Recent Developments in Cytotoxic Therapy for Advanced Gastric or Gastroesophageal Carcinoma: The Phase III Trials

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ABSTRACT

Gastric cancer remains a significant health problem around the world. It is often diagnosed in late stages and almost 50% of patients have unresectable disease. Median survival, when cancer is in advanced stages, is often less than 9 months. Once metastatic, it is an incurable condition, and in most circumstances, fewer than 10% of patients survive 24 months. Most patients with metastatic gastric or gastroesophageal cancer have baseline symptoms, some of which are quite severe. Therapy for advanced gastric or gastroesophageal cancer is palliative in nature. For a long time, the number of randomized trials conducted in patients with gastric or gastroesophageal cancer had been unacceptably low; however, in the past 10 years, the number of phase III trials has increased and it is hoped that the momentum will continue to build and more trials will be completed. Several new classes of active agents have emerged, including taxanes, camptothecins, fluoropyrimidine analogs (particularly, capecitabine and S-1), and a platinum analog (oxaliplatin). The most recent phase III data suggest that docetaxel, when added to the reference regimen of cisplatin and 5-FU (CF), results in a statistically significant prolongation of time-to-progression and overall survival, higher response rate, doubling of the 2-year survival rate, better quality of life, improved clinical benefit, and a higher rate of complicated neutropenia. Other important phase III trials demonstrate that 5-FU can be substituted with capecitabine and cisplatin can be substituted with oxaliplatin. However, in a randomized phase III trial, irinotecan plus infusional 5-FU, when compared with CF, was not superior (it was noninferior), suggesting that irinotecan may be best suited for second-line treatment of these patients. Further developments in cytotoxic therapy will be driven by the use of more sophisticated oral agents (eg, S-1) and newer clinical algorithms that will employ therapy only until maximum response is attained. In conclusion, docetaxel should be combined with other active agents in the front-line treatment of advanced gastric or gastroesophageal cancer. When docetaxel is combined with CF, it becomes an intense regimen requiring stringent patient selection and active management including primary prophylaxis. Capecitabine is noninferior to 5-FU and oxaliplatin is noninferior to cisplatin.

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Gastric cancer remains a serious health problem around the world and is responsible for approximately 10% all cancer-related deaths.[1] Approximately 800,000 new cases of gastric cancer are diagnosed each year and approximately 22,280 of these are diagnosed in the United States.[1] Gastric cancer is endemic in Japan, Korea, China, Taiwan, Chile, Peru, Costa Rica, and many other South American and Eastern European countries and countries of the former Soviet Union. In the West, despite an overall decline in the number of cases, there has been a steady rise in adenocarcinoma of the proximal stomach and gastroesophageal junction.[2] Gastric or gastroesophageal cancer is rarely a subject of orchestrated early detection approaches, except in Japan, Korea, and Venezuela. Therefore, it is often diagnosed when patients already have cancer symptoms. In endemic areas, early detection programs may be worth-

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while; in reality, however, they are not in place, and nearly 50% of patients diagnosed with gastric or gastroesophageal cancer have unresectable cancer (locally advanced or metastatic). Once metastatic, gastric or gastroesophageal carcinoma is incurable and patient life span is short, usually less than 9 months.

Patients with metastatic gastric or gastroesophageal junction carcinoma are often symptomatic, and 25% have severe symptoms.[3] The goal of therapy in this group of patients is to provide palliation, prolong time-to-progression (TTP) of the cancer, and also prolong overall survival (OS). In addition, it is desirable to improve quality of life (QoL) and improve clinical benefit (CB). However, the progress in gastric or gastroesophageal cancer research has lagged far behind that in other gastrointestinal cancers, such as colorectal cancer or pancreatic cancer. The number of phase III trials and the quality of trials conducted has not been optimum until recently. In pancreatic cancer studies, investigators have been able to combine a new agent with gemcitabine and compare it with gemcitabine alone, but this type of approach has not been employed in gastric or gastroesophageal cancer, because reference regimens have differed in various regions, and comparisons were often of one combination vs. another combination.

More recently, many new classes of agents or analogs (alone and in combination) have been identified as being active against gastric or gastroesophageal cancer.[4–16] In addition, fortunately, all new agents to be discussed in this paper have undergone or are about to complete phase III trials. These cytotoxics include irinotecan, docetaxel, oxaliplatin, capecitabine, and S-1. Due to space limitations, this paper focuses only on representative studies and does not address every published study of cytotoxics in gastric or gastroesophageal cancer.

PHASE III TRIAL OF IRINOTECAN

Irinotecan is an active agent against gastric and gastroesophageal cancer as a single agent and in combination chemotherapy.[17] Dank et al described results of the phase III trial,[18] wherein the experimental arm consisted of irinotecan 80 mg/m^2, folinic acid 500 mg/m^2 (over 2 hours) and 5-fluorouracil (5-FU) 2,000 mg/m^2 (over 22 hours) given weekly for 6 weeks followed by a 1-week break (the IF regimen); and the reference regimen was cisplatin 100 mg/m^2 on day 1 and 5-FU 1,000 mg/m^2 as an infusion on days 1 to 5 every 28 days (the CF regimen). The primary end point was TTP (looking for superiority but also accepting inferiority), and important secondary end points were OS, QoL, CB, and safety. A total of 333 patients were randomly assigned to receive IF or CF. This study did not meet its primary end point of demonstrating the superiority of IF regarding TTP (P = .088), but IF was considered noninferior to CF. The OS was not significantly different (P = .5; median survival, IF = 9.0 months vs. CF = 8.7 months). QoL was also comparable between the two arms. Differences were observed in the safety profile, with more diarrhea from IF and more neutropenia and stomatitis from CF. This study demonstrates that irinotecan does not significantly contribute to TTP, OS, or QoL in patients with gastric or gastroesophageal cancer. Irinotecan is more suitable for second-line therapy for this group of patients.

DOCETAXEL IN PHASE III TRIALS

Docetaxel is an established active agent against gastric or gastroesophageal cancer with response rates ranging from 11% to 24%.[4–6] When combined with other agents, it has demonstrated high response rates.[13,19–24] In a phase II randomized trial by the Swiss Group for Clinical Cancer Research (SAKK), three regimens were compared in patients with untreated, advanced gastric or gastroesophageal cancer.[24] Patients received epirubicin, cisplatin, and 5-FU (ECF, a reference regimen) or one of the two docetaxel-based regimens: docetaxel/cisplatin (DC) or docetaxel/cisplatin/ 5-FU (DCF). The SAKK-DCF regimen employs protracted infusion of 5-FU, as opposed to the DCF regimen used in the V325 trial, where infusional 5-FU is given on days 1 to 5 only. Data from 119 evaluable patients indicated that SAKK-DCF was superior to ECF or DC in terms of the externally reviewed confirmed response rate. However, SAKK-DCF produced a much higher rate of complicated neutropenia (40%), emphasizing the need for proper patient selection and patient management. SAKK-DCF, unlike the V325 DCF, is not conducive to primary prophylaxis.

V325 Trial

The V325 trial had two components: a randomized phase II portion that compared DC with DCF, and a phase III component that compared the reference regimen of CF with the winner in the phase II portion (it turned out to be DCF). Details of the phase II randomized study were recently published.[25] It should be noted that the decision to select DCF over DC was made by the independent data monitoring committee (IDMC) and was based on the response rate and safety data.

In the V325 trial, the largest international phase III trial in advanced gastric or gastroesophageal cancer published to date, 457 chemotherapy-naïve patients were randomly assigned to receive DCF chemotherapy or the reference regimen of CF.[3] The total weekly administered doses of cisplatin and 5-FU were identical in both treatment groups (docetaxel 75 mg/m^2 day 1, cisplatin 75 mg/m^2 day 1, and 5-FU 750 mg/m^2/day as continuous infusion on days 1–5 every 3 weeks; or cisplatin 100 mg/m^2 day 1 and 5-FU 1,000 mg/m^2/day as continuous infusion on days 1–5 every 4 weeks), thereby allowing assessment of the contribution of docetaxel. TTP was the primary end point, while OS, duration of response, safety, and QoL were secondary end points. The median patient age was 55 years, and 97% of patients had metastatic disease (this is a distinct group of patients compared with those entered in previously published phase III trials).

Final results of the V325 study were recently published (Table 1).[3] The primary end point of TTP was met, demonstrating that DCF was significantly superior to CF. The reduction in risk of disease progression was 32.1% (hazard ratio [HR] 1.473, 95% CI, 1.189–1.825). Similarly, OS was statistically significantly superior with DCF vs. CF, with a 22.7% reduction in risk of death (HR 1.293, 95% CI, 1.041–1.606). As expected, grade 3/4 adverse events occurred more frequently in the DCF group compared with the CF group (81% vs. 75%), with diarrhea and stomatitis as the most common events (20% vs. 8% and 21% vs. 27%, respectively). These adverse events were manageable. Grade 3/4

Table 1. Summary of final results of V325 trial.[42]

	DCF (n = 227)	CF (n = 230)	*P* Value
Response rate, %	37	25	.0106
Time to progression, months	5.6	3.7	.0004
Overall survival, months	9.2	8.6	.0201
2-year survival, %	18	9	NR

Abbreviations: C, cisplatin; D, docetaxel; F, 5-fluorouracil; NR, not reported.
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Table 2. One-year and overall survival results from the REAL 2 trial (4 therapy arms in a 2 × 2 design).[31]

2 × 2 Comparisons Per Protocol	1-year OS (95% CI)	Median OS	HR (95% CI)
5-FU: ECF + EOF	39.4% (35.0–43.7)	9.6 months	1
Capecitabine: ECX + EOX	44.6% (40.1–49.0)	10.9 months	0.86 (0.75–0.99)*
Cisplatin: ECF + ECX	40.1% (35.7–44.4)	10.1 months	1
Oxaliplatin: EOX + EOF	43.9% (39.4–48.4)	10.4 months	0.92 (0.80–1.05)*
Regimens ITT			
ECF (n = 263)	37.7% (31.8–43.6)	9.9 months	1
EOF (n = 245)	40.4% (34.2–46.5)	9.3 months	0.95 (0.79–1.15)
ECX (n = 250)	40.8% (34.7–46.9)	9.9 months	0.92 (0.76–1.11)
EOX (n = 244)	46.8% (40.4–52.9)	11.2 months	0.80 (0.65–0.97)†

There were no significant differences in response rates comparing ECF to EOF, ECX and EOX (41%, 42%, 46%, and 48%, respectively); grade 3/4 nonhematologic toxicity 36%, 42%, 33%, and 45%; and grade 3/4 neutropenia 42%, 30% ($P = .008$), 51% ($P = .043$), and 28% ($P = .001$), respectively.

* The upper limit of the 95% CI < 1.23. We can therefore conclude noninferiority.
† $P = .025$ comparison with ECF

Abbreviations: CI, confidence interval; ECF, epirubicin/cisplatin/5-FU; ECX, epirubicin/cisplatin/capecitabine; EOF, epirubicin/oxaliplatin/5-FU; EOX, epirubicin/oxaliplatin/capecitabine; HR, hazard ratio; ITT, intent to treat; OS, overall survival.

Reprinted with permission from the American Society of Clinical Oncology. Cunningham D, Rao S, Starling N, et al: Randomized multicenter phase III study comparing capecitabine with fluorouracil and oxaliplatin with cisplatin in patients with advanced esophagogastric cancer. The REAL 2 trial. 2006 ASCO Annual Meeting Proceedings. *J Clin Oncol* 24:18S, 2006 (abstr LBA4017)

neutropenia was also more frequent in the DCF arm compared with the CF arm (82% vs. 57%). Complicated neutropenia (febrile neutropenia including infection during neutropenia) was more common with DCF (30% vs. 15%) than CF. Primary prophylaxis with growth factors to reduce the duration or severity of neutropenia was not allowed in V325; however, when secondary prophylaxis was used, the rate of complicated neutropenia was reduced substantially. Primary prophylaxis is highly recommended when using DCF. Of note, however, QoL, including global health status, was maintained for a longer period of time with the DCF than with the CF regimen.[26] These results suggest that, compared with CF alone, docetaxel added to CF improves response rate, TTP, OS, QoL, and CB for patients with advanced gastric or gastroesophageal cancer (Table 1). The higher rate of complicated neutropenia remains a concern, but with proper patient selection, primary growth factor prophylaxis, and aggressive patient management, it can be less problematic. Whether docetaxel should always be combined with CF (as in the DCF regimen) as front-line therapy of untreated patients with advanced gastric cancer remains an open question, and probably the correct answer should be, "not always". However, docetaxel should become part of the front-line therapy for advanced gastric cancer. Because the addition of docetaxel to CF resulted in many advantages over CF (and also increased the rate of complicated neutropenia), it may be safe to extrapolate that docetaxel, when combined with other active combinations (or single agents), would produce the same advantages (and safety issues). If one were to use DCF as constituted in the V325 protocol, then primary granulocyte-colony stimulating factor (G-CSF) prophylaxis must be considered.

When considering modern clinical methodology, the V325 study excels compared with previous randomized studies.[27–30] In V325, there were five stratifications, continuous monitoring of trial results by the IDMC, exclusion of patients with esophageal cancer (when gastroesophageal junction was not involved), exclusion of patients who could potentially undergo surgery if the size of the cancer could be reduced, and 95% statistical power with 2-sided log-rank test to detect differences in TTP and OS. The other unique features include 97% of patients having widely disseminated metastatic cancer and QoL/CB assessments beyond the treatment duration (patients participated in these validated instruments up to 6 months after stopping assigned chemotherapy).

OXALIPLATIN IN PHASE III TRIALS

Oxaliplatin, when combined with 5-FU, is active against gastric or gastroesophageal carcinoma.[7] It has been substituted for cisplatin in recent phase III trials.[31,32] In the REAL 2 trial, more than 1,000 patients were randomized in a 2 × 2 design to receive ECF (serving as the reference regimen) or to one of three other regimens that systematically substituted oxaliplatin for cisplatin or capecitabine for 5-FU (as in epirubicin, oxaliplatin, 5-FU [EOF]; or epirubicin, oxaliplatin, capecitabine [EOX]; or epirubicin, cisplatin, capecitabine [ECX]).[31] The primary end point of this trial was to focus on OS (acceptable HR up to 1.23), with the goal of demonstrating noninferiority when substituting capecitabine for 5-FU and substituting oxaliplatin for cisplatin. Secondary end points were to compare all four regimens, review safety, and TTP. Mature results are available. Median follow-up time is more than 17 months and more than 850 events have already

occurred. The 60-day all-cause mortality was approximately 8% for all four regimens. Similarly, mortality rates 30 days from last chemotherapy administration were similar in the four arms. One-year survival rates and median survival durations were also similar (Table 2). Hazard ratios were 0.86 for the primary comparison between capecitabine and 5-FU, and 0.92 for the primary comparison between oxaliplatin and cisplatin. In addition more hand-foot syndrome developed in the capecitabine arms and more neuropathy was seen in the oxaliplatin arms. Finally, all four regimens were generally well tolerated with a maximum rate of complicated neutropenia of 10%. At baseline, QoL was similar for all four arms, and QoL remained similar at 3 months. REAL 2 is an important trial that demonstrated that capecitabine is noninferior to 5-FU and oxaliplatin is noninferior to cisplatin.

Al-Batran et al,[32] in a small trial, provided confirmation for the REAL 2 trial assertion that oxaliplatin is noninferior to cisplatin. A total of 220 patients were randomly assigned to 5-FU 2,000 mg/m^2, leucovorin 200 mg/m^2, plus cisplatin 50 mg/m^2 (FLP) administered every 2 weeks; or 5-FU 2,600 mg/m^2/day, leucovorin 200 mg/m^2, plus oxaliplatin 85 mg/m^2 (FLO) administered every 2 weeks. The primary end point was demonstration of superiority of FLO over FLP in TTP (from 3.5 months to 5 months [asking for 43% improvement in TTP], with one-sided log-rank test, P = .05). Currently available data suggest that the primary end point of superiority of FLO was not demonstrated (TTP, 5.7 months for FLO and 3.8 months for FLP [33% improvement]; P = .08), although response rate was somewhat better for FLO than for FLP. The survival data are not available. Clearly, this trial was conducted in far too many patients with very high expectations; nonetheless, it supports that oxaliplatin is a reasonable substitute for cisplatin. The most important end point is OS, which has not been fully addressed by this trial.

CAPECITABINE IN PHASE III TRIALS

Capecitabine has been extensively studied in gastric and gastroesophageal cancer as a single agent and in combination regimens.[33] The REAL 2 trial (see above) demonstrated that capecitabine is noninferior to 5-FU.[31]

Kang et al have confirmed the findings of the REAL 2 trial in a multinational phase III trial conducted in 46 centers in three countries.[34] In this recently presented trial, 316 patients with untreated advanced gastric carcinoma received infusional 5-FU 800 mg/m^2 on days 1 to 5 and cisplatin 80 mg/m^2 (FP) administered every 3 weeks, or capecitabine 1,000 mg/m^2 twice daily for 14 days and cisplatin 80 mg/m^2 (XP) administered every 3 weeks. The primary end point was to demonstrate noninferiority when capecitabine is substituted for 5-FU in OS, with acceptable HR of < 1.4. Median follow-up time of the trial was 22 months. The HR for the primary end point was 0.81 (median survival durations were 10.5 months for XP and 9.3 months for FP; P = .27). Both regimens had similar toxicity profiles, and there was no QoL assessment in this trial. In conclusion, this trial shows that capecitabine is noninferior to 5-FU.

S-1 IN PHASE III TRIALS

S-1, a fourth-generation oral fluoropyrimidine, is an oral formulation of tegafur (FT), 5-chloro-2,4-dihydroxypyridine (CDHP), and potassium oxonate (Oxo) at a molar ratio of 1:0.4:1.[35] FT is the prodrug for cytotoxic 5-FU and CDHP prevents its degradation. In animal models, Oxo is protective against FT-induced diarrhea.[36,37] The diarrheagenic property of 5-FU is due to its phosphorylation in the intestine, primarily by orotate phosphoribosyltransferase (OPRT). Oxo is a specific inhibitor of OPRT. Thus, the protective effect of Oxo derives from its ability to reduce phosphorylation of 5-FU; however, 5-FU can also be phosphorylated by uridine phosphorylase or thymidine phosphorylase, generating FdUMP (5-fluorodeoxyuridine monophosphate) and thus resulting in diarrhea. CDHP is a potent and competitive inhibitor of dihydropyrimidine dehydrogenase (DPD), which results in higher concentrations of 5-FU.[38] Pharmacokinetic studies of S-1 have demonstrated substantial prolongation of the half-life of 5-FU.[39] Because FT is metabolized differently in Asians and whites due to polymorphic differences in the *CYP2A6* gene, a phase I pharmacokinetic study in Western patients determined the maximum tolerated dose (MTD) of S-1 at 25 mg/m^2 bid (on days 1–21) and that of cisplatin at 75 mg/m^2 on day 1 of each 28-day cycle.[13] Fluoropyrimidines remain the most extensively incorporated agents in the treatment of patients with gastroesophageal cancer. Effective oral fluoropyrimidines are highly desirable. S-1 falls into the DIF (DPD-inhibiting fluoropyrimidines) category, whereas capecitabine is a non-DIF compound.

In that respect, S-1 has entered a rapid development track in the West. After defining the MTD, a multicenter efficacy trial met its primary end point of achieving a confirmed overall response rate (CORR) of at least 45% with a favorable safety profile.[40] Once the initial phase II study results were reviewed, a global phase III trial called First-Line Advanced Gastric Cancer Study (FLAGS) was conceived. In FLAGS, S-1 plus cisplatin is the experimental arm and 5-FU plus cisplatin is the reference arm. However, because Western experience with S-1 plus cisplatin had been quite limited, it was decided to generate additional safety and efficacy data. Thus, accrual was increased from the initial 47 patients to a total of 72 patients in the multicenter setting to gain more experience.[41] In the resulting publication of this study, we were also able to relate the strengths and weaknesses of conducting an elaborate external review—noting that both parties (the investigators and external reviewers) have access to the same set of objective imaging data, but the investigators make their decisions in real-time in the clinics (using many forms of objective and subjective data) and the external reviewers make it much later based only on objective data. However, the tolerance and efficacy of S-1 plus cisplatin has been excellent.

CONCLUSIONS

The momentum to conduct multiple phase III trials in patients with advanced gastric or gastroesophageal appears sustained. With the advent of several new classes of agents or new analogs of previously recognized active classes of agent, one can suggest possible new combinations for untreated patients with advanced gastric or gastroesophageal cancer. Docetaxel, when added to CF, resulted in improve-

ment of many coveted end points. With the exception of docetaxel, no single cytotoxic agent has ever been shown to contribute to efficacy or QoL in this group of patients. However, an increase in complicated neutropenia as a result of the addition of docetaxel to other active combinations should remain a concern and needs to be addressed appropriately. Irinotecan, in contrast to docetaxel, has not succeeded in producing similar benefits, and should therefore be considered more suitable for inclusion in second-line therapy. We now have sufficient studies to suggest that capecitabine can substitute for 5-FU and oxaliplatin can substitute for cisplatin in the front-line setting for this group of patients. S-1 is being developed rapidly, and the FLAGS trial (which is comparing S-1/cisplatin vs. CF) is asking a superiority OS question. Investigators are now focusing on further modifications of DCF to make it safer, and incorporating S-1 in combinations that may be appealing (eg, S-1 plus oxaliplatin; or S-1, oxaliplatin, plus docetaxel). Biochemotherapy is discussed elsewhere in this issue by Jwaher et al.

Further developments should also focus on shifting the strategic paradigm in which patients will not be treated until disease progression and/or intolerance to therapy occurs, but to maximum response followed by some form of chronic therapy to reduce the possibility of cancer progression without excessive toxicity.

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