Review of docetaxel in the treatment of gastric cancer

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Abstract: Gastric cancer is a global health problem accounting for 800,000 cancer related deaths annually. Often diagnosed at an advanced stage, the treatment of gastric cancer with chemotherapy is directed towards palliating cancer related symptoms with only modest improvements in survival. In addition, no regimen has emerged as a globally accepted standard. New therapeutic options are desperately needed for the treatment of gastric cancer. Docetaxel given in combination has recently emerged as a new option for patients with advanced gastric cancer. This review focuses on the treatment of advanced gastric cancer utilizing docetaxel-based therapy and the novel additions of biotherapy to the existing cytotoxic platforms. In addition, the current investigations of docetaxel for the treatment of potentially curable gastric cancer will be discussed.

Keywords: docetaxel, gastric cancer, chemotherapy, biotherapy

Introduction

Although the rate of gastric cancer in developing countries has declined over the last 50 years, gastric cancer remains the fourth most common cancer worldwide. For the year 2007, gastric cancer was estimated to be the second leading cause of cancer related death among men and the fourth among women, accounting for 800,000 cancer-related deaths overall (Garcia et al 2007) Gastric cancer is often diagnosed at an advanced stage when a cure is not possible, and treatment is palliative with the intent of improving the quality and quantity of life.

Early studies in advanced gastric cancer demonstrated a survival benefit for patients treated with systemic chemotherapy compared with patients that received best supportive care alone (Murad et al 1993; Glimelius et al 1994; Pyrhonen et al 1995). The backbone of early chemotherapy regimens was often 5-fluorouracil (5-FU) or cisplatin (CDDP). After these early studies, several phase III trials were completed to determine the optimum chemotherapy regimen for the treatment of advanced gastric cancer. Commonly investigated regimens included FAMTX (5-FU, doxorubicin, high-dose methotrexate), FAM (5-FU, adriamycin, mitomycin-C), ECF (epirubicin, CDDP, 5-FU), ELF (etoposide, leucovorin, 5-FU), and CF (CDDP, 5-FU). However, no globally accepted regimen emerged. In addition, the results were generally disappointing as response rates did not exceed 45% and the median survival time did not exceed 10 months in any study (Wils et al 1991; Webb et al 1997; Vanhoefer et al 2000; Ross et al 2002; Ohtsu et al 2003). Recently, docetaxel given in combination with cisplatin and 5-fluorouracil has emerged as a new therapeutic option for patients with advanced gastric cancer. This review will focus on the benefit of docetaxel for the treatment of gastric cancer, as well as the promising future directions.

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Docetaxel monotherapy

Initial investigations of single agent docetaxel revealed promising activity and suggested further evaluation was warranted. Administration of docetaxel was commonly repeated every 3 weeks at a dose of 60–100 mg/m^2. The overall response rate (ORR) in the front-line setting was 17%–24%, while in the salvage setting the ORR was 4.8%–22% (Sulkes et al 1994; Einzig et al 1996; Taguchi et al 1998; Graziano et al 2000; Mavroudis et al 2000; Bang et al 2002). The most common toxicities included neutropenia, leucopenia, nausea, vomiting, stomatitis, diarrhea, fatigue, and neuropathy. The early studies of docetaxel monotherapy indicated the taxane was well tolerated, active in advanced gastric cancer, and deserved further investigation in combination with other cytotoxic agents.

Docetaxel, cisplatin, and 5-FU

Based on the initial activity of docetaxel as a monotherapy, the V-325 study group developed docetaxel to be given in combination with CDDP and 5-FU (DCF). The initial phase of investigation compared the doublet of docetaxel (85 mg/m^2) and CDDP (75 mg/m^2) every 3 weeks (DC) with the triplet regimen of docetaxel (75 mg/m^2), CDDP (75 mg/m^2), and 5-FU (750 mg/m^2/day × 5 days) every 3 weeks in a randomized phase II trial (Ajani et al 2005). The purpose of this trial was for an independent data monitoring committee (IDMC) to select one of the two regimens to be the investigational arm in a future randomized phase III trial to be compared with the reference regimen of cisplatin and 5-FU. This trial enrolled and randomized 158 patients with advanced gastroesophageal cancer, of which 155 received treatment (DCF; n = 79, DC; n = 76). ORR rate favored DCF over DC; 43% and 26%, respectively. Time to progression (TTP) for DCF was 5.9 months vs 5.0 months for DC, while overall survival (OS) was 10.5 months for DC and 9.6 months for DCF. The DCF regimen was associated with more thrombocytopenia; otherwise hematologic toxicity was similar between the treatment regimens. Non-hematologic toxicity was more common in the DCF arm and was mostly gastrointestinal in origin. Common toxicities included nausea, vomiting, stomatitis, diarrhea, and anorexia. Based on the higher confirmed ORR for the DCF and acceptable toxicity profile, DCF was chosen by the IDMC as the investigational regimen to be compared with CF in the planned phase III trial.

The second phase of development completed by the V325 study group was the multinational, multicenter, open label, phase III, randomized trial comparing DCF with the reference regimen CF (Van Cutsem et al 2006). The primary endpoint of the trial was to demonstrate the superiority of DCF compared with CF based on TTP. Secondary endpoints included OS, ORR, clinical benefit, and quality of life. In less than 4 years, the V325 study group randomly assigned and treated 455 patients across 72 centers and 16 countries with DCF (n = 221) and CF (n = 224). The treatment arms were well balanced for baseline patient characteristics. Of note, 97% of the patients overall had metastatic disease and 42% had more than 2 organ sites involved; representing a patient population with very advanced disease.

With a median follow up time of 13.6 months, the primary endpoint of the trial was achieved as DCF had a significantly longer TTP compared with CF (5.6 months vs 3.7 months; p = 0.01). Overall survival was significantly prolonged with DCF compared with CF (9.2 months vs 8.6 months; p = 0.02) and the ORR was higher with DCF (37%) compared with only 25% with CF (p = 0.01). In addition, the percentage of patients treated with DCF and alive at 1 year was 40% vs only 32% for CF. At 2 years, the percent of patients alive was doubled with the DCF regimen as compared to CF (18% vs 9%).

As expected, the triplet regimen resulted in greater toxicity than the doublet regimen. DCF was associated with significantly greater grade III/IV neutropenia (82% vs 57%), leucopenia (65% vs 31%), febrile neutropenia/neutropenic infection (63% vs 27%), diarrhea (19% vs 8%) and neuropathy (17% vs 6%). It should be noted, that with the use of granulocyte colony stimulating factors (GCSF) as secondary prevention, the rate of complicated neutropenia was reduced to 12% with DCF as compared to 27% without GCSF in patients treated with DCF. In addition, infection (grade III or IV) was greater with DCF (20%) in patients greater than 65 years of age as compared to patients treated with CF (9%). The most common reason for treatment discontinuation in both arms was progressive disease. However, disease progression as the reason for treatment discontinuation was less common with the DCF regimen (29.9% vs 43.8%). More patients treated with the DCF regimen withdrew consent (21.7 vs 11.6%) while similar numbers of patients discontinued treatment due to adverse events (treatment related or unrelated). Within 30 days of the last infusion of chemotherapy the number of deaths for DCF was 23 (10%) compared with 19 (8%) with CF. The toxicity associated with the DCF regimen underscores the need for proper patient selection to reduce the probability of significant adverse events.

Although the acute treatment related toxicity was greater with the DCF regimen than the CF regimen, the increased toxicity did not appear to negatively affect quality of life or clinical benefit. In fact, as part of the planned secondary

endpoint analysis, it was demonstrated that the DCF regimen significantly prolonged the time to definitive detoriation in quality of life and time to definitive worsening of Karnofsky performance status (KPS) compared with CF (Ajani et al 2007a, b). The time to weight loss and definitive worsening of appetite favored the DCF regimen but did not reach statistical significance. There was no difference in pain-free survival or time to cancer-related opioid use between the two regimens. The superiority of the DCF regimen in quality of life and clinical benefit is consistent with the previously mentioned improvements in TTP, OS, and ORR compared withj CF.

Modifications of the original DCF (mDCF) regimen have been pursued to evaluate the safety and efficacy of the triplet regimen approach. In a large randomized phase II trial, Roth et al (2007) randomized patients to treatment with mDCF (docetaxel 85 mg/m^2, cisplatin 75 mg/m^2 and FU 300 mg/m^2/d × 14 days), DC (docetaxel 85 mg/m^2, cisplatin 75 mg/m^2), or ECF (epirubicin 50 mg/m^2, cisplatin 60 mg/m^2, and FU 200 mg/m^2/day × 21 days). Each treatment cycle was repeated every 3 weeks. 119 chemotherapy-naïve patients with unresectable or metastatic gastric cancer were included in the analysis and were randomly assigned to treatment with mDCF, DC, or ECF. The independently reviewed ORR favored mDCF compared with ECF and DC (36.6%, 25%, and 18.4%, respectively). With a median follow-up time of 27.6 months, TTP favored mDCF and ECF (4.6 months vs 4.9 months respectively) compared with DC (3.6 months). OS was also improved with triplet therapy (mDCF = 10.4 months, ECF = 11.0 months) compared with the doublet regimen (8.3 months). Toxicity was considerable for all three treatment regimens. Due to a high rate of febrile neutropenia in the docetaxel containing arms, a protocol amendment reduced the dose of docetaxel from 85 to 75 mg/m^2. The dose reduction resulted in a decrease in febrile neutropenia for mDCF and DC (mDCF 28%–12%, DC 15%–4%). Grade III or IV toxicities occurring in more than 10% of patients for the mDCF regimen included neutropenia, febrile neutropenia, nausea/vomiting, alopecia, and diarrhea. Treatment delays greater than 7 days per cycle and per patient were most common with the ECF regimen compared with mDCF and DC (ECF = 12%/5%, DCF = 6%/24%, DC = 3%/11%; per cycle and per patient, respectively). Unacceptable toxicity as a reason for treatment failure was more common with the ECF regimen, while patient refusal as a reason for treatment failure was more common with the mDCF regimen. However, it should be noted that 50% of the patients who refused further treatment with mDCF had received 6 or more cycles of therapy. Quality of life (QoL) scores were obtained at baseline and were well balanced between treatment arms. Functional QOL scores for emotional functioning improved for all three regimens, while role functioning and numbness/paresthesia worsened for DC and mDCF, and remained the same for ECF. Constipation improved for mDCF at cycle 6 and remained the same for DC and ECF. Global health status improved with the ECF regimen, remained the same for mDCF, and declined for DC. Overall treatment burden was assessed by QoL forms and favored ECF compared with mDCF and DC after cycle 2 and cycle 6. The findings of this study confirm that the mDCF regimen is more promising than DC, although it is unclear if the modifications of the original DCF regimen significantly improved the safety and tolerability.

Two other trials have been completed with modified DCF regimens and have reported promising results. A trial by Lorenzen et al (2007) treated 60 patients with locally advanced (n = 24) or metastatic (n = 36) gastroesophageal adenocarcinoma with docetaxel (50 mg/m^2) day 1, 15, 29, cisplatin (50 mg/m^2) day 1, 15, 29, and 5-FU (2000 mg/m^2) and leucovorin (400 mg/m^2) weekly. Treatment was repeated every 8 weeks. The use of prophylactic GCSF support was not allowed in this trial. After treatment of the first 15 patients, a protocol amendment reduced the dose of both docetaxel and cisplatin to 40 mg/m^2 secondary to frequent grade III and IV toxicities. After modification of the initial DCF regimen, treatment was generally well tolerated. As expected, hematologic toxicity was common, but rates of grade III or IV neutropenia (22%), febrile neutropenia (5%) and thrombocytopenia (2%) were acceptable. Common non-hematologic toxicity with the mDCF regimen included grade III or IV diarrhea (20%), lethargy (18%), nausea (8%), and vomiting (8%). The mDCF regimen appeared to be an active regimen with an ORR of 47%, TTP of 9.4 months, and OS of 17.9 months. However, the survival data are misleading as 40% of the treated patients had locally advanced disease. Nevertheless, the regimen confirms the activity of the triplet combination and the improved safety profile is encouraging.

Another modification of the DCF regimen was investigated by Park et al (2005). They developed a mDCF regimen with low dose docetaxel (50 mg/m^2) day 1 given in combination with cisplatin (80 mg/m^2) day 1 and 5-FU (1200 mg/m^2) day 1–3. The mDCF regimen was repeated every 3 weeks. (Park, Chun et al 2005) The ORR in 47 chemotherapy naïve patients with metastatic gastric cancer was 40%, while TTP was 4.6 months and OS was 9.7 months. Rates of grade III or IV neutropenia (68%) and febrile neutropenia/neutropenic infection (26%) were less common than previously reported

high dose DCF regimens. In addition, non-hematologic grade III or IV toxicities appeared slightly more favorable with the low dose docetaxel regimen (stomatitis 21%, diarrhea 4%, nausea/vomiting 0%) compared with the toxicity profile of higher dose docetaxel regimens. However, the total dose of 5-FU in the mDCF regimen utilized by Park et al was 150 mg/m^2 lower per cycle than traditional DCF (3750 mg/m^2/cycle for DCF vs 3600 mg/m^2/cycle for mDCF). 5-FU was also infused over 3 days for mDCF compared with 5 days for DCF. The reduced total dose of 5-FU and decreased length of infusion may account for the decreased non-hematologic toxicity of the mDCF regimen. Regardless, the modified DCF regimen confirms the proof of principle that alterations of the original DCF regimen can achieve similar activity with more favorable toxicity profiles.

In summary, the pivotal trial performed by the V-325 study group led to Food and Drug Administration approval for the use of docetaxel in combination with cisplatin and 5-FU for the treatment of advanced gastric and gastroesophageal adenocarcinoma. The addition of docetaxel to the chemotherapy options for patients with advanced gastric cancer represents an important achievement. The toxicity associated with the DCF regimen is noteworthy and necessitates proper patient selection and subsequent aggressive management of toxicities. The use of GCSF for primary prophylaxis of neutropenia should be considered for all patients, as well as the use of a P/neurokinin 1 (NK_1) receptor antagonist for chemotherapy-induced nausea and vomiting. In addition, modifications of the DCF regimen can result in similar activity and better tolerated treatment regimens (Table 1).

Docetaxel, oxaliplatin, and 5-FU

As noted previously, the toxicity profile associated with the DCF regimen has led investigators to focus on modifying the DCF regimen so that treatment is better tolerated by patients. One promising approach is the substitution of oxaliplatin for cisplatin. It was demonstrated in the REAL-2 trial that oxaliplatin was not inferior to cisplatin when combined with epirubicin and 5-FU or capecitabine, based on the endpoints of OS and PFS (Cunningham et al 2008). Compared with cisplatin, oxaliplatin was associated with lower rates of neutropenia, alopecia, renal toxicity, and thromboembolism. However, oxaliplatin was associated with more diarrhea and neuropathy. Extrapolating from the REAL-2 trial results and incorporating the positive results from the V325 study, 2 trials have investigated treatment for advanced gastroesophageal cancer with docetaxel, oxaliplatin, and 5-FU.

Al-Batran et al enrolled 59 chemotherapy-naïve patients with advanced gastric cancer to be treated with docetaxel (50 mg/m^2), oxaliplatin (85 mg/m^2) leucovorin (200 mg/m^2), and 5-FU via CIV (2.6 g/m^2) over 24 hours (FLOT) (Al-Batran et al 2007). At the time of analysis (n = 57; 2 patients were found to have ineligible disease), ORR was 50.9% and disease stability rate was 70.2%. Survival data were available for 52 patients and median PFS was 5.3 months while median OS was 11.3 months. The FLOT regimen appeared to have a more favorable safety profile than the previously reported DCF regimen. Common grade III and IV toxicities with the FLOT regimen were neutropenia (46.3%), leukopenia (22.2%), neurosensory (9.3%), fatigue (9.3%), and diarrhea (14.8%). Febrile neutropenia was not common with the FLOT regimen (3.7%), and no treatment-related deaths were observed.

A phase I study initiated by Ajani et al (2007) was performed to determine the cycle 1, maximum tolerated dose of docetaxel when given in combination with oxaliplatin (85 mg/m^2) and 5-FU via CIV (2.2 mg/m^2) over 48 hours (D-FOX) every 2 weeks. Docetaxel was initiated at a dose of 20 mg/m^2 in the typical 3 × 3 phase I clinical trial design.

Table 1 Docetaxel in combination with cisplatin and 5-fluorouracil

Study	Treatment (months)	Number of patients	Response rate (%)	Median PFS (months)	Median OS
Van Cutsem	DCF	224	37	5.6	9.2
(V-325)	CF	221	25	3.7	8.6
Roth	DCF[a]	61	36.6	4.6	10.4
	ECF	59	25	4.9	11.0
	DC	58	18.4	3.6	8.3
Lorenzen	DCF[b]	60	47	9.4	17.9
Park	DCF[c]	47	40	4.6	9.7

[a]Low dose 5-FU with prolonged infusion.
[b]Split dose DCF every 2 weeks.
[c]Low dose docetaxel.
Abbreviations: DCF, docetaxel, cisplatin, and 5-FU; ECF, epirubicin, CDDP, 5-FU; PFS, progression-free survival; OS, overall survival.

Subsequent dose escalations of docetaxel in were performed at intervals of 5 mg/m^2. Preliminary results from the trial were presented in 2007. Response rate (43%), time to progression (6 months), and OS (13 months) suggested D-FOX was an active regimen in advanced gastric cancer (Tetzlaff et al 2008). The safety profile of the D-FOX regimen was acceptable, as grade III/IV toxicities were not common. In addition, the trial did not utilize prophylactic GCSF support; yet febrile neutropenia and neutropenic infection were not common during any cycle and were absent during cycle 1. The phase I portion of the trial was recently completed and 55 mg/m^2 was selected as the dose of docetaxel to be given in combination with oxaliplatin and 5-FU in the phase II trial (Ajani unpublished data). The final phase I results are awaited.

Several other studies have combined docetaxel with oxaliplatin (DO) ± capecitabine (DOX) in the first-line setting for untreated metastatic gastroesophageal cancer (Grothe et al 2006; Evans et al 2007; Kim et al 2008; Richards et al 2008). ORR for DO was 36%–45.2% and DOX was 19%–30%. OS reported for the two DO trials was 8.5 months to 9.9 months, respectively. The combination regimens were well tolerated with manageable toxicity (Table 2).

Docetaxel with irinotecan

Irinotecan is another active agent for the treatment of advanced gastroesophageal cancer. Irinotecan has a reported ORR of 14%–25% as a single agent, and 22%–51% when given in combination with 5-FU or cisplatin (Tetzlaff et al 2008). Phase II trials have added docetaxel to be given with irinotecan; however, the results have been generally disappointing. When docetaxel was given in combination with irinotecan, the response rate was 26%–45.7%, TTP/PFS was 4.5 months and 4.2, respectively, and OS was 7.3–8.2 months. Since the addition of irinotecan in 2 recent phase III trials did not show a survival benefit in the first-line setting for advanced gastric cancer, it may not be ideal in the front-line setting and may account for the disappointing results when it has been given in combination with docetaxel (Dank et al 2005; Boku et al 2007).

Docetaxel in combination with biotherapy

Bevacizumab

To develop the treatment of advanced gastric cancer beyond traditional cytotoxic therapy, research has focused on the development of biotherapy to be given in combination with chemotherapy. The development of biochemotherapy for advanced gastric cancer has focused on inhibition of vascular endothelial growth factor (VEGF), epidermal growth factor receptor (EGFR), and other pathways. Several biologic agents are under current investigation with the most mature results available for the monoclonal antibodies bevacizumab and cetuximab.

In a predominantly previously treated patient population, Enzinger et al evaluated single agent docetaxel (35 mg/m^2 day 1, 8, and 15) and bevacizumab (5 mg/kg day 1 and 15) in advanced gastroesophageal cancer, with the treatment cycle repeated every 4 weeks (Enzinger et al 2006). The ORR among 15 evaluable patients was 27%, with an additional 38% of patient with stable disease as their best response. All four patients with a radiographic response to therapy had received prior chemotherapy for metastatic disease. Common grade III/IV toxicities for all 20 enrolled patients were fatigue (15%), gastrointestinal bleeding (15%), anemia (15%), neutropenia (10%), and arterial thrombosis (10%).

A modified DCF regimen was developed by the gastroesophageal cancer group at the Memorial Sloan-Kettering Cancer Center to minimize the toxicity associated with the standard DCF regimen, and to be used as a platform for the addition of bevacizumab (Jhawer et al 2008). Treatment consisted of docetaxel (40 mg/m^2), 5-FU bolus (400 mg/m^2), leucovorin (400 mg/m^2), and infusional 5-FU (1000 mg/m^2 × 2 days) with bevacizumab (10 mg/kg) day 1. On day 3, cispla-

Table 2 Docetaxel in combination with oxaliplatin ± 5-fluorouracil or capecitabine

Study	Treatment (months)	Number of patients	Response rate (%)	Median PFS (months)	Median OS
Al-Batran	FLOT	59	50.9	5.3	11.3
Ajani	D-FOX	36	46	6.0	13.0
Kim	DOX	42	45.2	5.7	9.9
Grothe	DOX	14	30	3.9$^+$	NR

$^+$Censored.

Abbreviations: D, docetaxel; O, oxaliplatin; F, 5-fluorouracil; X, capecitabine; L, leucovorin; PFS, progression-free survival; OS, overall survival; NR, not reported.

tin was given at a dose of 40 mg/m^2. A preliminary analysis after enrolling 21 patients indicated an ORR of 71%, with 81% of the patients progression free at 6 months. Grade III toxicities included neutropenia (50%), febrile neutropenia (15%), venous thromboembolism (29%), and fatigue (15%). Grade III hypertension, proteinuria, and perforation were not observed. The study continues to enroll patients with a target accrual of 44 patients.

A second trial reported by Enzinger (2008) utilized a more aggressive cytotoxic chemotherapy regimen with docetaxel as the backbone of therapy. Thirty-two patients were enrolled to be treated on day 1 and 8 with docetaxel (30 mg/m^2), cisplatin (25 mg/m^2), and irinotecan (50 mg/m^2). Bevacizumab was given on day 1 of every 3-week cycle at a dose of 10 mg/kg. The biochemotherapy regimen appeared to have considerable activity in the chemotherapy-naïve patient population, with a partial response rate of 63% (an additional 30% had stable disease as their best response). Toxicity of the regimen was consistent with prior experience, and generally well tolerated. In addition, UGT1A1 gene testing was predictive of severe diarrhea and neutropenia in patients with the *28 allele present.

As discussed above, the combination of docetaxel and oxaliplatin is considered to be a reasonable foundation for the addition of biotherapy. In a phase II trial reported by El-Rayes (2008), untreated patients with advanced gastric cancer were treated with docetaxel (70 mg/m^2), oxaliplatin (75 mg/m2), and bevacizumab (7.5 mg/kg) every 3 weeks. With only 8 evaluable patients enrolled on the trial to date, the ORR was 50% with an additional 50% with stable disease. Gastrointestinal perforation occurred in 2 patients after cycle 2. Both patients had their primary tumor in place; one patient underwent surgical exploration and the other patient was medically managed. Other toxicities with the regimen include grade III IV neutropenia (38%), fever (13%), neuropathy (13%), and hypertension (13%). The biochemotherapy regimen appeared to be active in advanced gastric cancer. However the safety of bevacizumab (eg, gastrointestinal perforation) was of concern.

Cetuximab

Several trials were recently reported on the clinical activity of cetuximab in combination with docetaxel. A monoclonal antibody, cetuximab is targeted to inhibit the EGFR pathway. Cetuximab is typically administered with an initial loading dose (400 mg/m^2) followed by weekly maintenance therapy (250 mg/m^2). As second-line therapy, Tebbut (2008) combined docetaxel (30 mg/m^2) day 1 and 8 of a 3-week cycle with the traditional dosing schedule of cetuximab. Thirty-eight patients were accrued for therapy, and ORR was a modest 6%. With a median follow-up time of 19 months, PFS was 2.1 months and OS was 5.3 months. A subset analysis correlated increased grade of acneiform rash with improved PFS and OS, results that are consistent with prior studies of EGFR inhibitors. Grade III/IV toxicities with this salvage regimen included anorexia (16%), diarrhea (11%), nausea (8%), and acneiform rash (5%). Febrile neutropenia was uncommon (3%). There were no treatment related deaths with this regimen, but the 60-day all cause mortality was 15.8%; potentially representing the poor prognosis of patient with treatment refractory gastric cancer.

In the front-line setting, Pinto (2008) treated 48 patients with the doublet regimen of docetaxel (75 mg/m^2) plus cisplatin (75 mg/m^2) every 3 weeks and standard dose cetuximab (DOCETUX). Patients were treated with the doublet regimen for a maximum of 6 cycles, but could continue with cetuximab in the absence of disease progression. In 42 evaluable patients, ORR rate was 40.5% (1 complete response), and an additional 38.1% had stable disease as their best response. With 75% of the patients still alive at the time of reporting, PFS at 3 months was 80%, and survival data have not yet been presented. Toxicity assessment of 48 evaluable patients showed the most common grade III/IV to be the hematologic toxicities of neutropenia (45.8%), febrile neutropenia (22.9%), and anemia (6.25%). Other toxicities included fatigue (22.9%), hyponatremia (20%), hypokalemia (16%), skin reaction (31.3%), vomiting (8.3%), and stomatitis (6.3%). There were 3 deaths within 60 days from the initiation of therapy, but the relationship with therapy was not clear. In a companion study of 21 patients treated with the DOCETUX regimen, it was shown that a reduction in basal VEGF levels in plasma and serum correlated with the disease control rate (Di Fabio 2008). These findings suggest that this biochemotherapy regimen can affect circulating VEGF levels, and an early reduction in serum and plasma VEGF may be used as an early surrogate marker for disease control.

Although the results from the biochemotherapy trials are not mature at this time, the response rates and predictors of toxicity and response are of significant interest (Table 3). It will be of great importance to complete well-designed phase III trials to define the clinical benefit of biochemotherapy in advanced gastric cancer. In addition, correlative studies to predict response to therapy and expected toxicity will be of significant benefit to patients and clinical oncologists, so that treatment can be tailored to the individual patient to maximize response while minimizing toxicity risks from treatment.

Table 3 Docetaxel in Combination with Biotherapy

Study	Treatment	Number of patients	Response rate (%)	PFS	Median OS (months)
Enzinger	Docetaxel/ Bevacizumab	15	27	NR	NR
Tebbutt	Docetaxel/ Cetuximab	38[a]	6	2.1 months	5.3
Jhawer	mDCF/ Bevacizumab	21	71	81% at 6 months	NR
El-Rayes	Docetaxel Oxaliplatin Bevacizumab	8	50	NR	NR
Pinto	Docetaxel Cisplatin Cetuximab	48	40.5	80% at 3 months	NR
Enzinger	Docetaxel Cisplatin Irinotecan Bevacizumab	32	63	NR	NR

[a]Previously treated patients.
Abbreviations: PFS, progression-free survival; OS, overall survival; NR, not reported; mDCF, modifed docetaxel, cisplatin, and 5-FU regimen.

Localized gastric cancer

Several treatment strategies have emerged for the treatment of localized gastric cancer. Options for localized gastric cancer in the Western Hemisphere include primary surgical resection followed by adjuvant chemoradiation, or perioperative chemotherapy and surgical resection (ie, preoperative chemotherapy, followed by surgical resection, and then adjuvant chemotherapy) (Macdonald et al 2001; Cunningham et al 2006). In the East, surgery consisting of a gastrectomy and a D-2 lymph node dissection followed by adjuvant chemotherapy with S-1 has been shown to improve overall survival compared to surgery alone (Sakuramoto et al 2007). Since the benefit of docetaxel has been established in the advanced disease setting, it is reasonable that docetaxel be investigated in the localized disease setting.

Utilizing a neoadjuvant approach for localized gastric cancer, Vuidez et al (2008) reported preliminary results of a phase I dose escalation study of docetaxel, oxaliplatin, and capecitabine given concurrently with radiotherapy. Dose escalation of docetaxel at intervals of 5 mg/m^2 (starting at 15 mg/m^2 weeks 1, 2, 4, 5) was given with fixed doses of oxaliplatin (50 mg/m^2 weeks 1, 2, 4, 5) and capecitabine (650 mg/m^2 twice daily Monday through Friday). Radiation was completed to a total dose of 45 Gy in 25 fractions. Twenty-three patients were enrolled on the trial and it was determined that 25 mg/m^2 was the recommended dose of docetaxel in this combination for future phase II trials. An R0 resection was achieved in 90% of the patients, and 68.4% of the patients had a major response to therapy (Becker criteria). Based on the promising results in advanced gastric cancer with the DOX regimen, and the high R0 resection rate in this trial, further investigation of this combination is warranted.

The Italian Trial in Medical Oncology (TIMO) group completed a feasibility study with docetaxel as adjuvant therapy in gastric cancer. They investigated sequential adjuvant chemotherapy for radically resected gastric cancer (Di Bartolomeo et al 2006). Patients were randomly assigned to treatment with 4 cycles of FOLFIRI followed by 4 cycles of docetaxel and cisplatin (DC), or assigned to treatment with mitomycin C (MMC) monotherapy for 6 cycles. 166 patients were enrolled and treated on the study (FOLFIR/DC; n = 85, MMC n = 81). With the exception of pN2–pN3 being more prevalent in the DC arm, the two arms were well balanced for baseline characteristics. The quality of surgical resection appeared reasonable in the trial, with a median of 25 lymph nodes examined, and 85% of patients having 15 or more lymph nodes sampled. Treatment in the polychemotherapy arm was generally well tolerated with 76% of the patients completing the planned sequential therapy. In the monotherapy arm, only 39% of patients completed treatment with MMC necessitating a protocol amendment to reduce the dose

Table 4 Ongoing and completed phase III and IV trials of docetaxel for the treatment of gastroesophageal cancer

Study phase indentifier	Patient population	Treatment setting	Treatment	Trial status	
NCT00290966	Metastatic gastric and GEJ	Palliative	DCF vs CF	Completed	III
NCT00287768	Metastatic gastric and GEJ	Palliative	Docetaxel + S-1 vs S-1 alone	Recruiting	III
NCT00005060	Locally advanced gastric and GEJ	Adjuvant/ Neoadjuvant	DCF (pre vs post-operative)	Active	III
NCT00525200	Locally advanced esophageal cancer	Neoadjuvant	Docetaxel vs CF	Recruiting	IV[a]

[a]p53 genotype study to predict response to induction chemotherapy.
Abbreviations: DCF, docetaxel, cisplatin, and 5-FU; CF, cisplatin and 5-FU; GEJ, gastroesophageal junction.

of MMC to 8 mg/m^2 for 4, rather than 6 cycles of therapy. The amended MMC therapy was more tolerable as 83% of the patients completed 4 cycles of MMC, and 72% did not require additional dose reductions. After a median follow up of 29 months, 3-year estimates of disease-free survival and OS favored the FOLFIRI/DC arm compared with the MMC arm; 67.4% vs 50.2% (p = 0.0449) and 73.5% vs 62.4% (p = 0.1634) respectively. Some investigators suggest a multicenter national trial comparing sequential therapy with a standard reference regimen is warranted to confirm the efficacy of the FOLFIRI/DC strategy. However, it would be more intriguing to investigate the more active docetaxel-based therapy chemotherapy regimens in the preoperative setting either in combination with biotherapy or radiation therapy.

Conclusion

The addition of docetaxel to the treatment options available for patients with advanced gastric and gastroesophageal junction adenocarcinoma is a notable achievement. With careful patient selection and aggressive supportive measures, DCF represents a reasonable treatment option. Modifications to the dose and schedule of the DCF regimen can improve the safety and tolerance of docetaxel-based therapy for patients. In addition, the substitution of cisplatin with oxaliplatin to create the D-FOX regimen has demonstrated promising results for docetaxel-based therapy. Several phase III trials are ongoing and recruiting patients for treatment with gastroesophageal cancer (Table 4). In addition, phase II trials investigating the addition of biotherapy to docetaxel-based therapy are promising, and may significantly advance the impact of systemic therapy. In addition, the incorporation of docetaxel in the neo-adjuvant and adjuvant setting is under active investigation, and may improve the benefits of multimodality therapy for potentially curable gastric cancer.

Disclosures

None of the authors has any conflicts of interest to disclose.

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