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Novel cytotoxic regimens in gastric cancer

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Abstract

The docetaxel–cisplatin–5-fluorouracil (TCF) triplet has demonstrated superiority over cisplatin–5-fluorouracil (CF) and subsequently gained approval in the USA and Europe for the treatment of advanced gastric cancer. While this is a major advancement in gastric cancer therapy, there is potential to further improve outcomes by optimizing and building on the TCF regimen. The availability of 'new' cytotoxic agents such as oxaliplatin, irinotecan, capecitabine and S-1, as well as the biological agents, provides many options for modifying the standard TCF regimen, as used in the TAX 325 study. Potential strategies to improve efficacy, tolerability and/or convenience include variations in the dosing schedule, the substitution of cisplatin with oxaliplatin, the substitution of 5-fluorouracil with oral fluoropyrimidines, and the addition of biological agents. Emerging data support the feasibility of these strategies and will be reviewed in this article.

Keywords: Chemotherapy; Clinical trial; Docetaxel; Gastric cancer; novel; Oxaliplatin

1. Introduction

On the strength of results from TAX 325 and ensuing approvals in the USA and Europe, the docetaxel (Taxotere®)–cisplatin–5-fluorouracil (TCF) triplet has become a new reference regimen in advanced gastric cancer [1–3]. Compared to a previous reference regimen, cisplatin–5-fluorouracil (CF), TCF achieved a significantly longer time to tumour progression (TTP) and overall survival (OS), a doubling of the 2-year survival rate, a significantly higher overall response rate (ORR), improved clinical benefit and better preservation of quality of life [1–3]. Although TCF represents an important step forward, there remains scope to build on this progress and to further improve chemotherapy in this setting. Numerous studies are ongoing to try to optimize both the efficacy and safety of existing regimens and to investigate the potential of new drug combinations in gastric cancer. Potential modifications of the TCF regimen include variations in the TCF schedule, the substitution of cisplatin with oxaliplatin, the substitution of 5-fluorouracil (5-FU) with oral fluoropyrimidines, and the addition of biological agents. This paper will review some of the emerging data and new directions of investigation.

2. Modification of the TCF schedule

At the recent 2006 American Society of Clinical Oncology (ASCO) annual meeting, data were presented from a randomized Phase II study of 79 patients with previously untreated metastatic gastric or oesophageal carcinoma who received one of two different docetaxel-based regimens: the first regimen (mTCF) was administered every 3 weeks and comprised docetaxel 30 mg/m^2 on days 1 and 8, cisplatin 60 mg/m^2 on day 1, and 5-FU 200 mg/m^2/day continuous infusion; the second regimen (mTX) was administered every 3 weeks (2 weeks on and 1 week off) and comprised the same schedule of docetaxel combined with capecitabine 1600 mg/m^2/day on days 1–14 [4]. The ORR (complete response + partial response) was 44% (95% confidence interval [CI], 29–61%) for mTCF and 20% (95% CI, 10–37%) for mTX. Median progression-free survival (PFS) was 5.5 months and 3.7 months for mTCF and mTX, respectively. Safety and tolerability were good in both treatment arms, with diarrhoea, hand–foot syndrome and febrile neutropenia reported in less than 10% of patients in each arm. In contrast, in the TAX 325 study, grade 3/4 diarrhoea was reported in 19% of patients and febrile neutropenia in 30% (hand–foot syndrome not reported) [1, 3]. Hence, mTCF has demonstrated encouraging activity with a potentially favourable toxicity profile compared to the standard TCF regimen.

3. Substitution of cisplatin with oxaliplatin

The REAL-2 study [5], as discussed by David Cunningham in this issue, demonstrated the favourable safety profile of oxaliplatin (Eloxatin®)-based chemotherapy in patients with metastatic gastric and distal oesophageal cancers.

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Oxaliplatin was clearly not inferior to cisplatin; indeed, the EOX regimen (epirubicin, oxaliplatin and capecitabine) was associated with significantly improved median OS compared with ECF (epirubicin, cisplatin and 5-FU) (11.2 months vs. 9.9 months, respectively; $P = 0.02$), the current UK reference regimen [5].

A new strategy under investigation in gastric cancer is the administration of oxaliplatin and docetaxel in combination. In addition to the known activity of both agents in advanced gastric cancer, the rationale for the docetaxel–oxaliplatin pairing includes their distinct and complementary mechanisms of action, lack of cross-resistance, different toxicity profiles and favourable tolerability profiles. A large Phase II study by the US oncology group assessed first-line docetaxel 60 mg/m^2 intravenously (iv) over 1 hour on day 1 combined with oxaliplatin 130 mg/m^2 iv over 2 hours on day 1, every 3 weeks, in 71 patients with metastatic adenocarcinoma of the stomach and/or gastro-oesophageal junction [6]. ORR, the primary endpoint, was 38% and a further 52% of patients had stable disease. Median duration of response was quite long at 4.6 months (range, 2.7–18.3 months) and median OS was 9.2 months (95% CI, 6.5–11.2 months). The incidence of grade 3/4 non-haematological adverse events was acceptable; the most common events were vomiting in 17% of patients, nausea in 16%, and dehydration, diarrhoea and fatigue all in 13%. Grade 3/4 neutropenia was observed in 70% of patients, but febrile neutropenia was reported in just 7%.

A second study investigated the combination of docetaxel 75 mg/m^2 on day 1 and oxaliplatin 80 mg/m^2 on day 2 every 3 weeks in 20 patients with advanced gastric cancer who had progressed on 5-FU-based chemotherapy [7]. Previous first-line therapy included ECF (60% of patients), cisplatin plus infusional 5-FU (30%) and irinotecan plus infusional 5-FU (10%). An objective response was achieved in 15% of patients and 40% had stable disease. Median TTP was 4.8 months (range, 1–7 months) and median OS was 6.0 months (range 2–20 months). Grade 3/4 non-haematological toxicities were neurotoxicity and asthenia, each reported for 10% of patients. Grade 3/4 neutropenia was reported for 40% of patients but none had febrile neutropenia or other grade 3/4 haematological toxicities.

The combination of docetaxel (50 mg/m^2 over 1 hour) with modified FOLFOX6 (oxaliplatin 85 mg/m^2 iv over 2 hours plus 5-FU 400 mg/m^2 bolus then 3000 mg/m^2 iv over 48 hours plus leucovorin 400 mg/m^2 iv over 2 hours), all administered on days 1 and 14 every 3 weeks, was also investigated in a small Phase II study of 16 patients with locally advanced or metastatic gastric cancer. This regimen achieved a high objective response rate (44%; six partial responses, one complete response) and was well tolerated [8].

On the basis of these promising preliminary data for the docetaxel–oxaliplatin combination, a large Phase II study – the GATE study – has been initiated. Two hundred and seventy patients with previously untreated advanced gastric or gastro-oesophageal junction adenocarcinoma will be randomized to receive one of three treatment regimens: docetaxel–oxaliplatin (TE); docetaxel–oxaliplatin–folinic acid/5-FU (TEF); or docetaxel–oxaliplatin–capecitabine (TEX) (Fig. 1). The primary endpoint is TTP. The study will include two cohorts of patients. Patients in each of the two cohorts will be randomized to the same treatment regimens, but the doses of oxaliplatin and docetaxel will be reduced in the first compared with the second cohort. In this way, the study will assess which is the best of the three docetaxel–oxaliplatin treatment regimens and also the best doses for optimal efficacy and safety.

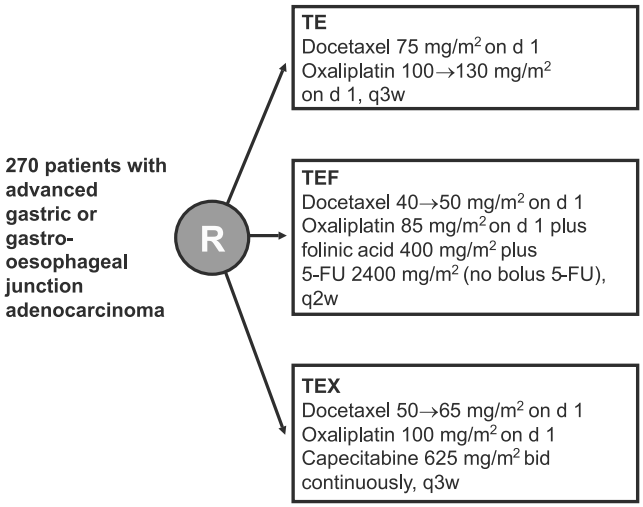

Fig. 1. Phase II GATE study schema.

The docetaxel–oxaliplatin combination is also being investigated in the neoadjuvant setting. The planned Phase II EORTC study will investigate preoperative docetaxel–oxaliplatin–5-FU–leucovorin followed by concomitant oxaliplatin–5-FU plus radiotherapy and then surgery in patients with locally advanced gastric or gastro-oesophageal junction adenocarcinoma.

4. Substitution of 5-FU with oral fluoropyrimidines

As in other tumour types, the potential of oral fluoropyrimidines to replace iv 5-FU is an active area of investigation in gastric cancer, with the objective of improving the convenience of combination chemotherapy regimens. The REAL-2 study [5] (see also Cunningham in this issue) showed that capecitabine is at least as active as 5-FU in gastric cancer and has a favourable toxicity profile. The potential of capecitabine as first-line therapy for gastric cancer was also investigated in a Phase III study conducted in Korea, Asia and Latin America. In this non-inferiority study (primary endpoint PFS), 316 patients with previously untreated metastatic gastric adenocarcinoma were randomized to receive five cycles of either cisplatin (80 mg/m^2 on day 1) plus capecitabine (1000 mg/m^2 twice daily on days 1–14), every 3 weeks (XP), or the same regimen of cisplatin plus 5-FU (800 mg/m^2/day on days 1–5), every

3 weeks (FP). The XP regimen was clearly not inferior to FP ($P = 0.0008$; test for superiority $P = 0.0801$), with median PFS durations of 5.6 months (95% CI, 4.9–7.3 months) and 5.0 months (95% CI, 4.2–6.3) in the two treatment arms, respectively. In fact, XP was associated with improved median OS (10.5 months vs. 9.3 months; $P < 0.008$) and objective response rate (41% vs. 29%; $P = 0.030$) compared with FP, and had a similar safety profile [9].

Several Phase II studies have investigated the combination of docetaxel with capecitabine as first- or second-line [4,10–14] therapy for advanced gastric cancer (Table 1). Although these were small studies, the cumulative evidence supports the feasibility of docetaxel–capecitabine in gastric cancer, with objective response rates generally ranging from 39% to 55% (20% in one study [4]), median TTP ranging from 3.7 months to 6.1 months and median OS ranging from 8.4 months to 15.8 months. The main toxicities of this combination include acceptable levels of neutropenia, febrile neutropenia, diarrhoea, nausea, stomatitis and hand–foot syndrome.

The new oral fluoropyrimidine, S-1, which is commercially available for gastric cancer in Japan, was investigated in combination with docetaxel (40 mg/m^2 iv over 1 hour on day 1, every 3 weeks) in a Phase II study of 48 patients with inoperable or recurrent gastric adenocarcinoma [15]. The primary endpoint of the study was objective response rate, and 56% of patients had a partial response (Fig. 2). A further 38% of patients had stable disease, giving an overall tumour control rate of 94%. TTP was 7.3 months (95% CI, 4.2–10.7 months) and median OS was 14.3 months (95% CI, 10.7–20.3 months). The safety profile of the docetaxel–S-1 combination was very good, with a generally low incidence of grade 3/4 adverse events. Grade 3/4 neutropenia and leucopenia were reported for 58% and 42% of patients, respectively, and febrile neutropenia for 8%. Further to these promising Phase II data, a large Phase III trial (START) was recently initiated in Japan and Korea. A target of 628 patients with inoperable or relapsed gastric or gastro-oesophageal cancer will be randomized to receive either S-1 80 mg/m^2/day on days 1–14 plus docetaxel

Table 1
Phase II studies of docetaxel–capecitabine in advanced gastric cancer[a]

Study	No. of evaluable patients	ORR (%)	Median TTP (months)	Median OS (months)
Chun [10][b]	47	40	4.5	12.0
Lorenzen [11][c]	24	46	6.1	15.8
Kim [12]	30	44	5.1	8.4
Thuss-Patience [13][d]	11	55	–	–
Giordano [14]	44	39	4.2	9.4
Tebbutt [4][b]	35	20	3.7	–

[a] ORR, Overall response rate; OS, Overall survival; TTP, Time to tumour progression.
[b] Weekly docetaxel. [c] First- or second-line therapy. [d] Preliminary results.

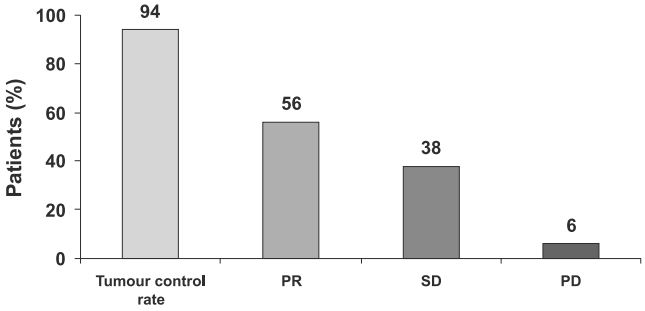

Fig. 2. Phase II study of docetaxel plus S-1 in advanced gastric cancer: response rates [15]. PD, Progressive disease; PR, Partial response; SD, Stable disease.

40 mg/m^2 on day 1 every 3 weeks, or single-agent S-1 80 mg/m^2/day on days 1–28 every 6 weeks. The primary endpoint is OS.

Irinotecan has also been investigated in gastric cancer. A Phase III study of first-line irinotecan and 5-FU (IF) vs. CF in 333 patients with advanced gastric cancer demonstrated similar efficacy for the two combinations in terms of TTP (5.0 vs. 4.2 months, respectively; $P = 0.088$), time to treatment failure (4.0 vs. 3.4 months, respectively; $P = 0.018$) and OS (HR 1.08 for IF vs. CF) [16].

5. Incorporating biological therapies into docetaxel-based chemotherapy

The addition of biological agents to optimal chemotherapy regimens represents perhaps the greatest opportunity to improve outcomes for patients with gastric cancer. There are currently few data available on biological agents in the gastric cancer setting; ongoing Phase II studies are investigating various treatment combinations, including: docetaxel and bevacizumab; docetaxel, oxaliplatin and bevacizumab; docetaxel, cisplatin and sorafenib; and docetaxel and imatinib. The tyrosine kinase inhibitor gefitinib demonstrated moderate activity (1 partial response, 12 stable disease) in 75 patients with pretreated metastatic gastric cancer [17]; however, no activity was observed for single-agent erlotinib as first-line therapy in 26 patients with locally advanced or metastatic disease [18]. Other novel biological agents under investigation in gastric cancer include cetuximab, matuzumab, bortezomib and trastuzumab.

Results were presented recently for a Phase II study of docetaxel (35 mg/m^2 iv over 30 minutes on days 1, 8 and 15, every 4 weeks) combined with bevacizumab (5 mg/kg iv over 30–90 minutes on days 1 and 15, every 4 weeks) in 26 patients with advanced gastric or oesophageal cancer [19]. Most patients had previously received irinotecan and/or cisplatin. Interim response data for 17 patients demonstrate the feasibility of this regimen, which achieved a partial response in 4 patients (24%) and disease stabilization in 4 patients (24%). Toxicity was acceptable; the main grade 3/4 toxicities were anaemia (15%), fatigue (12%), neutropenia (12%), gastrointestinal bleed (12%) and arterial

thrombosis (8%) – the latter two toxicities most likely related to bevacizumab.

Some of the first data for irinotecan and targeted therapy combinations were presented at the 2006 ASCO annual meeting. First-line irinotecan–cisplatin plus bevacizumab was investigated in a non-randomized Phase II study in 47 patients with advanced gastric or gastro-oesophageal cancer [20]. The results suggest acceptable toxicity and improved efficacy for irinotecan–cisplatin plus bevacizumab compared with historical controls: TTP was 8.9 months (historical, 5.0 months); median OS was 12.3 months (historical, 8–10 months); and the ORR was 65%. In another study in 38 patients with advanced gastric or gastro-oesophageal cancer, first-line FOLFIRI (irinotecan, leucovorin and bolus plus continuous infusion 5-FU) plus cetuximab was well tolerated and achieved an objective response rate of 56% [21].

6. Conclusions

The treatment of advanced gastric cancer remains a major challenge but significant advances have been made. The recent TAX 325 study showed that TCF is superior to CF and provided a new standard in advanced gastric cancer. We now have the basis to further improve chemotherapy by modifying and optimizing the TCF regimen, and investigating novel treatment combinations incorporating oxaliplatin, capecitabine, irinotecan and S-1. Docetaxel–oxaliplatin is a promising new chemotherapy backbone, and emerging data suggest that oxaliplatin may be a favourable substitute for cisplatin in combination chemotherapy regimens. There is growing evidence that oral fluoropyrimidines are active, well tolerated and convenient alternatives to 5-FU. Finally, the addition of biological agents to the optimal chemotherapy regimen may achieve further improvements in efficacy.

It is notable that much of the data discussed in this paper are from non-randomized Phase II studies. There are now several agents with proven activity in gastric cancer; therefore, single-arm studies of combination regimens comprising one or more active agents are inconclusive with regard to determining which components are essential for the observed activity. To decrease the risk of initiating potentially negative Phase III trials, it may be beneficial to include randomized Phase II trials in the research and development of novel regimens – an approach successfully utilized to establish the role of docetaxel in gastric cancer. With such a variety of investigations ongoing in order to optimize the efficacy and tolerability of gastric cancer therapy, we may hope for further major advances in the near future.

References

1. Moiseyenko V, Ajani J, Tjulandin SA, et al. Final results of a randomized controlled phase III trial (TAX 325) comparing docetaxel (T) combined with cisplatin (C) and 5-fluorouracil (F) in patients (pts) with metastatic gastric adenocarcinoma. *J Clin Oncol* 2005, **23**(Suppl 16), 308s (Abstract 4002).
2. Moiseyenko V, Van Cutsem E, Tjulandin S, et al. Adding docetaxel to cisplatin–5-fluorouracil improves quality of life in advanced gastric cancer: a Phase III trial. *7th World Congress on Gastro-intestinal Cancer*, Barcelona, Spain, 15–18 June 2005 (Abstract O-013).
3. Van Cutsem E, Moiseyenko V, Tjulandin S, et al. Docetaxel when added to cisplatin–5-fluorouracil improves survival in advanced gastric cancer: a Phase III trial. *7th World Congress on Gastro-intestinal Cancer*, Barcelona, Spain, 15–18 June 2005 (Abstract O-012).
4. Tebbutt N, Gebski V, Strickland A, et al. Randomized phase II study evaluating weekly docetaxel in combination with cisplatin and 5FU or capecitabine in metastatic oesophago-gastric cancer. *J Clin Oncol* 2006, **24**(Suppl 18), 194s (Abstract 4067).
5. 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 oesophagogastric (OG) cancer: the REAL 2 trial. *J Clin Oncol* 2006, **24**(Suppl 18), 182s (Abstract LBA4017).
6. Richards DA, Wilfong L, Reznick D, et al. Phase II multicenter trial of docetaxel+oxaliplatin in stage IV gastroesophageal and/or stomach cancer. *J Clin Oncol* 2006, **24**(Suppl 18), 195s (Abstract 4071).
7. Barone C, Basso M, Quirino M, et al. Docetaxel and oxaliplatin combination as second line treatment in patients with advanced gastric cancer. *ASCO Gastro-intestinal Cancers Symposium*, Hollywood, Florida, 27–29 January 2005 (Abstract 27).
8. Dima G, Caputo A, De Simone R, et al. Phase II study of docetaxel, oxaliplatin, and folinic acid in locally advanced or metastatic gastric cancer patients. *Ann Oncol* 2005, **15**(Suppl 7) (Abstract E27).
9. Kang Y, Kang WK, Shin DB, et al. Randomized phase III trial of capecitabine/cisplatin (XP) vs. continuous infusion of 5-FU/cisplatin (FP) as first-line therapy in patients (pts) with advanced gastric cancer (AGC): efficacy and safety results. *J Clin Oncol* 2006, **24**(Suppl 18), 183s (Abstract LBA4018).
10. Chun JH, Kim HK, Lee JS, et al. Weekly docetaxel in combination with capecitabine in patients with metastatic gastric cancer. *Am J Clin Oncol* 2005, **28**, 188–94.
11. Lorenzen S, Duyster J, Lersch C, et al. Three-weekly docetaxel (T) plus capecitabine (X) in 1st and 2nd line metastatic esophageal cancer (MEC): final results of the Phase II DACAPO trial. *J Clin Oncol* 2005, **23**(Suppl 16), 343s (Abstract 4142).
12. Kim JG, Sohn SK, Kim DH, Baek JH, et al. Phase II study of docetaxel and capecitabine in patients with metastatic or recurrent gastric cancer. *Oncology* 2005, **68**, 190–5.
13. Thuss-Patience PC, Kretzschmar A, Loew A, et al. Capecitabine and docetaxel in advanced gastric adenocarcinoma, an ongoing phase II study. *J Clin Oncol* 2005, **23**(Suppl 16), 343s (Abstract 4224).
14. Giordano KF, Jatoi A, Stella PJ, et al. Docetaxel and capecitabine in patients with metastatic adenocarcinoma of the stomach and gastroesophageal junction: a phase II study from the North Central Cancer Treatment Group. *Ann Oncol* 2006, **17**, 652–6.
15. Yoshida K, Ninomiya M, Takakura N, et al. Phase II study of docetaxel and S-1 combination therapy for advanced or recurrent gastric cancer. *Clin Cancer Res* 2006, **12**, 3402–7.
16. Dank M, Zaluski J, Barone C, et al. Randomized phase 3 trial of irinotecan (CPT-11) + 5FU/folinic acid (FA) vs. CDDP + 5FU in 1st-line advanced gastric cancer patients. J Clin Oncol 2005, **23**(Suppl 16S), 308s (Abstract 4003).
17. Doi T, Koizumi W, Siena S, et al. Efficacy, tolerability and pharmacokinetics of gefitinib (ZD1839) in pretreated patients with metastatic gastric cancer. *Proc Am Soc Clin Oncol* 2003, **22** (Abstract 1036).
18. Dragovich T, McCoy S, Urba SG, et al. SWOG 0127: Phase II trial of erlotinib in GEJ and gastric carcinomas. *ASCO Gastrointestinal Cancers Symposium*, Hollywood, Florida, 27–29 January 2005 (Abstract 49).

19. Enzinger PC, Fidias P, Meyerhardt J, et al. Phase II study of bevacizumab and docetaxel in metastatic esophageal and gastric cancer. *ASCO Gastrointestinal Cancers Symposium*, San Francisco, California, 26–28 January 2006 (Abstract 68).
20. Shah MA, Ramanathan RK, Ilson D, et al. Final results of a multicenter phase II study of irinotecan (CPT), cisplatin (CIS), and bevacizumab (BEV) in patients with metastatic gastric or gastroesophageal (GEJ) adenocarcinoma (NCI #6447). *J Clin Oncol* 2006, **24**(Suppl 18), 183s (Abstract 4020).
21. Pinto C, Di Fabio F, Siena S, et al. Phase II study of cetuximab plus FOLFIRI as first-line treatment in patients with unresectable/metastatic gastric or gastroesophageal junction (GEJ) adenocarcinoma (FOLCETUX study): preliminary results. *J Clin Oncol* 2006, **24**(Suppl 18), 186s (Abstract 4031).