Is There an Optimal Chemotherapy Regimen for the Treatment of Advanced Gastric Cancer That Will Provide a Platform for the Introduction of New Biological Agents?

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ABSTRACT

Globally, gastric cancer is the second most common cause of cancer-related death. The majority of gastric cancer patients will have at presentation or will ultimately develop overt metastatic disease. Meta-analysis has demonstrated not only that systemic chemotherapy can improve survival in patients with advanced disease but also that the best survival results in earlier randomized studies have been achieved with three-drug regimens containing a fluoropyrimidine, an anthracycline, and cisplatin. Although there has been little progress historically in improving median overall survival times beyond the 9-month plateau achievable with the standard epirubicin–cisplatin–infusional 5-fluoropyrimidine (ECF) combination, the availability of newer cytotoxic anticancer agents has provided some measure of optimism that current outcomes can be improved. A number of new triplet and doublet combinations incorporating docetaxel, oxaliplatin, irinotecan, capecitabine, and S-1 have been explored in randomized trials. Although some combinations, such as epirubicin–oxaliplatin–capecitabine, have been shown to be as effective as (or perhaps more effective than) ECF, and although promising early data have been derived for S-1 in combination with cisplatin, a lack of studies in which direct comparisons have been made currently hinders the identification of the optimal regimen in this setting. One factor that might contribute to the lack of clear progress is the absence of consensus on the utility of second-line cytotoxic treatments. It can therefore be concluded that, although there is no first-line regimen that is clearly the most appropriate platform for the investigation of biological agents, there are a number of combinations that have been shown to be effective and therefore good candidates. The Oncologist 2008;13:794–806
INTRODUCTION
Globally, gastric cancer is the second most common cause of cancer-related mortality, with over 700,000 attributable deaths reported in 2002 [1]. Although there are wide geographical variations in incidence, with peak age-standardized rates reported for East Asia (Japan and China), it has been estimated that this disease caused in excess of 188,000 deaths in Europe alone in 2006 [2]. Improvement of long-term survival times for patients with gastric carcinoma is an attainable aim in the case of localized disease, for which the quality of surgery and, to a lesser extent, of complementary treatments assumes a significant role. When the disease is at an advanced/metastatic stage, which is the case for approximately two thirds of patients at the time of diagnosis, the natural history is different and the outcome of currently available palliative treatments is rather disappointing. Despite the number of studies that have been carried out in this setting, the most effective regimen for the treatment of advanced disease is not yet clearly established, and it is also not clear in many cases whether particular three-drug combinations are better than individual two-drug combinations.

For many years, there were very few improvements reported in the efficacy of treatments for advanced gastric cancer, and the median survival time of patients in clinical studies remained at between 6 and 9 months. More recently, mirroring progress in colorectal cancer treatment, the availability of new active cytotoxic drugs with differing mechanisms of action and different cellular targets has raised the possibility that survival times might be improved in this setting. As well as the new cytotoxic agents, several phase II and III studies are currently exploring the efficacy and safety of molecularly targeted drugs in the treatment advanced gastric cancer, with the hope that the benefit seen in other tumor types conferred by combining biological agents with standard cytotoxic regimens can be achieved in this setting.

The choice of the optimal chemotherapy regimen for the treatment of advanced gastric cancer needs to be based on a careful consideration of the value of the generally small benefit that we can give to patients. In particular, treatment decisions should take into account the high toxicity that is typical of most chemotherapy regimens commonly used in this setting. For a patient who may often be frail, as a result of nutritional deficiencies and/or surgery-related complications, preserving a good quality of life (QOL), as well as extending the length of life, becomes a key goal. Accordingly, it is important to evaluate performance status (PS), age, and comorbidity, and to avoid the exposure of patients to severe toxicities without a reasonable expectation of a clear advantage in disease control and QOL.

In this review, we consider the outcome of recent randomized studies of newer cytotoxic combinations investigated as first-line treatments for advanced gastric cancer. As always, given that patient populations, measured endpoints, or the criteria used to define similar endpoints may differ, a degree of caution must be exercised when making and attempting to interpret cross-study comparisons. While overall survival is considered by many to be the most valid efficacy endpoint in studies of novel anticancer regimens, the use of other primary endpoints is not uncommon. Indeed, it has been argued that time to progression (TTP) of disease is also a powerful efficacy endpoint in that its use is backed by a solid biological rationale, it requires a shorter follow-up time than overall survival analysis, and its assessment is not affected by the differential use of subsequent lines of poststudy therapy [3]. It can nevertheless be argued that TTP is a surrogate endpoint and might not reflect true patient benefit in relation to extending overall survival or maintaining or improving QOL and/or PS. Alternatively, it can be argued that the insensitivity of this time-to-event parameter to the efficacy of subsequent-line treatment makes TTP particularly useful in relation to measuring the efficacy of first-line treatment. Such concerns, however, might currently be less of an issue in relation to advanced gastric cancer than other tumor types given that the benefit of additional lines of therapy is yet to be formally established in this setting [4].

EFFICACY OF CHEMOTHERAPY FOR GastrIC CANCER PATIENTS: RANDOMIZED STUDIES AND META-ANALYSES—AN HISTORICAL PERSPECTIVE
Until recently, there were many doubts concerning whether patients with advanced gastric cancer received a meaningful survival benefit from chemotherapy. Consequently, best supportive care (BSC) was a practicable and justifiable option for the clinical management of the disease. The systematic review and meta-analysis of randomized studies published in 2006 by Anna D. Wagner and colleagues provided the first unequivocal demonstration that chemotherapy was able to improve survival in this setting compared with BSC [5]. Based on an analysis of three studies of older combination chemotherapy regimens conducted on 184 patients [6–8], an overall hazard ratio (HR) of 0.39 (95% confidence interval [CI], 0.28–0.52) was calculated for chemotherapy versus BSC alone, which represented a weighted mean average survival benefit in favor of chemotherapy of 6 months (Fig. 1).

One crucial point to note in relation to this meta-analysis is the relatively small number of patients examined in the three included trials. These studies were carried out from the end of the 1980s to the beginning of the 1990s, and they showed clear methodological restrictions mainly in relation to difficulties in the accrual of patients. A further compari-
son was also made by Wagner and colleagues [5] between outcomes in advanced gastric cancer following combination (doublet/triplet) versus single-agent therapy. Data from 11 randomized trials [9–19] that included approximately 1,500 patients from several European and U.S. centers were examined (Fig. 2). In the majority of the studies, patients in the control arm received treatment based on 5-fluorouracil (5-FU) administered either as a bolus or continuous infusion. Examining the individual studies, nine of 11 did not show significant differences in survival between the two groups. However, the meta-analysis found a statistically significant advantage (p = .001) in favor of combination compared with single-agent chemotherapy (HR, 0.83; 95% CI, 0.74–0.93), which represented a weighted mean average survival benefit in favor of combination chemotherapy of 1 month. Although small, this benefit may be considered to be clinically relevant given the unfavorable prognosis of advanced gastric cancer, with typical median overall survival times of 5–7 months following 5-FU treatment [14]. Nevertheless, the side effects associated with combination therapy can be severe, and this can be a significant factor in treatment selection, particularly for patients with a poor PS. However, although overall levels of treatment-associated toxicity were generally higher in the combination therapy arms of the included studies, the meta-analysis did not show a statistically significant excess in this group in the number of treatment-related deaths. QOL was assessed in only one study [14], and both the combination and single-agent arms had significant improvements from baseline following treatment. In the future, evaluation of this aspect of treatment should be more often included as a study endpoint in randomized trials in order to facilitate a

Figure 1. Effect of chemotherapy versus BSC on overall survival [6–8].
Abbreviations: BSC, best supportive care; CI, confidence interval.

Figure 2. Effect of multidrug versus single-agent chemotherapy on overall survival [9–19].
Abbreviation: CI, confidence interval.
truly comprehensive assessment of the overall benefit of a new treatment. A new meta-analysis due to report in 2008, the GASTRIC (Global Advanced/Adjuvant Stomach Tumor Research through International Collaboration) project, will include more recent studies and will further examine the benefit of single-agent and combination chemotherapy in this setting.

A standard, commonly adopted regimen is the epirubicin–cisplatin–infusional 5-FU (ECF) combination, which provides objective response rates of 30%–35% and median overall survival times of 8–9 months [20–23]. However, the toxicity of this combination is sometimes a significant factor, particularly for elderly patients and those with comorbidities or a poor PS. Nevertheless, ECF has been reported to be better tolerated than other chemotherapy combinations that have been tested, for instance cisplatin–epirubicin–leucovorin–bolus 5-FU (3% toxic death rate versus 0.6% for ECF [5]). Furthermore, the meta-analysis showed a survival advantage for triple combinations containing 5-FU, cisplatin, and an anthracycline compared with doublets comprising 5-FU plus an anthracycline or 5-FU plus cisplatin [5].

The characteristics of the patients typically enrolled in clinical trials are generally not fully representative of patient populations encountered in routine clinical practice. Patients enrolled in trials are usually relatively young, with a good PS and no or few comorbidities, elements that are not typical of patients affected by advanced gastric carcinoma. Therefore, the question of the effectiveness of chemotherapy in elderly patients or patients with a poor PS essentially remains unanswered, especially with respect to those regimens employing more than one drug. It does not seem to be methodologically correct to draw conclusions relating to such groups from the retrospective analysis of relevant subsets of patients included in existing clinical studies. However, the use of such analyses would be inappropriate in relation to the planning of future ad hoc studies.

In summary, meta-analysis has confirmed that patients with advanced gastric cancer derive a survival benefit from chemotherapy. Of the many agents and combinations that have been tested, the ECF regimen is regarded by many people to provide a good level of efficacy with acceptable toxicity.

**LATEST GENERATION CHEMOTHERAPY AND RECENT PHASE III STUDIES: ARE WE OVERCOMING A PLATEAU?**

Over recent years, a series of new cytotoxic drugs, including docetaxel, irinotecan, oxaliplatin, and the oral fluoropyrimidines, have been shown to have activity in various chemotherapy combination regimens for the treatment of advanced gastric cancer. These agents were explored initially in phase II studies with doublets or triplets, containing 5-FU and sometimes cisplatin and anthracyclines. Although these early studies do not have the assessment of survival as a primary objective, they showed a general trend for overall survival going beyond the 9-month level that has been seen as a treatment plateau in this setting in relation to the ECF combination.

**Docetaxel**

Docetaxel has been shown to be active against advanced gastric cancer, both as first-line treatment, in combination with cisplatin and 5-FU, and as a single agent, when a previous first-line therapy has failed [24]. In the V-325 phase III registration study [25], 445 patients with metastatic and untreated gastric adenocarcinoma were randomly assigned and treated with either docetaxel, cisplatin, and 5-FU (DCF regimen) or cisplatin and 5-FU (CF regimen).

The primary objective of the V-325 study was to demonstrate the superiority in relation to TTP of DCF over CF as indicated by a 2-month longer TTP with the addition of docetaxel (from 4 to 6 months). TTP was defined as the time from the day of randomization to the first evidence of progression or death occurring within 12 weeks of the last assessable tumor evaluation. The study reported a median TTP of 5.6 months for DCF compared with 3.7 months for CF (p < .001), with a 32% lower risk for relapse (Fig. 3A). After a median follow-up of 23.4 months, the median overall survival time was significantly longer for DCF than for CF (9.2 months versus 8.6 months; p = .02). Although this represents a difference between the two arms at the median of only 0.6 months, with increasing follow-up time the survival curves can be seen to move apart and the number of patients alive at 2 years in the DCF arm was double that in the CF arm (18% versus 9%; Fig. 3B).

Survival in the V-325 study was in favor of the DCF regimen, despite the fact that the percentage of patients receiving subsequent lines of treatment was lower for the DCF than for the CF arm (32% versus 41%). Subsequent analyses of QOL and clinical benefit (time to definitive worsening of the Karnofsky PS score) confirmed the earlier conclusions regarding the benefit of adding docetaxel to CF and consequently supported the use of TTP in this study as a surrogate endpoint [26, 27].

However, the median age of patients enrolled in the V-325 study was 55, which is considerably lower than the median age at diagnosis for gastric cancer in the European Union, reported to be 62 years [28]. This raises some uncertainty regarding the tolerability of the DCF triplet in older patients with advanced gastric cancer. In this context, it should be noted that the addition of docetaxel in the V-325 trial resulted in significantly greater rates of grade 3
or 4 neutropenia (82% versus 57%), febrile neutropenia (29% versus 12%), and grade 3 or 4 diarrhea (4% versus 19%) in comparison with the CF doublet. These data suggest the need for prophylaxis with granulocyte growth factors and, further, that the 3-weekly schedule of the DCF regimen might be too toxic for frail patients. However, in relation to QOL, the higher levels of toxicity associated with DCF were balanced by the superior efficacy, with the consequence that patients in the DCF arm of V-325 had a better overall preservation of QOL for all time-to-deterioration analyses, compared with those receiving CF [26]. Whether this net benefit would hold true for an older patient population that would be more typical of a community practice setting is not currently clear.

Figure 3. V-325 study. (A): Time to progression. (B): Overall survival.


In summary, the V-325 study clearly confirms the superiority of the DCF triplet compared with the CF doublet in terms of response rate, TTP, overall survival, and QOL. These data corroborate the usefulness of the three-drug regimens. Especially important in the future may be the use of such combinations in specific situations, such as the neoadjuvant setting, where a key imperative is to obtain a volumetric reduction and thereby to increase the number of patients with locally advanced disease who are suitable for surgery.

Irinotecan

Dr. Wagner, in her meta-analysis [5], examined the intent-to-treat populations of three randomized studies [14, 30, 31] that reported the comparison of regimens containing 5-FU and leucovorin plus irinotecan versus 5-FU plus cisplatin, 5-FU and leucovorin plus cisplatin, or 5-FU and leucovorin plus etoposide (one study each comparison). The advantage in overall survival for regimens containing irinotecan seemed to be small (HR, 0.88; translating into a benefit in the pooled median survival time of 1 month) and needs further confirmation in phase III studies. Although treatment-
related deaths were less frequent in the irinotecan arms than in the nonirinotecan arms, this difference was not statistically significant (0.7% versus 2.6%; \( p < .088 \)), but the overall survival times were essentially equivalent in the two arms (9.0 months versus 8.7 months, respectively). However, perhaps the most significant aspect was the lower incidence of severe toxicity, except for diarrhea, in patients treated with irinotecan. A noninferiority margin of 0.93, as per the study protocol, was achieved for the irinotecan arm. This study therefore showed that a noncisplatin-based treatment can have equivalent efficacy to a cisplatin-based combination in advanced gastric patients, with fewer patients on such a regimen experiencing serious adverse events and treatment withdrawal because of toxicity. The combination of irinotecan and infusional 5-FU could therefore be a useful alternative for patients who cannot tolerate cisplatin and/or anthracycline-based regimens.

Although there are no other phase III studies specifically confirming the efficacy of the irinotecan–5-FU doublet in gastric cancer, the results of another phase III study including an irinotecan combination arm were presented by Boku and colleagues [33]. The three-arm Japan Clinical Oncology Group (JCOG) 9912 trial randomized 704 patients with advanced disease to either a cisplatin–irinotecan doublet or single-agent treatment with infusional 5-FU or the new oral fluoropyrimidine S-1. The cisplatin–irinotecan doublet achieved a superior response rate compared with the single-agent treatments (38% versus 9% versus 28%, respectively) and a median overall survival time of 12.3 months, narrowly failing to demonstrate superiority to single-agent 5-FU (\( p = .055 \)). However, in this patient population, the combined regimen was considerably more toxic than the monotherapy regimens and was associated with relatively high levels of toxicity-related withdrawal from treatment. The most common grade \( \geq 3 \) toxicity associated with the cisplatin–irinotecan doublet was neutropenia (65%), with febrile neutropenia reported for 9% of patients. In comparison, the rates of grade \( \geq 3 \) neutropenia in the 5-FU and S1 arms were 16% and 13%, respectively, and no febrile neutropenia was reported. Considering nonhematological toxicity, the rates of anorexia, hyponatremia, nausea, and fatigue were all notably higher in the doublet than in the monotherapy arms.

Despite a lack of clear evidence associated with the use of irinotecan in this setting, phase III studies continue. One example is the Fédération Francophone de Cancérologie Digestive (FFCD) 0307 trial, which will compare, in a planned 416 patients with metastatic or locally advanced gastric cancer, an epirubicin–cisplatin–capecitabine (ECX) regimen followed, in the event of disease progression, by an infusional 5-FU–leucovorin–irinotecan regimen (the FOLFIRI regimen) with the same chemotherapy in reverse sequence. This study is due to close at the end of 2009.

### Capcitabine

One of the main disadvantages of a chemotherapy combination containing infusional 5-FU is the need to implant a central venous catheter. This procedure increases the costs of treatment administration, the incidence of subsequent complications, and the level of treatment-associated discomfort for the patient. In this context, oral fluoropyrimidines therefore represent an attractive alternative to 5-FU in that they have the potential to reduce the number of medical examinations associated with i.v. administration, to reduce

### Table 1. Randomized phase II trial of three different advanced gastric cancer regimens [24]

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<th>ECF</th>
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<td><strong>Response, %</strong></td>
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<tr>
<td>CR</td>
<td>2.5</td>
<td>5.3</td>
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<td>PR</td>
<td>22.5</td>
<td>13.2</td>
<td>31.7</td>
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<tr>
<td><strong>Overall response rate (CR + PR), %</strong></td>
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<td>18.5</td>
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<tr>
<td>95% CI</td>
<td>13–41</td>
<td>8–34</td>
<td>22–53</td>
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<td><strong>Median time to progression</strong></td>
<td>5.4</td>
<td>4.4</td>
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<td><strong>Median overall survival time</strong></td>
<td>8.2</td>
<td>11.0</td>
<td>10.4</td>
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**Abbreviations:** 5-FU, 5-fluorouracil; CR, complete response; ECF, epirubicin, cisplatin, and infusional 5-FU; PR, partial response; TC, docetaxel and cisplatin; TCF, docetaxel, cisplatin, and infusional 5-FU.
the resources needed for the implantation of the i.v. device, and to eliminate catheter-related adverse events. In relation to the treatment of advanced gastric cancer, capecitabine and a fourth-generation chemotherapy drug, S-1 (discussed below), have shown particular promise.

A Korean phase III study compared the doublet of capecitabine and cisplatin (XP) with a control arm of continuous infusion 5-FU and cisplatin (FP) in 316 patients with advanced gastric adenocarcinoma [34]. The primary objective of the study was to demonstrate the noninferiority of XP versus FP in relation to progression-free survival (PFS). With median PFS times of 5.6 months for the XP arm and 5.0 months for the FP arm (HR, 0.81; 95% CI, 0.63–1.04), the study met this objective, confirming that capecitabine is able to substitute for continuous infusion 5-FU without any relevant reduction in efficacy. Toxicity was similar for the two regimens, with the most common grade 3 or 4 adverse event, neutropenia, occurring in 16% and 19% of patients, respectively. Indeed, the only toxicity that was notably higher in the capecitabine arm (all grades, 22% versus 4%, respectively) was hand–foot syndrome, an adverse event that is generally regarded as manageable.

Capecitabine has therefore overcome the doubts concerning the potential efficacy of oral drug administration in patients with gastric carcinoma, especially in relation to those patients who have undergone partial or total gastrectomy. With so few pharmacokinetic data available to date, the results coming from phase III clinical studies are of particular significance.

Oxaliplatin
Various studies have demonstrated the noninferiority of oxaliplatin versus cisplatin in relation to the treatment of patients with advanced gastric cancer and confirmed the acceptable tolerability profile of this third-generation platinum analogue. One of the most interesting studies was REAL-2. As described, the main objectives of the study were to demonstrate the noninferiority of oxaliplatin compared with cisplatin and the noninferiority of capecitabine compared with 5-FU. It was anticipated that the use of these newer agents as components of triplet regimens would reduce toxicity and thereby render an alternative to the standard ECF combination easier to handle as a consequence of replacing the cisplatin component with oxaliplatin (EOF).
replacing the infusional 5-FU component with capecitabine (ECX), or replacing both with the newer agents (EOX).

Data were presented after a median follow-up of 17 months. The noninferiority of oxaliplatin to cisplatin (HR, 0.92; 95% CI, 0.80–1.10) and capcitabine to 5-FU (HR, 0.86; 95% CI, 0.80–0.99) in relation to overall survival was demonstrated, with the upper limit of the confidence interval for the HR in each comparison excluding the predefined noninferiority margin of 1.23. Furthermore, achieving a median overall survival time of 11.2 months, the EOX regimen appeared to be more active than ECF (median overall survival time, 9.9 months), with 1-year survival rates correspondingly higher (47% versus 38%, respectively). This was confirmed in a secondary analysis of overall survival, with the HR for death in the EOX group compared with the ECF group calculated to be 0.80 (95% CI, 0.66–0.97; \( p = .02 \)). In considering these efficacy data, it should be noted that there were marginal imbalances in disease characteristics at baseline between the EOX and ECF groups (more patients with locally advanced disease and fewer patients with tumors of the gastroesophageal junction in the EOX arm), which may have contributed, at least to some extent, to the differences in clinical outcome between the arms.

Compared with the ECF regimen, EOX was associated with significantly lower rates of grade 3 or 4 neutropenia and grade 2 alopecia, but significantly higher rates of grade 3 or 4 lethargy, diarrhea, and peripheral neuropathy. Based on the results of this study, EOX is therefore tolerable, and at least as active as ECF. This modified regimen could therefore be considered to be a new standard treatment; one that may be an appropriate reference regimen for future studies in advanced gastric cancer. Essentially, such a shift is not a substantial change, more an incremental improvement of a previously established treatment, because EOX still comprises an anthracycline, a platinum derivative, and a fluoropyrimidine.

A recent phase III study in 220 patients with metastatic gastroesophageal adenocarcinoma compared 5-FU and leucovorin plus cisplatin (FLP) with 5-FU and leucovorin plus oxaliplatin (FLO) [36]. Overall, toxicity was lower in the group receiving FLO than in those receiving FLP, and there was a trend toward a longer PFS time in the FLO arm (\( p = .08 \)). Perhaps most importantly for the community use of such regimens, in a respective analysis of 94 patients >65 years of age, treatment with FLO was associated with a significantly higher response rate (41% versus 17%; \( p = .012 \)), significantly longer time to treatment failure (5.4 versus 2.3 months; \( p = .001 \)), and significantly longer PFS duration (6.0 versus 3.1 months; \( p = .029 \)), as compared with FLP. Although interesting, this possible benefit in older patients will need to be confirmed in a prospective study.

The Next Step for Oral Fluoropyrimidine Therapy: S-1

S-1 is a fourth-generation oral fluoropyrimidine–based drug with three pharmacological components: tegafur, which is a prodrug of 5-FU; 5-chloro-2,4 dihydropyridine, a powerful inhibitor of dihydropyrimidine dehydrogenase, which therefore acts by minimizing host degradation of 5-FU; and potassium oxonate, to protect against drug-induced diarrhea. S-1 is active in the treatment of advanced gastric cancer, with objective response rates for evaluable patients in single-agent phase II studies reported to be in the range of 32%–49% [37–39]. The results of a phase II study evaluating the efficacy of a combination of cisplatin (75 mg/m² given on day 1) and S-1 (50 mg/m² given daily, days 1–21) every 28 days have been reported [40]. Forty-seven patients with advanced disease were treated with this combination, achieving an objective response rate of 51% and a median overall survival time of 10.9 months. The toxicity profile was favorable, with grade 3 or 4 adverse events (mostly neutropenia, fatigue, nausea, and vomiting) in each case reported for <26% of patients. With reference to the toxicity of S-1, it should be noted that there is a different individual tolerability in relation to this drug for white and Japanese patients [41]. This differential sensitivity perhaps relates to variations between the two populations in the polymorphism frequency of genes in the cytochrome P-450 prodrug conversion pathway, with these genetic differences conferring a variable ability to assimilate the active drug. Because of this factor, the highest daily dose of S-1 tolerated in association with cisplatin is 80 mg/m² in Japanese patients and only 50 mg/m² in white patients.

In view of the results of phase II studies, Japanese oncologists have coordinated a randomized phase III study comparing cisplatin plus S-1 with S-1 alone in 305 advanced gastric cancer patients (SPIRITS [S-1 plus Cisplatin vs S-1 in Randomized Clinical Trial in the Treatment of Stomach Cancer] trial) [42]. S-1 was administered either alone, as a daily oral dose of 80 mg/m² (2 × 40 mg/m²) for 28 days, followed by a break of 14 days, or at the same dose given for 21 days, followed by a break of 14 days, in combination with cisplatin (60 mg/m² i.v.), administered on day 8. After a median follow-up of 35 months, the study met its primary endpoint in demonstrating a significantly longer median overall survival time in the combination arm than in the single-agent arm (13.0 months versus 11.0 months; HR, 0.77; \( p = .04 \)). With the caveats applicable to cross-study comparisons, these survival times appear to contrast favorably with the median overall survival time of 9.2 months reported with DCF [25]. The most frequent grade 3 or 4 toxicities in the S-1 monotherapy arm were neutropenia, reported for 11% of patients, followed by anorexia (6%),...
anemia (4%), and diarrhea (3%). Grade 3 or 4 events were more common in the cisplatin plus S-1 arm, with the most frequent being neutropenia (40%), anorexia (30%), anemia (26%), and nausea and leukopenia (both 11%). Given the promising efficacy data so far reported in Japanese patients, the results of a large ongoing phase III first-line advanced gastric cancer study (FLAGS) currently investigating S-1 plus cisplatin versus 5-FU plus cisplatin in a western patient population are eagerly awaited.

**Targeted Biological Agents**

Although several different chemotherapy regimens are now available for the treatment of advanced gastric cancer, it is hoped that the number of active combinations will increase still further with the introduction of the new rationally targeted biological agents that are currently under evaluation in phase III studies. Drawing on the pattern of efficacy of the therapeutic monoclonal antibodies cetuximab, bevacizumab, and panitumumab in colorectal cancer [43–48], such new agents may be effective in this setting either alone or in combination with other cytotoxic compounds after the failure of first- and subsequent-line treatments, or they may improve the efficacy of current first-line regimens that are active in this setting. It is also possible that such targeted agents may have a future role as single-agent maintenance treatments.

A number of different classes of targeted agents have shown promising activity in clinical studies of advanced gastric cancer, including epidermal growth factor receptor (EGFR) and human epidermal growth factor receptor (HER)-2–targeted monoclonal antibodies and tyrosine kinase inhibitors (TKIs) [49–54], antiangiogenic and antiangiogenic/antitumor compounds [53, 55, 56], and the proteasome inhibitor bortezomib [57]. In particular, early data from phase II trials [49–52, 55, 56] show encouraging response rates and overall survival times for first- and second-line combinations of cytotoxic agents and the EGFR- or vascular endothelial growth factor (VEGF)-targeted monoclonal antibodies cetuximab and bevacizumab (Table 2). In particular, high response and/or disease control rates have been reported for EGFR-targeted cetuximab combined with irinotecan and infusional 5-FU and leucovorin [50, 51] and VEGF-targeted bevacizumab combined with irinotecan and cisplatin [56].

In considering such studies, it is notable that the first-line cytotoxic regimens that have been selected for combination with biological agents tend not to be those that are generally considered to be optimal for the treatment of advanced gastric cancer. This begs the question of whether the impressive potential of these targeted agents might be more profitably explored in the future in combinations that include standard cytotoxic backbones such as ECF, DCF, EOX, or perhaps S-1 plus cisplatin. Indeed, a number of randomized phase III studies incorporating targeted agents in first-line regimens have recently been initiated: the ToGA (Trastuzumab with Chemotherapy in HER2-Positive Advanced Gastric Cancer) study will investigate the effect on PFS of trastuzumab in combination with a fluoropyrimidine plus cisplatin versus chemotherapy alone in patients with HER-2–positive advanced gastric cancer, AVAGAST (Avastin® in Gastric Cancer) will investigate overall survival times in advanced gastric cancer patients receiving either capecitabine and cisplatin plus bevacizumab or chemotherapy alone plus placebo, and the REAL-3 study will investigate the benefit of adding panitumumab to an EOX regimen in patients

<table>
<thead>
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<th>Treatment line</th>
<th>Treatment</th>
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<th>Disease control rate (%)</th>
<th>Time to progression (months)</th>
<th>Overall survival time (mos)</th>
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<td>First</td>
<td>Irinotecan, cisplatin, and bevacizumab [56]</td>
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<td>65</td>
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<td>8.3</td>
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<td>First</td>
<td>FOLFIRI + cetuximab [51]</td>
<td>38</td>
<td>44</td>
<td>91</td>
<td>8</td>
<td>16*</td>
</tr>
<tr>
<td>First</td>
<td>FUFOX + cetuximab [49]</td>
<td>52</td>
<td>65</td>
<td>83</td>
<td>7.6</td>
<td>9.5</td>
</tr>
<tr>
<td>Second/first</td>
<td>Docetaxel + bevacizumab [55]</td>
<td>30</td>
<td>26</td>
<td>57</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Second +</td>
<td>Irinotecan + cetuximab [52]</td>
<td>13</td>
<td>23</td>
<td>54</td>
<td>2.5</td>
<td>3.2</td>
</tr>
</tbody>
</table>

*a Estimated after median follow-up of 11 months.

Abbreviations: 5-FU, 5-fluorouracil; FOLFIRI, infusional 5-FU, leucovorin, and irinotecan; FUFOX, 5-FU/DL-folinic acid (AIO regimen), and weekly oxaliplatin; Na-FA, sodium-folinic acid (leucovorin).
with locally advanced or metastatic esophagogastric adenocarcinoma.

Although targeted agents tend to be generally well tol-erated, careful consideration will still need to be given in new studies as to whether the biological agent might be ex-pected to exacerbate to unacceptable levels the toxicity of the cytotoxic regimen.

**IS SECOND-LINE CYTOTOXIC TREATMENT IN GASTRIC CANCER LIKELY TO BECOME INCREASINGLY IMPORTANT?**

First-line chemotherapy for the treatment of advanced gas-tric cancer can provide high response rates that are of a sim-ilar magnitude to those achievable with the newer first-line combinations in colorectal cancer. However, a correspond-ing improvement in the median overall survival time has not yet been delivered by the currently available gastric cancer regimens. This lack of progress in relation to mark-edly improving overall survival times may be a result, in part, of the more limited efficacy of the currently available second- and third-line treatments for advanced disease, al-though it should be noted that only one third to one half of the gastric cancer patients in clinical studies may actually receive second-line treatments [11, 14, 25, 32]. Data pub-lished to date relating to the efficacy of subsequent-line reg-imens are restricted to phase II studies of small patient popu-lations [58 – 67], and these investigations are therefore not able to provide definitive results (Table 3). However, second-line treatments are clearly effective to some degree, with response rates in the region of 11%–32%, median TTP of 2.5–4.5 months, and median overall survival times of 5.4–9.3 months achieved in these early analyses. It may be that, in the future, the introduction of molecularly targeted agents will further improve outcomes in this setting [52, 68]. This potential is perhaps best illustrated by preliminary results from the phase II study of the oral, multitargeted TKI sunitinib in 42 evaluable gastric cancer patients with stage IV disease who had failed first-line chemotherapy. Single-agent sunitinib treatment was generally well toler-at-ed, and the median PFS and overall survival times were reported to be 2.8 and 11.7 months, respectively. Recruit-ment of a second cohort of patients is ongoing, and studies of sunitinib in combination with chemotherapy are planned [68]. As second-line regimens for the treatment of advanced gastric cancer patients become more effective, the number of patients receiving such therapies is likely to increase. In turn, this is likely to impact the choice of primary endpoints for first-line studies in a situation analogous to that seen al-ready in colorectal cancer [69]. It is therefore probable that the use of time to disease progression endpoints as surro-gate markers for the survival benefit conferred by new first-line gastric cancer regimens will become more common. Given this eventuality, the adoption of an appropriate stan-dard definition for time to disease progression will be de-sirable.

**SUMMARY**

The endpoint of a palliative treatment should be to slow as much as possible the development of therapy-resistant dis-ease. The currently available first-line treatments for ad-vanced gastric cancer offer a clear but relatively small survival benefit to patients compared with BSC alone. Three-drug regimens have shown some marginal benefit over traditional doublets in this setting, but there are no di-rectly comparable data suggesting which of these is the

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**Table 3. Phase II second-line chemotherapy studies in gastric cancer**

<table>
<thead>
<tr>
<th>Study</th>
<th>Regimen</th>
<th>n of patients</th>
<th>Response rate (%)</th>
<th>Median time to progression (mos)</th>
<th>Median overall survival time (mos)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ueda et al. [58]</td>
<td>Irinotecan + cisplatin</td>
<td>32</td>
<td>28</td>
<td>3.4</td>
<td>9.3</td>
</tr>
<tr>
<td>Lee et al. [59]</td>
<td>Docetaxel</td>
<td>49</td>
<td>16</td>
<td>2.5</td>
<td>8.3</td>
</tr>
<tr>
<td>Barone et al. [60]</td>
<td>Docetaxel + oxaliplatin</td>
<td>38</td>
<td>11</td>
<td>4.0</td>
<td>8.1</td>
</tr>
<tr>
<td>Giuliani et al. [61]</td>
<td>Irinotecan + mitomycin C</td>
<td>38</td>
<td>32</td>
<td>4</td>
<td>8</td>
</tr>
<tr>
<td>Kodera et al. [62]</td>
<td>Paclitaxel</td>
<td>45</td>
<td>16</td>
<td>2.6*</td>
<td>7.8</td>
</tr>
<tr>
<td>Kunisaki et al. [63]</td>
<td>Docetaxel + cisplatin</td>
<td>30</td>
<td>27</td>
<td>4.5</td>
<td>6</td>
</tr>
<tr>
<td>Rosati et al. [64]</td>
<td>Docetaxel + capecitabine</td>
<td>28</td>
<td>29</td>
<td>4</td>
<td>6</td>
</tr>
<tr>
<td>Baek et al. [65]</td>
<td>Irinotecan + cisplatin</td>
<td>32</td>
<td>16</td>
<td>3.7</td>
<td>6.0</td>
</tr>
<tr>
<td>Shin et al. [66]</td>
<td>Mitomycin C + S-1</td>
<td>26</td>
<td>23</td>
<td>4.4*</td>
<td>5.4</td>
</tr>
<tr>
<td>Stathopoulos et al. [67]</td>
<td>Carboplatin + paclitaxel</td>
<td>47</td>
<td>28</td>
<td>–</td>
<td>–</td>
</tr>
</tbody>
</table>

*a* Progression-free survival.
most effective. Given that a considerable number of cytotoxic agents and combinations have been explored in this setting without a marked improvement in treatment efficacy being achieved, and although early data for the new oral agent S-1 are promising, hope for significant advances in the near future would appear to rest in the combination of new targeted biological agents with existing standard frontline regimens. Consequently, we suggest that the DCF and EOX regimens perhaps represent cytotoxic backbones of choice for new studies investigating the addition of generally well-tolerated biological agents. Considering phase II data in gastric cancer and the tolerability and proven efficacy of such targeted agents across other indications, perhaps early studies might profitably also investigate the addition of cetuximab to standard regimens.

AUTHOR CONTRIBUTIONS

Conception/design: Carmelo Pozzo, Carlo Barone
Financial support: Carmelo Pozzo, Carlo Barone
Administrative support: Carmelo Pozzo, Carlo Barone
Provision of study materials or patients: Carmelo Pozzo, Carlo Barone
Collection/assembly of data: Carmelo Pozzo, Carlo Barone
Data analysis and interpretation: Carmelo Pozzo, Carlo Barone
Manuscript writing: Carmelo Pozzo, Carlo Barone
Final approval of manuscript: Carmelo Pozzo, Carlo Barone

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