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Review paper

Docetaxel in advanced gastric cancer

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Standard chemotherapy for advanced gastric cancer remains undefined. Two of the most popular regimens—ECF [epirubicin–cisplatin–5-fluorouracil (5-FU)] and PELF (cisplatin–epirubicin–5-FU–leucovorin)—have been shown to be active, but each has limitations. Phase II trials show that single-agent docetaxel is an active agent in advanced gastric cancer, producing overall response rates (ORRs) of 17.5–24%. Docetaxel has also been shown to lack cross-resistance with other drugs in gastric cancer, and is likely to be at least additive to cisplatin and 5-FU. Phase II results of docetaxel combinations in advanced gastric cancer are encouraging. Docetaxel–cisplatin has yielded response rates similar to those achieved by ECF and PELF. Adding 5-FU to docetaxel–cisplatin has achieved an ORR of 52 versus 45% for docetaxel–cisplatin in a randomized phase II trial. Docetaxel-based regimens demonstrate acceptable tolerability despite predictable hematotoxicity. Neutropenia, the major toxicity, is manageable by dose modification or by using prophylactic granulocyte colony stimulating factor. Several phase III trials are now ongoing, including a large-scale trial of docetaxel–cisplatin–5-FU versus cisplatin–5-FU. Results will show whether docetaxel improves overall response and survival, as suggested in the phase II setting. [© 2002 Lippincott Williams & Wilkins.]

Key words: Advanced gastric cancer, chemotherapy, docetaxel.

Introduction

For many years, advanced gastric cancer was assumed to be somewhat unresponsive to chemotherapy. Several new drugs, including the taxane docetaxel, have emerged that may form the basis of more effective or better-tolerated regimens in advanced gastric cancer.[1,2] In this review, we consider the evidence describing the role of docetaxel in the treatment of advanced gastric cancer, within the context of current best practice. Phase II studies suggest that docetaxel is associated with a high overall response rate (ORR), prolonged time to progression (TTP) and acceptable tolerability, both as monotherapy and in combination. Docetaxel-based regimens are currently being assessed in phase III trials.

Therapeutic innovations are needed to improve gastric cancer outcomes. Gastric cancer remains the second most common cause of cancer death worldwide,[3] despite a declining incidence in the west during the 20th century. The incidence of gastric cancer is particularly high in Asia, South America and many Eastern European countries. In Japan, gastric neoplasms are the most common cause of cancer death.[4]

Gastric cancer's epidemiologic profile reflects, in part, the differential distribution of *Helicobacter pylori* infection worldwide. Approximately half the world's population is infected with *H. pylori*.[5] *H. pylori* is a major factor in the development of gastric cancer, increasing the relative risk of developing gastric cancer by 2.2- to 2.5-fold.[5] It has been suggested that if the prevalence of *H. pylori* could be reduced, many gastric cancers would be avoided.[6]

The molecular pathway through which *H. pylori* infection leads to gastric cancer is unclear. The functional impairment of p53, a tumor suppressor protein, appears to contribute to most human cancers.[7] Notwithstanding this, *p53* mutations do not appear to occur at a significant rate in gastric cancer. For example, in a recent study, only approximately 20% of a Taiwanese cohort expressed *p53* mutations on polymerase chain reaction assessment and direct sequencing, with over-expression of p53 oncoprotein observed in 28% of patients.[8] A rare clustered mutation identified by this study suggests *p53* has an important role in the pathogenesis of some of these tumors. Studies are needed to

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characterize gastric cancer's molecular pathology more generally. This may lead to novel therapeutic targets.

The role of surgery in gastric cancer management

Surgery remains the gold standard in early gastric cancer management. Most stage IB and II cancers, and certain stage III gastric cancers, can be resected. Nevertheless, the risk of locoregional and distant failure is high for stage II–III disease. Despite poor results in advanced stages, surgery can be curative in early-stage gastric cancer. In a recent analysis of 87 patients, radical resection of early gastric cancer was associated with a 5-year survival rate of 88.8%, irrespective of lymph node metastases or tumor size. Postoperative morbidity and mortality were 23 and 4.5%, respectively.[9] Similarly, in early-stage disease, endoscopic mucosal resection appears to be associated with improved outcomes. Shimada *et al.* suggest that all microscopic mucosal tumors, with or without an ulceration scar, should be considered for surgery.[10] This approach is associated with a 5-year survival rate of higher than 90%. However, it may only be widely applicable if gastric cancer screening becomes commonplace outside Japan —the only country that currently screens for early detection of gastric cancer.

In the future, improved detection strategies may increase the proportion of patients identified with early disease. In Japan, the proportion of early cancers detected is approximately 50%.[10] In contrast, in countries not practicing routine screening, most gastric cancer patients present with advanced disease. Although surgery is possible in 80–90% of patients, less than half have resectable tumors and more than 50% will have recurrence of disease.[11]

This general finding is underlined by a study of radical gastrectomy with lymphadenectomy. This approach can achieve complete remission in patients with metastases restricted to perigastric lymph nodes. Five- and 10-year survival rates of 93.5 and 89.8%, respectively, were achieved in this study of 100 patients. However, metastatic spread beyond the perigastric lymph nodes reduced 10-year survival to 58.5%.[12]

In order to improve survival for patients with operable gastric cancer, postoperative adjuvant therapy may be required.[12] A variety of traditional chemotherapy regimens have been assessed, but without demonstration of clear benefit and with significant toxicity. A 1993 meta-analysis considering 14 randomized studies published before 1992 could not demonstrate a survival advantage for patients receiving adjuvant therapy.[13] Additional studies have since been reported and a more recent meta-analysis of 21 randomized adjuvant studies published before 1997 has revealed a statistically significant, but relatively small, survival benefit.[14] Despite this finding, there is insufficient evidence to recommend adjuvant chemotherapy for routine use.

Results of a US Intergroup trial suggest that the use of chemoradiation therapy after surgical resection in patients with stage II and IIIA–IIIB disease might be considered the standard of care.[15] In this study, patients with stage IB–IV M0 adenocarcinoma who had undergone gastric resection were randomized to postoperative follow-up or chemoradiation. The trial demonstrated a median overall survival of 36 months for the treatment arm compared with 27 months for the observation group. Notwithstanding this, the role of adjuvant therapy remains controversial. Further efforts are required to optimize postoperative adjuvant management.

The concept of neoadjuvant therapy in locally advanced gastric cancer is appealing. The preoperative approach can potentially downstage the primary tumor and, thereby, increase the rate of R0 resection, in addition to reducing the risk of peritoneal dissemination. Several phase II neoadjuvant studies in gastric cancer have been published, in addition to three randomized trials. The phase II data suggest that preoperative therapy is feasible and able to increase the rate of R0 resection, with reported response rates of 31–70% and resectability rates of 40–100%.[14] Two small randomized phase III Asian trials have reported significantly more downstaging and a higher resection rate for patients receiving preoperative chemotherapy.[16,17] In contrast, the interim analysis of a third randomized trial suggested a higher resection rate in the surgery-only group, although this was not significant.[18] There is currently little evidence for a survival advantage with neoadjuvant therapy. A phase II study by Fink *et al.* demonstrated a statistically significant survival benefit in 24 patients with R0 resection after neoadjuvant therapy compared with 24 matched controls who did not receive preoperative chemotherapy,[19] but this has yet to be convincingly confirmed in a phase III setting. Investigators are still refining treatment strategies and defining ideal patient populations for neoadjuvant therapy, and well-designed prospective randomized trials are required to demonstrate the advantage of this approach.

Chemotherapy for advanced disease

A survival benefit and a positive impact on quality of life have been shown in patients with unresectable or metastatic gastric cancer receiving chemotherapy with best supportive care compared with the best supportive care alone.[20] In the chemotherapy group, 45% of patients had an improved or prolonged high quality of life for a minimum of 4 months compared with 20% of those receiving best supportive care ($p < 0.05$). Median overall survival was longer in the chemotherapy group (8 versus 5 months), although this was not statistically significant. Chemotherapy for advanced gastric cancer is now widely accepted in Europe and the US, but a standard therapy has yet to be defined.

Pathologic and clinical prognostic factors relating to chemotherapy for gastric cancer are important in the planning and analysis of clinical trials. Prognostic factors in early-stage gastric cancer include the site of the primary tumor, degree of differentiation, lymph node extension, depth of invasion and stage. Studies of prognostic factors relating to chemotherapy in advanced gastric cancer have shown performance status (PS) to be the leading determinant for both objective tumor response and survival.[21,22] The presence of metastases and poorly differentiated tumor histology have a negative prognostic effect, with a strong correlation between position of the primary tumor and location of metastases. A tumor response advantage has been demonstrated in a phase II setting for patients with good PS, the primary located in the cardia, and a non-linitis plastica tumor form or a tumor with less than 50% of independent cells.[22] In this study, survival was positively impacted by good PS and lack of linitis plastica. The tumor markers β-human chorionic gonadotrophin (β-HCG) and CA125 in advanced gastric cancer prior to chemotherapy have been shown to convey independent poor prognosis, which may reflect high tumor burden or aggressive biology.[23]

Monotherapy with 5-fluorouracil (5-FU), doxorubicin, mitomycin C and cisplatin—historically considered the most active agents in gastric cancer—has produced response rates of 20–30% (median duration 2–4 months). Complete responses (CRs) with single agents are rare in gastric cancer and partial responses (PRs) tend to be of relatively short duration.[11] One of the first widely assessed combination regimens for gastric cancer—FAM (5-FU, doxorubicin and mitomycin C)—yielded only a marginal improvement compared with the single-agent results, with a 20–42% response rate, generally of short duration.[24]

A number of 'second-generation' regimens—usually based on 5-FU and often including cisplatin —have since been assessed. The combination of cisplatin and 5-FU (PF) is active and tolerable in patients with advanced gastric cancer.[22] The most widely used of the 'second-generation regimens' have included PF, FAMTX (5-FU, doxorubicin and methotrexate), EAP (etoposide, doxorubicin and cisplatin) and ELF (etoposide, leucovorin and 5-FU). While early clinical studies of these regimens showed promise, subsequent randomized studies have achieved response rates of only 20–25%, median TTPs of 5 months or less and no consistent improvement in overall survival compared with older regimens.[25,26]

Two more recently proposed regimens appear promising in gastric cancer. First, ECF (epirubicin, cisplatin and 5-FU as a protracted continuous infusion) has been shown to achieve a 71% ORR in a phase II setting.[27] A subsequent phase III randomized study in 274 patients showed an ORR of 45% with ECF compared with 21% for the control arm, FAMTX.[28] ECF yielded a superior median TTP of 7.4 versus 3.4 months for FAMTX, with a median survival duration of 8.9 versus 5.7 months, respectively. These are encouraging results, although questions remain about patients' acceptability of the in-dwelling catheter and external pump required for the protracted venous infusion of 5-FU. Secondly, a multicenter phase II trial of intensive weekly PELF (cisplatin, epirubicin, leucovorin and 5-FU) in 23 patients was associated with a 62% ORR and median survival duration of 11 months.[29] Granulocyte colony-stimulating factor (G-CSF) was administered daily between each course of chemotherapy. Although toxicity was described as acceptable (grade 3–4 toxicities occurred in 38% of patients), 86% of patients required at least one treatment delay during the first 8 weeks of therapy.

Despite recent advances in the treatment of advanced gastric cancer, there remains a need for new effective and well-tolerated regimens—probably incorporating 5-FU and cisplatin, which continues to represent an acceptable standard of care. A definitive standard regimen is unlikely to be described until promising new agents are fully assessed in randomized trials.

Docetaxel in advanced gastric cancer

Docetaxel has demonstrated activity in gastric cancer and the remainder of this review examines the scientific and clinical basis for its role in gastric

cancer. Docetaxel is a semisynthetic taxane derived from the needles of the European yew tree (*Taxus baccata*). Docetaxel shares a similar mechanism of action (tubulin stabilization and cell cycle arrest) and a number of pharmacologic characteristics with paclitaxel, which derives from the Pacific yew tree (*Taxus brevifolia*).[30,31]

Notwithstanding the similarities, these taxanes are distinctly different. For example, docetaxel has a greater affinity for tubulin, a longer plasma half-life and longer intracellular retention than paclitaxel.[30] The taxanes also exhibit different drug resistance profiles. Intrinsic and acquired docetaxel resistance is primarily dependent on P-glycoprotein—encoded by multiple drug resistance (MDR)-1—but is not related to multidrug resistance protein (MRP).[32] In contrast, paclitaxel resistance is mediated by both P-glycoprotein and MRP.[33] The main toxicity associated with docetaxel is predictable myelotoxicity, with a reduced degree of neuropathy, a major side effect of cisplatin and paclitaxel regimens. *In vitro* evaluations of the antitumor effects of docetaxel compared with paclitaxel in human gastric cancers have revealed an effectiveness rate for docetaxel of 56% compared with just 6% for paclitaxel.[31] It was determined that docetaxel's cytotoxicity was 2–80 times greater than that of paclitaxel. Using human gastric cancer xenografts in nude mice, docetaxel was shown to be active in well-differentiated, poorly differentiated and undifferentiated gastric cancers.[31]

These preclinical findings are supported by clinical evidence showing that docetaxel is active as monotherapy and in combination in a range of cancers. In particular, docetaxel is now widely used in the treatment of advanced breast, lung and ovarian cancer.[30]

Docetaxel phase II monotherapy studies

Several studies from Europe, the US and Japan have assessed first-line docetaxel monotherapy in advanced gastric cancer. Single-agent docetaxel at a range of doses, including 60, 75 and 100 mg/m^2, has achieved ORRs of 17.5–24% (Table 1). These response rates are comparable to those of conventional drugs in gastric cancer.[11]

The first evidence of docetaxel's activity in advanced gastric cancer emerged from a study in 37 patients with advanced, untreated gastric cancer with metastases.[34] Patients received docetaxel 100 mg/m^2 i.v. every 3 weeks, without premedication, for a median of 4 cycles (range 1–8). Partial responses in a variety of metastatic sites were achieved in eight (24%) of the 33 evaluable patients for a median duration of 7.5 months (range 3–11). Disease stabilized in another 33% of patients for a median of 4 months (range 3–8). Docetaxel was active at a variety of metastatic sites, including the liver and retroperitoneal lymph nodes.

Hematologic toxicity predictably emerged as the main side effect, with non-cumulative grade 3–4 neutropenia experienced by 95% of patients.[34] However, there were only 8 episodes (5%) of neutropenic fever requiring hospital admission.

Einzig *et al.*, confirmed the activity of docetaxel 100 mg/m^2 in 41 patients, previously untreated with cytotoxic chemotherapy, with adenocarcinoma of the esophagus and stomach.[35] In the 36 patients evaluable for response, a 20% ORR (6% CR and 14% PR) was achieved, with a median TTP of 2.8 months. Median overall survival was 7.8 months and the estimated survival at 18 months was 17%. Neutropenia was the major toxicity observed, with 90% of patients developing grade 3–4 neutropenia.

Two studies have confirmed the antitumor activity of docetaxel in advanced gastric cancer at a lower dose of 60 mg/m^2.[36,37] Both studies assessed docetaxel 60 mg/m^2 i.v. every 3–4 weeks in patients with advanced or recurrent gastric cancer and both achieved an ORR of 24% (CR 2% and PR 22%) in 59 evaluable patients (Table 1). Once again, grade 3–4 leukopenia and neutropenia emerged as the main toxicities, occurring in 56 and 81% of patients in the study by Taguchi *et al.*,[37] and in 68 and 90% of patients in the second study,[36] respectively. In the study by Mai *et al.*, 44 (77%) patients had received prior chemotherapy with pyrimidines or cisplatin.[36] This high proportion of patients receiving prior chemotherapy is of relevance: the docetaxel activity observed suggests a lack of cross-resistance with other chemotherapeutic agents.[36]

A phase II study of docetaxel 75 mg/m^2 every 3 weeks in metastatic or recurrent gastric cancer has recently been published.[38] Most of the patients enrolled had adenocarcinomas of the gastric antrum and/or body of the stomach, and all had metastatic disease. In the 40 evaluable patients, an ORR of 17.5% (95% CI: 7.3−32.8) was achieved, with 27.5% stable disease (SD). Median TTP and survival were 1.4 (95% CI: 1.3–2.6) and 11 (95% CI: 5.7–13.6) months, respectively, with a 48% probability of being alive at 1 year. In total, 48% of patients showed involvement of at least three organs, with two-thirds retaining the primary tumor, a high-risk prognostic factor.[21]

Table 1. Phase II studies with single-agent docetaxel in patients with advanced gastric cancer

Study	Evaluable patients	Patient/disease characteristics	Regimen	Response[a] (%)	Grade 3–4 toxicities in $>10\%$ of patients (%)
Sulkes *et al.*[34] (multicenter study, $n=37$)	33	advanced, untreated gastric cancer with metastases (WHO PS $\leqslant 2$)	docetaxel 100 mg/m^2 i.v. q3w (median 4 cycles; range 1–8)	ORR 24 (CR 0, PR 24, SD 33, PD 43)	neutropenia (95), leukopenia (70), fatigue/asthenia (16)
Einzig *et al.*[35] (multicenter study, $n=41$)	36	adenocarcinoma of the esophagus and stomach, previously untreated with cytotoxic chemotherapy (ECOG PS $\leqslant 2$)	docetaxel 100 mg/m^2 i.v. q3w (median 4 cycles; range 1–17)	ORR 20 (CR 6, PR 14, SD 8, PD 72)	neutropenia (90), nausea (12), pulmonary dysfunction (12)
Taguchi *et al.*[37b] (multicenter study, $n=66$)	59	advanced or recurrent gastric cancer	docetaxel 60 mg/m^2 i.v. q3–4w	ORR 24 (CR 2, PR 22, MR 2, SD 32, PD 42)	neutropenia (81), leukopenia (56), nausea/vomiting (17), anorexia (14)
Mai *et al.*[36b] (multicenter study, $n=63$)	59	advanced or recurrent gastric cancer (PS $\leqslant 2$)	docetaxel 60 mg/m^2 i.v. q3–4w	ORR 24 (CR 2, PR 22, MR 5, SD 34, PD 37)	neutropenia (90), leukopenia (68)
Mavroudis *et al.*[39] (single-center study, $n=30$)	30	advanced gastric cancer (WHO PS $\leqslant 2$)	docetaxel 100 mg/m^2 i.v. q3w (median 3.5 cycles); G-CSF 5 μg/kg s.c. d2–8	ORR 20 (CR 3, PR 17, SD 23, PD 57)	neutropenia (36)
Bang *et al.*[38] (multicenter study, $n=44$)	40	metastatic or locally recurrent gastric adenocarcinoma (Karnofsky PS >70)	Docetaxel 75 mg/m^2 i.v. q3w (median 3 cycles; range 2–18)	ORR 17.5 (CR 0, PR 17.5, SD 27.5, PD 55)	neutropenia (82)

ECOG, Eastern Cooperative Oncology Group; MR, minor response.
[a]Evaluable population.
[b]Foreign language reference; abstract analysis.

Although 87% of patients experienced at least one adverse event that was possibly or probably related to docetaxel, there was no event more severe than grade 3.[38] Neutropenia was reported by 82% of patients, with a 5% occurrence of febrile neutropenia. These findings suggest that docetaxel 75 mg/m^2 is active and tolerable, meriting further investigation in combination with other active agents in gastric cancer. Indeed, as the next section details, combination studies using docetaxel 75 mg/m^2 suggest that this dose is associated with acceptable hematologic toxicity compared with higher doses, but without compromising response.

The hematotoxicity identified in the single-agent docetaxel studies in advanced gastric cancer is predictable and comparable to that of other agents used in this disease. A study of docetaxel monotherapy (100 mg/m^2 i.v. every 3 weeks) given with G-CSF as first-line therapy in advanced gastric cancer showed that G-CSF attenuates docetaxel-related hematotoxicity and helps avoid the need for dose reduction.[39] In this study of 30 patients, an ORR of 20% (95% CI: 6–34) was achieved (3% CR and 27% PR) with a median duration of response of 4.5 months (range 2–12) and 23% SD. The median TTP was 6 months (range 2–14), with a median survival of 7 months (range 1–24) and 1-year survival probability of 28%. The administration of G-CSF reduced the incidence of grade 3–4 neutropenia (36%) and febrile neutropenia (2% of cycles), and reduced the need for docetaxel dose reduction (7% of cycles). There were no toxic deaths.

Patients typically receive routine steroids prior to docetaxel administration to reduce hypersensitivity reactions, with steroid treatment continued for 2 days to reduce fluid retention. In the trial by Mavroudis *et al.*,[39] this resulted in fewer hypersensitivity reactions (10% of patients) and fluid retention (17%) than observed in the previously described study by Sulkes *et al.*,[34] for example. In the Sulkes trial, no such pre- and postmedication was administered, and the incidence of these adverse events was 24 and 22%, respectively.

Docetaxel-based combinations—phase II studies

The combination of docetaxel with other drugs is pharmacologically feasible in the management of gastric cancer. As several of the monotherapy studies show, docetaxel has demonstrated activity in patients who were either pretreated with other agents or in whom previous chemotherapy has failed. This suggests that there is no consistent cross-resistance to other agents commonly used to treat gastric cancer.

Pharmacologic studies add credence to the clinical observations that combination therapy should be at least additive. For example, Scanlon *et al.*, characterized the biochemical basis for the synergism between cisplatin and 5-FU: cisplatin increases the availability of reduced folate needed for the latter's DNA cross-linking.[40] As docetaxel has a different mechanism of action, the effects are likely to be additive to cisplatin and 5-FU. Indeed, docetaxel has been shown to lack cross-resistance with cisplatin and 5-FU *in vitro*.[41] Currently, four studies of combinations incorporating docetaxel in advanced gastric cancer have been published. Other studies are detailed in abstracts and their findings are broadly consistent with the fully published data (Table 2).

Docetaxel in combination with cisplatin. Three studies have considered the docetaxel plus cisplatin (TP) combination.[42–44] First, in the phase I/II study by Roth *et al.*,[44] TP achieved a high response rate and was well tolerated in locally advanced gastric cancer. The study assessed docetaxel (85 mg/m^2 with dose escalation to 100 mg/m^2 in a phase I fashion) plus cisplatin (75 mg/m^2) in 48 patients, who received a median of 5 cycles. In total, 45 patients were evaluable for response. The ORR was 60% (4% CR and 56% PR), with median TTP and overall survival of 6.6 and 9 months, respectively. These phase II findings compare favorably with other second-generation regimens (e.g. FAMTX, EAP, PF and ELF) in gastric cancer.[25,26] They are also similar to the results of the more recently reported ECF[28] and PELF[29] regimens. PR was achieved in 37% of responders after only 2 cycles (6 weeks).[44] Such rapid and high response rates suggest TP might be suitable for neoadjuvant therapy in gastric cancer.

Grade 3–4 neutropenia, anemia and alopecia occurred in 81, 32 and 36% of patients, respectively.[44] Dose escalation to docetaxel 100 mg/m^2 was performed in five patients, but discontinued due to excessive toxicity. Using docetaxel 85 mg/m^2, 79% of cycles were administered as planned. There were nine episodes of non-fatal febrile neutropenia. These tolerability results are comparable with other common chemotherapeutic regimens in gastric cancer.[25,26] TP would appear to be as well tolerated as ECF—but without the need for an in-dwelling catheter and external pump—and better tolerated than the more intensive PELF regimen.[28,29]

In a second study, Ridwelski *et al.*, also assessed the TP regimen, using a lower dose of docetaxel

Table 2. Phase II studies with docetaxel in combination with other agents in patients with advanced gastric cancer

Study	Evaluable patients	Patient/disease characteristics	Regimen	Response[a] (%)	Grade 3–4 toxicities in $>10\%$ of patients (%)
Ajani *et al.*[45b] (multicenter study, $n=70$)	60	advanced gastric or GE junction cancer (Karnofsky PS >70)	arm A: docetaxel 85 mg/m^2 i.v. d1, cisplatin 75 mg/m^2 i.v. d1 q3w; arm B: docetaxel 75 mg/m^2 i.v. d1, cisplatin 75 mg/m^2 i.v. d1, 5-FU 750 mg/m^2/d d1–5 q3w	arm A (TP): ORR 45 (CR 0, PR 45, SD 42, PD 13); arm B (TPF): ORR 52 (CR 0, PR 52, SD 38, PD 10)	arm A: neutropenia (50); arm B: neutropenia (72)
Cascinu *et al.*[46] (multicenter study, $n=40$)	40; 34 patients received sequential docetaxel	advanced gastric cancer (ECOG PS $\leqslant 2$; Karnofsky PS >70)	cisplatin 40 mg/m^2 i.v. d1, 5-FU 500 mg/m^2 i.v. d1, epirubicin 35 mg/m^2 i.v. d1, leucovorin 250 mg/m^2 i.v. d1, glutathione 1.5 g/m^2 i.v. d1, filgrastim SC 5 μg/kg d2–7 q3w (PELF); sequential therapy with docetaxel 100 mg/m^2 i.v. q3w	PELF alone: ORR 40 (CR 7.5, PR 32.5, SD 52.5, PD 3.5); PELF+docetaxel: ORR 58	PELF alone: alopecia (88); PELF+docetaxel: alopecia (94), neutropenia (29)
Roth *et al.*[44] (multicenter study, $n=48$)	45	advanced gastric cancer (PS $\leqslant 1$)	docetaxel 85 mg/m^2 i.v. d1, cisplatin 75 mg/m^2 i.v. d1 q3w (median 5 cycles; range 1–17); dose escalation to 100 mg/m^2	ORR 60 (CR 4, PR 56, SD 27, PD 13)	neutropenia (81), anemia (32), alopecia (36)
Kettner *et al.*[42b] (single-center study, $n=39$; multicenter study, $n=46$)	39 (single-center study); 46 (multicenter study)	advanced or recurrent gastric cancer (ECOG PS $\leqslant 3$)	Docetaxel 75 mg/m^2 i.v. d1, cisplatin 75 mg/m^2 i.v. d1 q3w	single-center study: ORR 41 (CR 10, PR 31, SD 28, PD 31); multicenter study: ORR 33 (CR 7, PR 26, SD 39, PD 28)	single-center study: myelotoxicity (19), gastrointestinal toxicity (16); multicenter study: myelotoxicity (19), alopecia (89)
Ridwelski *et al.*[43] (multicenter study, $n=43$)	39	locally advanced or metastatic gastric cancer (WHO PS $\leqslant 2$)	Docetaxel 75 mg/m^2 i.v. d1, cisplatin 75 mg/m^2 i.v. d1 q3w (median 6 cycles; range 1–12)	ORR 41 (CR 10, PR 31, MR 2, SD 26, PD 31)	leukopenia (19)

[a]Evaluable population.
[b]Meeting abstract.

75 mg/m^2 plus cisplatin 75 mg/m^2 in locally advanced gastric cancer. In the 39 evaluable patients, an ORR of 41% (CR 10% and PR 31%) was achieved.[43] Surgery was performed in three of the complete responders, again indicating the potential usefulness of TP in the neoadjuvant setting. The median TTP and overall survival were 6.1 and 10.4 months, respectively, with 42 and 12% of the cohort alive after 1 and 2 years, respectively. Although the 41% ORR was somewhat lower than in the study by Roth *et al.* (60% ORR), median overall survival was at least equivalent at 10.4 versus 9 months.[44]

Treatment was administered at the planned dose in 90% of cycles.[43] Grade 3–4 leukopenia was the major toxicity, occurring in 19% of patients. There were no cases of febrile neutropenia. This appears to be an improvement on the hematologic toxicities associated with the higher docetaxel doses of 85–100 mg/m^2, suggesting that the 75 mg/m^2 dose may reduce such toxicity, without compromising response.

A third analysis by Kettner *et al.* has been published as an interim analysis of the combined results of a single- and multicenter phase II study assessing docetaxel 75 mg/m^2 and cisplatin 75 mg/m^2 in advanced or recurrent gastric cancer.[42] The ORRs were 41 and 33% in the single- and multicenter studies, respectively, with estimated median survivals of 9 and 10.4 months. Grade 3–4 myelotoxicity was the major toxicity, occurring in 19% of each of the single- and multicenter populations. These findings are generally consistent with results from previous studies of PF.[43,44] Based on these encouraging findings, a phase III trial comparing TP with PF plus leucovorin is currently ongoing.

Docetaxel in combination with cisplatin and 5-FU. The two-drug TP regimen has potential as the basis of docetaxel-based combinations incorporating three or more active drugs in gastric cancer. These additional drugs might best include agents like 5-FU, which can be administered without hematologic toxicity. This is borne out by a study by Ajani *et al.*,[45] which assessed docetaxel 75 mg/m^2, cisplatin 75 mg/m^2 and 5-FU 750 mg/m^2 (TPF) versus TP (docetaxel 85 mg/m^2 and cisplatin 75 mg/m^2) in a randomized phase II study of 158 patients. In an interim analysis of 60 evaluable patients, TP produced an ORR of 45%, with 42% SD and 13% progressive disease (PD). The addition of 5-FU was associated with an ORR of 52% (38% SD and 10% PD). The safety profile was found to be acceptable, with hematologic toxicity similar in both arms. Neutropenia was the major grade 3–4 toxicity (72% TPF and 50% TP), with febrile neutropenia/infection in 7% (TPF) and 8% (TP) of patients. The higher response achieved with TPF has led to the inclusion of this regimen in a currently ongoing phase III clinical trial, in which TPF will be compared with PF (cisplatin 100 mg/m^2 plus 5-FU 1000 mg/m^2).

Sequential chemotherapy with docetaxel. The combination of newer agents with conventional chemotherapy regimens is a challenge, with increased support required to optimize the efficacy/toxicity ratio. Sequential chemotherapy is one approach currently under investigation in a range of tumor types. It is expected that sequential regimens might maximize the dose intensity of each single agent, while avoiding overlapping toxicity due to the concomitant administration of active drugs.

A recent phase II trial utilized sequential docetaxel after intensive weekly PELF, and showed a high objective response rate with manageable toxicity in advanced gastric cancer.[46] The regimen comprised sequential chemotherapy with docetaxel 100 mg/m^2 after 8 weekly cycles of PELF. In total, 40 patients were evaluable for response and toxicity. After PELF alone, the ORR was 40%. However, after sequential administration of docetaxel the ORR increased significantly to 58%. Again, hematologic side effects were the most common adverse events associated with docetaxel. Grade 3–4 neutropenia and thrombocytopenia arose during 10 and 19% of cycles, respectively. It is possible that patients were more likely to experience such toxicity due to cumulative toxicity from prolonged chemotherapy. These results suggest that sequential chemotherapy with docetaxel after PELF is worthy of further investigation as palliative or neoadjuvant chemotherapy. These investigators are planning a phase II randomized trial of PELF versus PELF–docetaxel.

Conclusions

Unmet needs in advanced gastric cancer have stimulated the investigation of newer agents in third-generation regimens. The taxane docetaxel is one such agent that has shown promise in clinical trials. Preclinical studies demonstrate that docetaxel is active in gastric cancer without cross-resistance to other widely used agents, such as 5-FU and cisplatin. Indeed, docetaxel may offer superior efficacy—with potentially less neurotoxicity—compared with paclitaxel,[31] although this requires confirmation in direct comparisons in the clinical setting.

Phase II clinical trials with docetaxel-based combinations incorporating cisplatin and/or 5-FU have yielded response and overall survival rates comparable with those achieved by the most active combinations in advanced gastric cancer.[42–45] Docetaxel has also shown promise as sequential therapy in advanced gastric cancer.[46]

Docetaxel is generally well tolerated in advanced gastric cancer. Consistently, the major toxicity is neutropenia. However, this tends to be non-cumulative and manageable. Current findings suggest that a relatively lower dose of docetaxel 75 mg/m^2 is likely to reduce the risk of grade 4 toxicity and febrile neutropenia, without compromising response.[43] Furthermore, prophylactic G-CSF has been shown to attenuate this toxicity.[39]

These promising phase II results await confirmation in the several ongoing, randomized phase III studies assessing docetaxel-containing regimens in advanced gastric cancer. As results from the phase III studies of docetaxel and other new therapies emerge, the standard of care for advanced gastric cancer—as well as the role of chemotherapy—will be gradually redefined.

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