randomized phase III trials are necessary to determine the role of paclitaxel in advanced gastric cancer.

1.3 Oxaliplatin

This platinum-based agent acts by forming bulky platinum-DNA adducts, generating intrastrand and interstrand cross-links and thus blocking DNA replication. It is considered standard therapy, in combination with 5-FU, in the adjuvant and metastatic treatment of colorectal cancer. The main toxicity associated with oxaliplatin is sensory peripheral neuropathy, which can be of two types: an acute, temporary cold-related dysaesthesia and a chronic cumulative, persistent sensory neuropathy, which is dose limiting. It is considerably less nephrotoxic than cisplatin and is not ototoxic.

There have been multiple phase II studies evaluating oxaliplatin for advanced or metastatic gastric cancer in combination with 5-FU plus folinic acid, docetaxel or irinotecan, which have demonstrated response rates up to 56% and median survival up to 11.5 months.[38-41] Results of a phase III trial comparing FLO (5-FU, folinic acid and oxaliplatin) with FLP (5-FU, folinic acid and cisplatin) have recently been reported.[22] In this study of 220 patients, time to progression was 5.7 months (FLO) versus 3.8 months (FLP) [$p = 0.08$], and time to treatment failure was 5.3 versus 3.1 months ($p = 0.028$). Overall survival data are not yet available. Toxicities such as leukopenia, fatigue, alopecia and renal impairment were less in the FLO arm, whereas peripheral neuropathy was increased.

Preliminary results of the REAL-2 study, involving 964 patients, have been reported.[23,42] This four-arm study uses ECF as the reference arm to compare

the efficacy of oxaliplatin with cisplatin and capecitabine with 5-FU in a two-by-two factorial design. Previously untreated patients with metastatic oesophageal or gastric cancer were randomized to ECF, EOF (epirubicin, oxaliplatin, 5-FU), ECX (epirubicin, cisplatin, capecitabine) or EOX (epirubicin, oxaliplatin, capecitabine). This study was powered for noninferiority, and this was demonstrated when comparing oxaliplatin-containing with cisplatin-containing regimens, as well as capecitabine with 5-FU-containing arms. The median overall survival for the oxaliplatin arms was 10.4 months versus 10.0 months for the cisplatin arms. The HR was 0.92 (95% CI 0.8, 1.1), which met the endpoint for noninferiority. Progression-free survival was best for the EOX arm – 7.0 months versus 6.7, 6.5 and 6.2 months for the other arms. The best response rate was seen in the EOX arm with a 47.9% response rate (not statistically significantly different from the 40.7% response rate in the reference ECF arm; $p = 0.112$). In terms of toxicity, there was less neutropenia and alopecia, but more diarrhoea and peripheral neuropathy in the oxaliplatin-containing arms. Neutropenia was significantly less in the oxaliplatin arms (27–30% vs 41–50%), although the rates of febrile neutropenia were similar (6.7–9.3% over the four arms). There were also significantly fewer thromboembolic events (both arterial and venous) in the oxaliplatin arms compared with the cisplatin arms (8.2% vs 15.9%; $p = 0.0003$).[43] On the basis of the results of this phase III trial, it appears that oxaliplatin can be substituted for cisplatin in terms of efficacy in the treatment of advanced gastric cancer, and decisions regarding the most appropriate regimen for an individual may be determined by their different toxicity profiles.

1.4 Irinotecan

Irinotecan is a camptothecin (natural plant alkaloid) derivative that inhibits topoisomerase I, thereby impeding DNA uncoiling and replication leading to double-stranded DNA breaks. Toxicities include diarrhoea (in up to 40% of patients in colorectal cancer trials[44,45]) and neutropenia.[46] Several randomized phase II studies have been reported that demonstrate impressive results with irinotecan in combination with other agents. Bouche et al.[29] reported a study of 136 patients that compared 5-FU and folinic acid either alone, with cisplatin or with irinotecan and found response rates of 13%, 27% and 40% and median overall survival of 6.8, 9.5 and 11.3 months, respectively. Another study compared ILF (irinotecan, 5-FU and folinic acid) with ELF (epirubicin, 5-FU and folinic acid) in 114 patients and found a 43% versus 24% response rate and a 10.8- versus 8.3-month median overall survival, in favour of irinotecan.[30] A third randomized phase II study compared ILF with irinotecan and cisplatin in 115 patients, and found a 42.4% versus 32.1% response rate, and median time to progression of 6.5 versus 4.2 months ($p < 0.0001$).[31] As a result of this trial, ILF was further investigated in a phase III setting (V306 study), which has been reported in an abstract.[32] This trial of 337 previously untreated patients compared ILF with CF. Time to progression was 5.0 versus 4.2 months ($p = 0.088$, not significant), with no difference in overall survival. The irinotecan-containing arm was associated with more diarrhoea, but the cisplatin arm was associated with more neutropenia, stomatitis and nausea. Unfortunately, this phase III study has not confirmed the initially promising phase II results; however, it appears that irinotecan is not inferior to cisplatin-containing arms, although the study was not powered to demonstrate this. Although the toxicity profiles are different, it appears that, on balance, the irinotecan-based regimen may be better tolerated than the cisplatin-based regimen.

Irinotecan has also been combined with taxanes in phase II trials, where response rates of 20–50% have been observed. However, toxicity has been considerable and may preclude the routine use of these combinations. Overall, it is likely that irinotecan can be appropriately added to the range of active agents used in combination against metastatic gastric cancer, although there is no efficacy advantage over cisplatin shown to date in the phase III setting. Again, it seems that the toxicity profile will be the main factor deciding the choice of regimen.

1.5 Oral Fluoropyrimidines

There are a number of new oral prodrugs of 5-FU undergoing evaluation in phase I–III clinical trials for metastatic gastric cancer. The advantage of the oral route of therapy is ease of administration. There is no need for central venous access devices with their inherent complications such as thrombosis and infection. In addition, oral administration dispenses with the need for ambulatory pumps and frequent visits to hospital. Oral delivery, rather than intravenous infusion, is preferred by most patients, and it may be associated with a potentially improved therapeutic index and possible pharmacokinetic advantages. However, caution is required in the elderly or confused patient, where polypharmacy may result in administration or compliance errors with the risk of severe toxicity or reduced efficacy.

1.5.1 Capecitabine

This oral fluoropyrimidine prodrug is converted to 5-FU in three enzymatic steps. The final step involves the enzyme thymidine phosphorylase, which is present at higher concentrations in tumour cells, thereby resulting in an increased concentration of 5-FU at the site of the tumour.[47] It is now used commonly in the treatment of metastatic breast cancer, and both in the adjuvant and metastatic setting for colorectal cancer. In colorectal cancer, capecitabine has been shown to be at least equivalent in efficacy to bolus 5-FU.[48] Therefore, it could potentially be used in place of intravenous infusional 5-FU in combination chemotherapy for metastatic gastric cancer. The main adverse effects of capecitabine are diarrhoea and hand-foot syndrome (red, dry, cracked palms and soles which in severe cases can be associated with fissuring of the skin).

Numerous phase I and II clinical trials of capecitabine have shown clinical benefit in patients with gastric cancer.[49] Most of these have been in previously untreated patients. As a single agent, response rates between 6% and 32% have been observed,[50-52] and in combination with other agents (cisplatin, taxanes, irinotecan, oxaliplatin) response rates up to 67% and median survival rates as high as 17.2 months have been reported.[53] Even as second-line treatment, capecitabine has demonstrated clinical benefit with phase II trials showing response rates of 14–32% and median survivals of 6.3–9.9 months.[54,55]

Two important noninferiority phase III trials involving capecitabine in metastatic gastric cancer have been reported recently. The first study (REAL-2) of 964 patients, which compared ECF, EOF, ECX and EOX, has been described in section 1.3.[23,42] When comparing the arms containing capecitabine with those containing 5-FU, the median overall survival was 10.9 months for capecitabine versus 9.6 months for 5-FU (HR on multivariate analysis 0.89; 95% CI 0.89, 1.02). Progression-free survival differences were not statistically significant. Overall, the EOX arm demonstrated the best overall response (complete and partial responses) with 47.9%, versus 46.4% for ECX, 42.4% for EOF and 40.7% for ECF. None of these were statistically significantly different from the reference ECF arm. The best overall survival was also seen in the EOX arm (11.2 vs 9.9 months for ECF; p = 0.02).

The second study, a phase III trial (ML07132) of 316 patients, compared capecitabine and cisplatin (XP) with 5-FU and cisplatin (FP) in previously untreated patients with metastatic gastric cancer.[33] This study was also powered for noninferiority. Progression-free survival was 5.6 months for XP versus 5.0 months for FP, (HR 0.81; 95% CI 0.63, 1.04; p = 0.08). Response rates were 41% (XP) versus 29% (FP) [p = 0.03]. Again, noninferiority was shown between 5-FU and capecitabine, with a superior response rate demonstrated for capecitabine. Median overall survival was 10.5 months for XP versus 9.3 months for FP (HR 0.85; 95% CI 0.64, 1.13; p-value not significant).

Overall, capecitabine is a promising new drug in the treatment of metastatic gastric cancer and seems likely to move into regular clinical use in the near future. Rather than providing major efficacy advantages compared with 5-FU, its main benefit is in the ease of administration and thus quality-of-life gains for patients.

1.5.2 S-1

S-1 has been described as a 'fourth-generation designer drug',[56] because the combination of mole-

cules used to create the drug is based on the pharmacokinetics of 5-FU. It is an oral fluoropyrimidine containing tegafur (a 5-FU prodrug) combined with 5-chloro-2,4-dihydroxypyridine (an inhibitor of dihydropyridine dehydrogenase [DPD], which metabolizes 85% of 5-FU[57]) and oxonic acid (a pyrimidine phosphoribosyltransferse inhibitor, which reduces phosphorylation of 5-FU in the gastrointestinal tract to potentially reduce gastrointestinal toxicity[58]). Thus, in theory, more 5-FU is able to be delivered via the oral route with fewer gastrointestinal adverse effects. Myelosuppression is more common than with other oral fluoropyrimidine derivatives.[59] S-1 is registered for use in Japan, where phase II studies have demonstrated response rates of up to 49% and median survival up to 16.7 months[60,61] when used as a single agent. S-1 has also been examined in combination with irinotecan, paclitaxel and cisplatin in phase I/II studies, again mainly in Japan. For the combination of S-1 and cisplatin, in 19 evaluable patients a response rate of 74% was obtained and median survival time of 383 days.[62] A retrospective review of 110 Japanese patients that compared those who had been given S-1 versus those treated with any other chemotherapy demonstrated a median survival time of 429 days for patients treated with S-1 therapy compared with 236 days for patients without S-1.[63]

The majority of data supporting the use of S-1 to date has come from Japan. However, early data from Western nations do not demonstrate the same degree of benefit for S-1. A European phase II study of 23 patients found a response rate of 26.1%.[64] A US phase II study of 47 patients using S-1 and cisplatin was more promising with a response rate of 51% and median survival of 10.9 months.[65] The differences are possibly attributable to ethnic and genetic variation in enzyme levels. Certainly the degree of toxicity reported in Western compared with Asian studies differs; this is thought to be due to genetic polymorphisms in the cytochrome P450 (CYP) system, particularly CYP2A6 responsible for metabolizing tegafur to 5-FU.[56] Large phase III trials are currently under way to further evaluate the efficacy of S-1 in combination with cisplatin, but certainly its use is already established in the Japanese population, despite the fact that to date only phase II studies have been completed.

1.5.3 Tegafur/Uracil

Another oral fluoropyrimidine is tegafur/uracil or UFT, which contains the competitive inhibitor of DPD, uracil. Although early studies with tegafur/uracil reported response rates between 9% and 40% and median survival times from 5.8 to 15 months,[66-69] these results have not been reproduced in the phase III setting. A Japanese, three-arm, phase III study comparing tegafur/uracil and mitomycin with 5-FU alone or 5-FU and cisplatin revealed disappointing results, with inferior response rate and median overall survival in the tegafur/uracil plus mitomycin arm.[70] Currently, there is no evidence to support the use of tegafur/uracil in advanced gastric cancer.

With respect to the oral fluoropyrimidines, it is likely that future research efforts will be devoted to the development of capecitabine and S-1 in the management of advanced gastric cancer.

1.6 Summary

In summary, the role of chemotherapy in the management of advanced gastric cancer continues to evolve. The recent addition of new and active agents used in various combinations allows the optimal choice of first-line treatment to be tailored to individuals based on patient co-morbidity and the toxicity profiles of particular drugs.

The optimal duration of chemotherapy in the metastatic disease setting will depend on treatment response and tolerability. While the duration of some chemotherapy agents may be limited by toxicity (e.g. maximum 6–8 cycles of anthracycline owing to cumulative cardiotoxicity; cumulative neuropathy with oxaliplatin or taxanes), it is not unreasonable to continue with chemotherapy if a patient continues to derive clinical benefit and quality of life is not adversely affected. However, most trials have decreed 6–8 cycles of chemotherapy treatment and this is generally reflected in clinical practice.

Table II. Efficacy of targeted therapies in advanced gastric cancer (phase II)[a]

Study	No. of patients	Prior treatment	Treatment	Response rate	Median survival
Bevacizumab					
Shah et al. (2006)[71]	47	No	Bevacizumab + irinocetan + cisplatin	65%	12.3 mo
Enzinger et al. (2006)[72]	20	Yes (most)	Bevacizumab + docetaxel	27%	Ongoing
Cetuximab					
Stein (2007)[73]	13	Yes	Cetuximab + irinotecan	'Tumour control rate' 62%	3.61 mo
Pinto et al. (2007, 2006)[74,75]	38	No	Cetuximab + irinotecan + 5-FU + folinic acid (FOLFIRI)	44.1%	Ongoing (55.3% alive at 11 mo)
Gefitinib					
Doi (2003)[76]	75	Yes	Gefitinib monotherapy	'Disease control rate' 18.3% (1 PR, 13 SD)	Not reported
Erlotinib					
Dragovich et al. (2006)[77]	70	No	Erlotinib	0 (for gastric cancer)	3.5 mo
Bortezomib					
Ocean (2007)[78]	40	Yes (12)	Bortezomib monotherapy	9%	5.4 mo
		No (28)	Bortezomib + irinotecan	44%	4 mo

a Some of these studies have also included gastroesophageal junction.

5-FU = fluorouracil; **PR** = partial response; **SD** = stable disease.

2. Targeted Therapies and Novel Agents

Rationally designed inhibitors of circulating growth and angiogenic factors, their cell surface receptors and corresponding intracellular downstream pathways including those activated by tyrosine kinases are being increasingly used, either in combination with or as an alternative to chemotherapy (table II). Rather than directly affecting DNA and mitosis as with conventional chemotherapy, targeted therapies aim to affect other mechanisms by which cancer cells grow (i.e. cell proliferation, apoptosis, angiogenesis, etc.) and are an ever-expanding component of oncology therapies used across a range of tumour types.

2.1 Bevacizumab

Bevacizumab is a humanized monoclonal antibody targeting vascular endothelial growth factor (VEGF), a potent angiogenic factor contributing to tumour growth. The antibody-bound form of VEGF is unable to bind to its cell surface receptor, preventing activation of an intracellular tyrosine kinase pathway that regulates cell proliferation, angiogenesis and cell survival. Its use is already well established in the treatment of metastatic colorectal cancer, and promising results have been seen in trials for breast and lung cancer. In gastric cancer, the expression of VEGF increases with increasing stage and tumour burden.[79,80] Shah et al.[71] have recently reported the results of a phase II study involving 47 previously untreated patients with metastatic gastric or gastroesophageal junction cancer who were treated with bevacizumab combined with irinotecan and cisplatin. In the 34 patients with measurable disease, the response rate was 65% and median survival was 12.3 months. However, the treatment was associated with considerable toxicity. Grade 3 hypertension was seen in 28% of patients, while two patients developed gastric perforation and one had a myocardial infarction. Twelve patients (25.5%) developed venous thromboembolism and, although this is a recognized complication of bevacizumab therapy, the observed rate is higher than that documented in other tumour types.[81] Despite potentially serious adverse effects, these early

encouraging results with bevacizumab warrant further evaluation in the treatment of advanced gastric cancer. The UK Medical Research Council (MRC) has opened a randomized phase II/III study (ST03) that will evaluate perioperative chemotherapy (ECX) with or without bevacizumab, in patients with resectable gastric cancer.[82]

2.2 Cetuximab

Cetuximab is a chimeric monoclonal antibody targeting the epidermal growth factor receptor (EGFR)-1 and inhibiting its function. It is administered intravenously and is currently used in the treatment of metastatic colorectal cancer. A recently reported study[73] examined 13 heavily pretreated patients with metastatic gastric cancer undergoing treatment with cetuximab and irinotecan, and reported a tumour control rate of 62% and median overall survival of 101 days. The FOLCETUX (FOLFIRI/cetuximab) study, a phase II study of 38 previously untreated patients with advanced gastric or gastroesophageal adenocarcinoma, used FOLFIRI (bolus and infusional 5-FU, folinic acid and irinotecan) in combination with cetuximab, and demonstrated an overall response rate of 44.1% and median time to progression of 8 months.[74] At the time of publication, the median follow-up time was 11 months and 55.3% of the patients were alive. These early results are encouraging, albeit at the expense of some moderate toxicity – grade 3–4 neutropenia in 42.1% and grade 3–4 rash (a common toxicity of cetuximab) in 21.1%.

2.3 Gefitinib and Erlotinib

Gefitinib is an orally administered tyrosine kinase inhibitor, which blocks signal transduction arising from EGFR-1. This receptor promotes cell proliferation and is overexpressed in up to one-third of advanced gastric malignancies.[83] Common adverse effects of tyrosine kinase inhibitors include acneiform rash and fatigue. Gefitinib has demonstrated mixed results when used as monotherapy in early studies in advanced gastric cancer, with one phase II trial in pretreated patients demonstrating an 18.3% disease control rate.[76] A substudy showed that while EGFR activation was reduced, not all further downstream signalling pathways were inhibited,[84] suggesting that as monotherapy, gefitinib is not likely to demonstrate significant activity in gastric cancer.

Erlotinib is also an oral tyrosine kinase inhibitor blocking EGFR-1, with an adverse effect profile similar to that of gefitinib. A recent phase II trial has been reported in 70 previously untreated patients with metastatic or unresectable gastroesophageal junction and gastric cancer.[77] No response was seen in patients with gastric cancer and median survival was only 3.5 months. For gastroesophageal junction tumours, the response rate was 9% and median survival 6.7 months. These results are disappointing given that with chemotherapy the median survival of patients with advanced gastric cancer is about 10 months. Although the assessment of response by conventional radiographic techniques can be difficult with targeted therapies (they may be cytostatic without causing marked tumour shrinkage), the poor median survival suggests that erlotinib as monotherapy has no activity in previously untreated patients with advanced gastric cancer.

On the basis of the limited data available, it appears that when used as monotherapy, oral tyrosine kinase inhibitors have minimal clinical benefit for pretreated or never-treated patients with advanced gastric cancer. To date, their role in combination therapy is unknown, but given the relatively poor results demonstrated in phase II trials, it is unclear whether they will be pursued in further studies.

2.4 Trastuzumab

Trastuzumab is a humanized monoclonal antibody targeting the EGFR-2 (or human epidermal receptor – HER-2 or erb B2). Its role is established in the treatment of breast cancer, both in the adjuvant and metastatic disease settings. HER-2 is overexpressed in up to 12% of gastric cancers, with the highest rate of overexpression seen in patients with advanced disease.[85-89] Isolated case reports exist suggesting clinical efficacy with the use of trastuzumab in advanced gastric cancer.[90,91] An ongo-

ing phase III study (ToGA study) is currently comparing trastuzumab and chemotherapy versus chemotherapy alone for patients with HER-2-positive previously untreated advanced gastric cancer.

2.5 Bortezomib

Bortezomib is a proteasome inhibitor, which prevents the degradation of ubiquinated proteins by the mammalian 26S proteasome. This inhibition of proteolysis affects multiple signalling pathways within the cell. Bortezomib is given intravenously and its use is established in multiple myeloma. Results of a phase II trial have been presented in an abstract[78] for both pretreated (n = 12) and treatment-naive (n = 28) patients with advanced gastric cancer. Pretreated patients (arm A) were given single-agent bortezomib, which achieved a response rate of 9%; untreated patients (arm B) received bortezomib in combination with irinotecan, which achieved a response rate of 44%. However, median overall survival was poor: 5.4 months in arm A and only 4 months in arm B. Severe toxicities were observed including one cardiac arrest, one stomach perforation and three toxic deaths. Despite a good response rate for previously untreated patients, the poor overall survival and considerable toxicity suggest that bortezomib will not become commonly used in the treatment of advanced gastric cancer.

2.6 Summary

In summary, targeted therapies have, to date, demonstrated only modest clinical activity and benefit in advanced gastric cancer, although their use will continue to be explored in ongoing and future trials. Advanced gastric cancer provides an ideal environment for pharmacodynamic studies of markers of response to targeted therapies, as it is relatively easy to obtain tissue samples from gastroscopy, as well as blood samples at baseline and during therapy. Potential markers such as intratumoral EGFR, phosphorylated EGFR, mitogen-activated protein kinase and transforming growth factor-α are being investigated for their role in prediction of clinical outcome.[77,84]

3. New Developments in Locally Advanced Gastric Cancer

The major advances seen in the last 5 years with respect to the treatment of gastric cancer have been in the neoadjuvant and adjuvant settings. Significant progress has been made, with statistically significant survival advantages being achieved with the addition of perioperative treatment to patients undergoing curative resection. It is likely that further progress will be seen as the newer-generation cytotoxic agents showing promise in metastatic disease are evaluated in the adjuvant setting.

The majority of patients with potentially curable gastric cancer present with stage II or III disease (implying either a large, invasive primary tumour or node-positive disease). Given that the risk of postoperative recurrence is high, multiple trials have been carried out in an attempt to reduce the risk of recurrence in this setting. Until recently, no survival benefit has been seen for adjuvant radiotherapy or chemotherapy treatment. In fact, several meta-analyses evaluating the role of adjuvant chemotherapy in the Western world have not demonstrated convincing evidence of benefit, although some demonstrate marginal benefits.[92-95] Even more recently published adjuvant chemotherapy trials have failed to show any convincing evidence of benefit.[96-100] However, adjuvant chemotherapy is used more commonly in Asian countries, particularly Japan, where a number of studies have demonstrated survival benefits in this population,[101-103] including a recently reported trial showing an 80.5% versus 70.1% overall survival benefit at 3 years with S-1 monotherapy when compared with surgery alone.[104]

The landscape has changed significantly with the recent publication of two landmark trials: the US Intergroup trial 0116 (postoperative chemoradiation)[105] and the UK MRC MAGIC (Medical Research Council Adjuvant Gastric Infusional Chemotherapy) trial (perioperative chemotherapy).[106]

The Intergroup trial (INT 0116) is the largest adjuvant study in gastric cancer conducted in North America. It randomized 556 patients with resected gastric or gastroesophageal junction adenocarcino-

ma to surgery alone or surgery plus postoperative chemoradiation (5 weeks of radiotherapy plus 5-day cycles of daily bolus 5-FU and folinic acid before, during and after radiation). A statistically significant median survival benefit of 36 versus 27 months ($p = 0.005$) was seen for the chemoradiation arm, with a HR for relapse (without adjuvant treatment) of 1.52 ($p < 0.001$). The 3-year survival rate was 50% in the chemoradiation arm versus 41% in the surgery-alone arm ($p = 0.005$).

The results of this trial have not been embraced by all clinicians, for a number of reasons. There has been much debate regarding the quality of the surgical techniques, in particular the level of nodal dissection. It has been claimed that the benefits of chemoradiation are only due to the compensation of poor surgery, and that these benefits would not be seen if a D1 (limited) or D2 (extended) node dissection had been performed. In support of this argument, the proponents of this view cite the similar survival rates for patients receiving chemoradiotherapy in INT 0116 (50%) and patients undergoing D2 dissection in the Dutch randomized trial of extended lymph node dissection (47%).[107] However, the patient populations for these two studies are different, with patients enrolled to INT 0116 having generally more advanced tumours. It is possible that better surgery using a formal D1 or D2 dissection may decrease the need for radiation. On the other hand, it is also possible that when better surgery is combined with chemoradiation, there may be a further improvement in local control as seen in INT 0116. In addition, the chemotherapy regimen of bolus 5-FU and folinic acid is considered outdated by today's standards given that more active regimens, particularly infusional rather than bolus 5-FU, and newer agents in combination with 5-FU are now available. Toxicities were not insignificant: grade 3 or higher haematological and gastrointestinal toxicities were seen in 54% and 33% of patients, respectively; and three patients (1%) died from treatment-related toxicity. While local control was improved, the rate of distant metastatic disease was unchanged, suggesting that this chemotherapy regimen may be merely acting as a radiation sensitizer rather than producing adequate systemic benefits. There have also been concerns regarding the radiotherapy planning and treatment techniques used in INT 0116. Nevertheless, given the striking survival benefits seen, adjuvant chemoradiation has become a standard of care after resection of gastric cancer with curative intent.

The MAGIC trial, published in 2006, randomized 503 patients to perioperative chemotherapy or surgery alone. The chemotherapy consisted of ECF given as three cycles before surgery (i.e. neoadjuvant) and three cycles postoperatively. There were no differences in surgical mortality or morbidity following neoadjuvant treatment. The 5-year survival rate was 36% for perioperative chemotherapy versus 23% for surgery alone ($p = 0.009$). The hazard ratio for progression was 0.66 (95% CI 0.53, 0.81; $p < 0.001$). Neoadjuvant chemotherapy appeared to downstage tumours, with 69.3% of patients who received chemotherapy undergoing a curative (R0) resection compared with 66.4% in the surgery-alone group. Eighteen percent of operations in the chemotherapy arm were considered palliative compared with 28% in the surgery-alone arm. Postsurgical histopathological findings also supported the observation of tumour downstaging by chemotherapy, with the finding of lower-stage tumours in the perioperative chemotherapy arm.

The chemotherapy was difficult to complete. Only 54.8% of those assigned to receive chemotherapy began postoperative chemotherapy for multiple reasons. In total, 104 of 250 patients (42%) completed all six cycles of chemotherapy. Despite this, the survival advantages for perioperative chemotherapy were both statistically and clinically significant. Preoperative chemotherapy alone may thus carry a survival advantage, although the study was not powered for such analysis and does not answer this question. Toxicity was acceptable in patients receiving chemotherapy, with 25% experiencing grade 3 or 4 granulocytopenia, and while nearly all experienced some diarrhoea, it was grade 3 or 4 in only 2.6% (preoperatively) and 3.6% (postoperatively). Grade 3 or 4 nausea was experienced in 6.4% (preoperatively) and 12.3% (postoperatively). Perioper-

ative ECF chemotherapy now represents an alternative standard of care for patients seen preoperatively.

Further studies are being proposed to answer some of the new questions that have arisen as a result of the INT 0116 and MAGIC trials. For example, what are the relative roles of postoperative chemotherapy (as given in MAGIC) versus postoperative chemoradiation (as given in INT 0116) in patients who have received preoperative chemotherapy followed by surgery? Another important question relates to the role of preoperative chemotherapy or chemoradiation. Given that the majority of postoperative adjuvant chemotherapy trials have been negative, interest is now turning to preoperative chemotherapy alone, partly based on the MAGIC trial results, and some clinicians believe that preoperative rather than postoperative chemotherapy may be a more effective treatment.[108] A previous trial attempting to address the question of preoperative versus postoperative chemotherapy was stopped prematurely because of slow accrual.[109] Although phase II studies of neoadjuvant chemotherapy alone appear promising, its true efficacy remains to be proven. A small randomized trial of 59 patients demonstrated worse overall survival in the arm receiving preoperative chemotherapy.[110] The role of preoperative chemoradiation is also being actively investigated given the impressive results that have been obtained in the postoperative setting.

Ongoing trials are now investigating new systemic agents with radiotherapy to establish efficacy compared with 5-FU and folinic acid. A prospective study by Leong et al.[111] examined 26 patients with either resected or locally advanced unresectable gastric cancer who were treated with one cycle of ECF, followed by radiotherapy with continuous infusional 5-FU and another two cycles of ECF. Grade 3 and 4 toxicities occurred in 38% and 15% of patients, respectively (most commonly haematological and gastrointestinal). This small study suggests that combining ECF with chemoradiotherapy is indeed feasible, with an acceptable toxicity profile. A similar study employing the same regimen in 21 patients after surgery also demonstrated an acceptable toxicity profile.[112] This postoperative regimen is currently being compared with the INT 0116 regimen in an ongoing randomized phase III trial in the US.[113] Other drugs have also been shown to be useful radiosensitizers, and both irinotecan and paclitaxel combined with radiotherapy have demonstrated response rates of 56–58% in patients with gastric cancer.[114,115]

Neoadjuvant chemoradiation has shown promising results in early phase studies. Ajani et al.[116] reported a phase II study involving 34 patients with potentially resectable gastric cancer, who received two cycles of induction chemotherapy (5-FU, folinic acid and cisplatin) followed by chemoradiation (infusional 5-FU) and then surgery. At surgery, the pathological complete response rate was 30% and the R0 resection rate was 70%. The median survival time was 34 months and the 2-year survival rate was 54%. A RTOG (Radiation Therapy Oncology Group) phase II study of 49 patients has investigated the role of preoperative paclitaxel-based chemoradiation prior to surgery, and achieved an R0 resection rate of 77% and pathological complete response rate of 27%.[117] These promising results with preoperative chemoradiation warrant further evaluation in a randomized phase III trial.

These new developments in the management of locally advanced gastric cancer have resulted in a surge of renewed interest in gastric cancer treatment. Researchers will endeavour to improve cure rates even further with new trials under way that build on the beneficial information that has come to light in the last few years. Currently, patients who present with locally advanced gastric cancer should ideally be discussed in a multidisciplinary team setting, and considered for clinical trials of preoperative plus or minus postoperative therapy where available; beyond this, in the absence of definitive guidelines, the choices for such a patient depend on regional and geographical preferences.

4. On the Horizon

While clinical trials will continue to evaluate new cytotoxic agents and targeted therapies, several alternative and novel methods of managing gastric

cancer are being examined, some of which are discussed in this section.

4.1 Pharmacogenomic Profiling

A recent study has described the results of genotyping 13 polymorphisms in nine genes from 175 patients with advanced gastric cancer, and correlating these with subsequent outcomes.[118] All patients were treated with 5-FU plus cisplatin-based chemotherapy. The study found that chemoresistance and poor survival was significantly associated with certain polymorphisms; in particular, two genotypes (thymidylate synthase [TS] 5′-UTR 3G- and glutathione S-transferase [GST] P1 105A/A). Of the 175 patients, 114 (65%) had either one or both risk genotypes, and their progression-free and overall survival was significantly worse than for patients who did not have either of these genotypes. Pretreatment genotyping may therefore select certain patients who may benefit more from palliative chemotherapy than others. Alternatively, the future selection of which chemotherapy regimen to use may become guided by an individual patient's genotype, thereby allowing individualization of treatment. Further development in the area of pharmacogenomic profiling will need to consider studies in larger patient cohorts treated in a uniform fashion, and with prospective validation of results.

4.2 Vaccine Therapy

Gastrin is a naturally occurring hormone, which is a potent growth factor for gastrointestinal cancers. A vaccine named G17DT has been developed that produces an antigastrin antibody, which opposes gastrin and its effects. Results of a phase II study examining the effects of this vaccine have been reported.[119] Gastrin, which is trophic to gastric cancer, is overexpressed in gastric malignancies, and antigastrin antibodies ideally produce an antiproliferative effect. This study examined 103 treatment-naive patients treated with G17DT combined with cisplatin and 5-FU; the overall response rate was 30% and the median survival was 9.0 months, but for immune responders (>60%) the median survival was 10.3 months, versus 3.8 months for immune nonresponders. Successful vaccination was shown to be an independent prognostic factor. Given that the response rate and median survival are similar to published data with chemotherapy alone, the role of G17DT remains uncertain.

4.3 Intraperitoneal Chemotherapy

Intraperitoneal administration of chemotherapy following surgery has demonstrated significant survival benefits in phase III studies for ovarian cancer.[120,121] The basis of its success in this setting is that ovarian cancer tends to spread by local shedding and seeding of the peritoneal cavity. Early studies also suggest benefit in gastric cancer.[122-124] The role of intraperitoneal chemotherapy following curative resection of gastric cancer is to be examined in a phase I/II study where patients will receive two cycles of intraperitoneal floxuridine (a pyrimidine analogue similar to 5-FU) followed by postoperative chemoradiation as delivered in INT 0116. Although distant relapse is unlikely to be reduced, intraperitoneal administration of chemotherapy may provide greater tumour control within the abdomen.

4.4 Novel Agents

Other therapies continue to be examined for their potential role in the treatment of gastric cancer. For example, preclinical studies have shown apoptosis of gastric cancer cells in response to pterostilbine (an active constituent of blueberries) and acacetin (a flavonoid compound).[125,126] Increasing understanding of other pathways, such as the mitogen activated protein (MAP) kinase, phosphoinositide 3 (PI3) kinase and mammalian target of rapamycin (mTOR) pathways, in gastric cancer cells may lead to the development of other potential targets for novel therapies.

5. Conclusions

While progress in the treatment of patients with advanced gastric cancer has been slow, there have nevertheless been some clear advancements. Clinical trials demonstrating efficacy of newer cytotoxic agents including the taxanes, oxaliplatin and irinote-

can have resulted in alternative, effective regimens, and while work on targeted therapies is still early, it is hoped that future studies will provide evidence of further benefit. The development of orally administered 5-FU analogues means that chemotherapy administration will become much easier for patients undergoing treatment. Finally, it is hoped that improvements in adjuvant therapy for localized gastric cancer will see a reduction in the number of patients progressing to metastatic disease.

Acknowledgements

No sources of funding were used to assist in the preparation of this review. The authors have no conflicts of interest that are directly relevant to the contents of this review. No other persons have made substantial contributions to the work.

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