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Docetaxel and its potential in the treatment of refractory esophagogastric adenocarcinoma

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***Abstract*:** Adenocarcinomas of the esophagus and stomach are a major cause of cancer-related morbidity and mortality worldwide. For patients with advanced disease, first-line chemotherapy with platinum–fluoropyrimidine combinations prolongs survival, but inevitably the disease progresses with a median progression-free survival of approximately 6 months. At the time of progression, approximately 40–50% of patients remain fit and eligible for second-line treatment. Docetaxel has been extensively studied in this chemorefractory setting, mostly in small single arm studies, either as a single agent or in combination with platinum agents, fluoropyrimidines or anthracyclines. However, two randomized controlled trials published since 2012 have convincingly shown that treatment with docetaxel modestly prolongs survival compared with best supportive care alone. Moreover, treatment with docetaxel is associated with relief from cancer-related constitutional and gastrointestinal symptoms with manageable, predominantly haematological, toxicity. Therefore, it represents a valuable treatment option for patients with relapsed esophagogastric cancer. Nevertheless, in view of the short survival time for the majority of these patients, further research is necessary to identify, on the one hand, combinations with targeted agents that will further improve outcomes and, on the other, biomarkers that will allow selection of those patients most likely to benefit.

Keywords: docetaxel, taxanes, chemotherapy, oesophago-gastric cancer, oesophageal cancer, gastric cancer

Introduction

Esophageal and gastric cancers remain major causes of morbidity and mortality with an estimated 480,000 and 990,000 cases worldwide in 2008, respectively [Ferlay *et al.* 2010]. There is marked difference in incidence across world regions with rates of squamous esophageal cancer (SEC) particularly high in Central Asia [Pennathur *et al.* 2013], gastric adenocarcinoma (GAC) in East Asia [Hartgrink *et al.* 2009] and rapidly rising rates of esophageal adenocarcinoma (EAC) in Western Europe and the United States [Lepage *et al.* 2008; Bohanes *et al.* 2012]. The fact that esophageal cancers consist of two different histologies, squamous and adenomatous, and that many cancers arise from the esophagogastric junction (EGJ) and are often difficult to classify as gastric or esophageal [Mariette *et al.* 2011] complicates the study of these tumours. Indeed, many studies enrol patients based on anatomic location, irrespective of histology, whereas others enrol patients with adenocarcinomas irrespective of anatomic origin. This, in addition to the well described differences in outcomes between East Asian and Caucasian patients [Hartgrink *et al.* 2009], renders cross-trial comparisons and extrapolations difficult.

This review focuses on the role of docetaxel in the treatment of advanced esophagogastric adenocarcinoma (EGAC) following failure of first-line chemotherapy with only secondary reference to SEC where appropriate. However, it should be kept in mind that EGAC is not a homogeneous entity, a fact expanded upon in the next section.

Esophagogastric adenocarcinoma (EGAC): many different diseases

Barrett's esophagus, characterized by intestinal metaplasia of the squamous esophageal epithelium, is the only known precursor lesion of EAC

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and EGJ adenocarcinoma (EGJAC) [Ong *et al.* 2010]. Whereas SEC incidence is decreasing in the Western world, marked increases in EAC have been noted [Castro *et al.* 2014; Lepage *et al.* 2008], mirroring the increase in Barrett's esophagus prevalence, itself driven primarily by increasing rates of obesity and gastric reflux and declining incidence of *Helicobacter pylori* infection [Lagergren and Lagergren, 2013]. Whether a Barrett's esophagus-independent route for EAC pathogenesis exists is unclear at present. In contrast to EAC and EGJAC, the incidence of GAC is decreasing, primarily due to better sanitation, food refrigeration and *H. pylori* eradication [Hartgrink *et al.* 2009].

Recently, the Cancer Genome Atlas (TCGA) consortium reported on the comprehensive molecular characterization of 295 cases of EGJAC and GAC, and classified these tumours into 4 distinct subtypes: Epstein–Barr virus (EBV) positive; microsatellite unstable; genomically stable; and tumours with chromosomal instability (CIN) [Bass *et al.* 2014]. Although specific molecular subtypes were enriched in some anatomical subsites (e.g. CIN tumours showed elevated frequency in the EGJ and cardia), there was considerable overlap among sites and, at least in this initial publication, no correlations were detected between molecular subtypes and outcomes. Therefore, with the exception of HER2 overexpression / amplification [Bang *et al.* 2010], molecular pathology considerations do not yet impact on EGAC treatment.

Preclinical evidence for docetaxel activity in EGAC

Docetaxel, a semi-synthetic paclitaxel derivative [Clarke and Rivory, 1999], exhibits a wide spectrum of anticancer activity and, in addition to gastric cancer, is licensed for the treatment of breast, prostate, head and neck, and non small cell lung cancers. Its principal mechanism of action is interference with the mitotic spindle function through promotion of tubulin polymerization and stabilization of the microtubules against depolymerization, eventually leading to mitotic arrest and induction of apoptosis [Jordan, 2002; Rowinsky, 1997]. Initial evaluation of docetaxel in a panel of gastric cancer cell lines, primary tumour cultures and xenografts showed encouraging activity that significantly exceeded that of paclitaxel [Tanaka *et al.* 1996]. In gastric cancer cell lines, docetaxel is able to induce apoptosis through AP-1 activation in a p53-independent manner [Kim *et al.* 1999], an important consideration given the high frequency of *TP53* mutations in EGAC [Bass *et al.* 2014; Dulak *et al.* 2013]. Similarly, docetaxel exhibited considerable *in vitro* activity against SEC and EAC cell lines that significantly exceeded that of paclitaxel, cisplatin or 5-fluorouracil (5FU) [Shakuto *et al.* 2006].

Before proceeding to discuss in detail the role of docetaxel in treatment refractory EGAC, we briefly summarize the main modalities of radical and first-line metastatic treatment of EGAC and docetaxel use in these settings.

Overview of the radical treatment of EGAC and the role of docetaxel

Radical treatment modalities for EGAC are primarily determined by its anatomical location. Neoadjuvant platinum–fluoropyrimidine based chemotherapy or concurrent chemoradiotherapy is frequently employed in EAC and Siewert Type I EGJAC following the results of phase III randomized controlled trials (RCTs) that showed a 10–15% initial survival advantage compared with surgery alone [van Hagen *et al.* 2012; MRC Oesophageal Cancer Working Group, 2002] that is maintained at 5 years [Allum *et al.* 2009]. Radical treatment of Siewert Type II and III EGJAC and GAC is primarily surgical with adjuvant fluoropyrimidine-based chemotherapy frequently employed in East Asia [Sakuramoto *et al.* 2007] and chemoradiotherapy preferred in the United States [Macdonald *et al.* 2001; Smalley *et al.* 2012]. Based on the results of the Medical Research Council (MRC) ST02 (MAGIC) trial, peri-operative epirubicin–cisplatin–5FU (ECF) or epirubicin-cisplatin-capecitabine (ECX) chemotherapy is frequently preferred in Europe [Cunningham *et al.* 2006].

As docetaxel shows at least additive activity when combined with radiotherapy in preclinical EGAC models [Balcer-Kubiczek *et al.* 2006], multiple phase II studies have investigated the addition of docetaxel to neoadjuvant chemoradiotherapy regimens in radically treated EAC. Preliminary reports show encouraging activity without excessive toxicity [Lockhart *et al.* 2014; Ruhstaller *et al.* 2009; Spigel *et al.* 2010] but, as yet, docetaxel has not been directly compared with standard-of-care platinum–fluoropyrimidine regimens and its use for this indication remains limited. Similarly, a small phase II study showed

considerable activity of docetaxel–cisplatin–5FU (DCF) chemotherapy in the peri-operative treatment of EGAC [Ferri *et al.* 2012] with more studies underway. However, a large Italian phase III RCT failed to show any benefit from sequential irinotecan–infusional 5FU (FOLFIRI) followed by docetaxel plus cisplatin compared with infusional 5FU alone in the adjuvant treatment of resected GAC [Bajetta *et al.* 2014].

Overview of docetaxel in the treatment of advanced/metastatic EGAC

In contrast to radically treated EGAC, the anatomical location of the tumour has much less of an impact on the choice of treatment in the metastatic setting. Chemotherapy prolongs survival compared best supportive care (BSC) in previously untreated tumours and a Cochrane meta-analysis has shown that triplet chemotherapy incorporating a fluoropyrimidine, a platinum analogue and an anthracycline results in modest survival prolongation compared with fluoropyrimidine–platinum or fluoropyrimidine–anthracycline doublets [Wagner *et al.* 2010]. The large REAL-2 study showed equivalent efficacy of cisplatin and oxaliplatin and of infusional 5FU and oral capecitabine in the first-line treatment of metastatic EGAC [Cunningham *et al.* 2008], leading to the frequent use of the epirubicin–oxaliplatin–capecitabine (EOX) regimen in clinical practice. In 2010, the trastuzumab for gastric cancer (ToGA) study for the first time showed benefit from the addition of a targeted agent to chemotherapy in a molecularly defined subset of EGAC. In this study, trastuzumab significantly improved survival when added to a cisplatin–fluoropyrimidine backbone in HER2-overexpressing tumours, leading to a new standard of care for these patients [Bang *et al.* 2010].

The V325 study is the main source of support for the use of docetaxel in the first-line treatment of advanced EGAC. A total of 445 patients with advanced EGAC were randomized to treatment with cisplatin and infusional 5FU with or without docetaxel every 3 weeks. The addition of docetaxel improved the median time-to-progression (TTP, primary endpoint) to 5.6 compared with 3.7 months [hazard ratio (HR) 0.68, $p < 0.001$] as well as overall survival (OS, 9.2 *versus* 8.6 months, HR 0.77, $p = 0.02$) [van Cutsem *et al.* 2006]. However, the use of DCF is associated with significant myelotoxicity, which has limited its clinical adoption and has led investigators to study modified regimens in an attempt to improve its tolerability [Anter and Abdel-Latif, 2013; Inal *et al.* 2012; Polyzos *et al.* 2012]. A detailed presentation of studies incorporating docetaxel in the first-line treatment of EGAC can be found in the review published by Nishiyama and Wada [Nishiyama and Wada, 2009].

Docetaxel in the treatment of refractory EGAC

Despite aggressive multimodality treatment, the majority of EGAC will recur. Similarly, the median progression-free survival (PFS) for patients treated in the first-line metastatic setting is approximately 6 months [Cunningham *et al.* 2008; Van Cutsem *et al.* 2006]. At the time of progression, approximately 40–50% of patients remain fit and eligible for second-line treatment [Thallinger *et al.* 2011; Wesolowski *et al.* 2009]. Tables 1–3 summarize the main features of studies incorporating docetaxel in this setting, including SEC in order to provide a more complete overview. The two excellent reviews by Thallinger and colleagues [Thallinger *et al.* 2011] and Wesolowski and colleagues [Wesolowski *et al.* 2009] served as a starting point to identify older relevant prospective studies and were supplemented with a MEDLINE search for studies published since 2009. Additionally, the American Society of Clinical Oncology (ASCO) and European Society for Medical Oncology (ESMO) databases were queried for conference abstracts presented at the last three annual meetings (2012–2014). As is evident from the tables, there is considerable variability among the included studies regarding the anatomical location and histological subtypes studied. This, in addition to the fact that it is not always clear what chemotherapy regimens the included patients were previously exposed to and whether prior chemotherapy was administered as part of radical multimodality treatment or in the metastatic setting, makes drawing conclusions from single arm studies difficult.

Single arm, single agent docetaxel studies

Our search identified six single arm studies of single agent docetaxel in pretreated esophagogastric cancer (Table 1). All except for the study by Muro and colleagues, which predominantly included patients with SEC and will not be discussed further [Muro *et al.* 2004], enrolled patients with adenocarcinoma, mostly of gastric origin. The

Table 1. Non-randomized single agent docetaxel studies in pretreated esophagogastric cancer.

Docetaxel schedule	Previous treatment	Study population (patient numbers)	ORR	TTP	OS	Reference
Docetaxel 75 mg/m^2 day 1 q3w	? (4 had paclitaxel based regimens)	EAC, EGJAC (11)	0%	1.4 months	4 months	Heath *et al.* [2002]
Docetaxel 70 mg/m^2 day 1 q3w	Cisplatin / Nedaplatin ± 5FU ± RT	SEC (46), EAC (3)	16%		8.1 months	Muro *et al.* [2004]
Docetaxel 36 mg/m^2 days 1 + 8 + 15 + 22 + 29 + 36 q8w	Cisplatin + 5FU (12) or PELF (9)	GAC (21)	5%		3.5 months	Graziano *et al.* [2000]
Docetaxel 100 mg/m^2 day 1 q3w	ECF or PELF	GAC (30)	17%		6 months	Guiliani *et al.* [2003]
Docetaxel 75 mg/m^2 day 1 q3w	Cisplatin + 5FU	GAC (49)	16%	2.5 months	8.3 months	Lee *et al.* [2008]
Docetaxel 35–50 mg/m^2 day 1 q2w	S-1 ± Cisplatin	GAC (15)	8%			Kimura *et al.* [2011]

5FU, 5-fluorouracil; EAC, esophageal adenocarcinoma; ECF, epirubicin, cisplatin, 5FU; EGJAC, esophagogastric junction adenocarcinoma; GAC, gastric adenocarcinoma; ORR, overall response rate; OS, overall survival; q3w, every 3 weeks; q8w, every 8 weeks; PELF, cisplatin, epirubicin, leucovorin, 5FU; RT, radiotherapy; SEC, squamous esophageal cancer; TTP, time-to-progression.

largest included study enrolled 49 Korean patients, all of whom had received previous chemotherapy that included at least a platinum analogue (36 cisplatin, 13 oxaliplatin) and a fluoropyrimidine (26 capecitabine, 6 S-1, 10 doxifluridine, 5 5FU) [Lee *et al.* 2008]. Additionally, two-thirds of patients had progressed during first-line chemotherapy and only 17 had undergone gastrectomy, implying a poor prognosis population. Treatment with docetaxel 75 mg/m^2 every 3 weeks (q3w) resulted in a 16% overall response rate (ORR). As is common in studies enrolling East Asian patients, median OS was relatively long at 8.1 months despite a short median TTP of 2.5 months. The largest study in a Caucasian population enrolled 30 Italian patients who were refractory to first-line triplet chemotherapy [Giuliani *et al.* 2003]. Despite frequent myelosuppression requiring growth factor support, administration of docetaxel 100 mg/m^2 q3w was feasible and resulted in encouraging ORR (17%) and median OS (6 months). Contrary to these two studies, Heath and colleagues [Heath *et al.* 2002] reported disappointing efficacy of docetaxel 75 mg/m^2 q3w in a small study of just 11 patients with EAC and EGJAC. Very limited information regarding prior treatments and extent of disease is available from that study, rendering the drawing of conclusions difficult. A further two studies explored fractionated weekly or biweekly docetaxel regimens [Graziano *et al.* 2000; Kimura *et al.* 2011]. ORRs were low at 5–8% in accordance with evidence from other tumour sites such as breast or prostate cancer that show that docetaxel q3w is superior to weekly administration [Sparano *et al.* 2008; Tannock *et al.* 2004]. In summary, although based on small patient numbers, these studies showed encouraging activity of single agent docetaxel administered in a q3w schedule.

Single arm docetaxel combination studies

Combinations of docetaxel and platinum analogues have been frequently employed in the second-line treatment of EGAC (Table 2). Nedaplatin, a cisplatin analogue associated with decreased gastrointestinal and renal toxicity, has shown activity in esophageal cancer [Shimada *et al.* 2013]. However, studies of docetaxel–nedaplatin combinations in previously treated esophageal tumours have almost exclusively enrolled patients with squamous histology and therefore conclusions regarding the activity of this doublet in EGAC cannot be made [Akutsu *et al.* 2012; Jin *et al.* 2009; Nakajima *et al.* 2008; Osaka *et al.* 2006; Yoshioka *et al.* 2006].

Docetaxel 70 mg/m^2 in combination with cisplatin 70–75 mg/m^2 q3w has shown encouraging activity in East Asian patients with SEC; ORRs in two studies enrolling 38 and 20 patients were 34% and 35%, respectively [Shim *et al.* 2010; Tanaka *et al.* 2007]. At least three phase II studies have investigated the activity of this combination

Table 2. Nonrandomized combination docetaxel studies in pretreated esophagogastric cancer.

Docetaxel schedule	Previous treatment	Study population (patient numbers)	ORR	TTP	PFS	OS	Reference
Docetaxel 30 mg/m^2 days 1 + 15, Nedaplatin 80 mg/m^2 day 1 q4w	Cisplatin + 5FU + RT	SEC (12)	25%				Yoshioka *et al.* [2006]
Docetaxel 60 mg/m^2 day 1, Nedaplatin 80 mg/m^2 day 1 q4w	Cisplatin ± 5FU ± RT	SEC (20)	25%		14 weeks	26 weeks	Nakajima *et al.* [2008]
Docetaxel 30 mg/m^2 day 1, Nedaplatin 50 mg/m^2 day 1 q2w	Cisplatin + 5FU	SEC (48)	27%	3.1 months		5.9 months	Jin *et al.* [2009]
Docetaxel 30 mg/m^2 day 1, Nedaplatin 40 mg/m^2 day 1 q2w	Chemotherapy ± RT	SEC (27), EAC (1)	39%			8.5 months	Osaka *et al.* [2006]
Docetaxel 50 mg/m^2 days 1 + 8, Nedaplatin 50 mg/m^2 d8 q4w	Cisplatin + 5FU	SEC (12)	0%		2 months	7.8 months	Akutsu *et al.* [2012]
Docetaxel 70 mg/m^2 day 1, Cisplatin 75 mg/m^2 day 1 q3w	Cisplatin + 5FU ± RT	SEC (38)	34%		4.5 months	7.4 months	Shim *et al.* [2010]
Docetaxel 60 mg/m^2 day 1, Cisplatin 60 mg/m^2 day 1 q3w	S-1 (20), Cisplatin + 5FU (10)	GAC (30)	27%	4.5 months		13 months	Kunisaki *et al.* [2005]
Docetaxel 70 mg/m^2 day 1, Cisplatin 70 mg/m^2 day 1 q3w	ECF (12), non platinum 5FU combinations (20)	GAC (32)	16%	5 months		6 months	Polyzos *et al.* [2006]
Docetaxel 60 mg/m^2 day 1, Cisplatin 60 mg/m^2 day 1 q3w	5FU	GAC (43)	17%			5.8 months	Park *et al.* [2004]
Docetaxel 60 mg/m^2 day 1, 5FU 500 mg/m^2 days 1–5, Cisplatin 20 mg/m^2 days 1–5	Cisplatin + 5FU ± RT	SEC (20)	35%	4 months		8 months	Tanaka *et al.* [2007]
Docetaxel 60 mg/m^2 day 1, Oxaliplatin 130 mg/m^2 day 1 q3w	Cisplatin + 5FU	GAC (48)	23%	4.4 months		7.2 months	Zhong *et al.* [2008]

(Continued)

Table 2. (Continued)

Docetaxel schedule	Previous treatment	Study population (patient numbers)	ORR	TTP	PFS	OS	Reference
Docetaxel 75 mg/m^2 day 1, Oxaliplatin 80 mg/m^2 day 2 q3w	Cisplatin + 5FU ± Epirubicin	GAC, EGJAC (38)	10.5%	4 months		8.1 months	Barone *et al.* [2007]
Docetaxel 35 mg/m^2 days 1 + 8, Oxaliplatin 100 mg/m^2 day 1 q3w	5FU ± Cisplatin (all adjuvant)	GAC (34)	56%		5.3 months	13.8 months	Choi *et al.* [2012]
Docetaxel 30 mg/m^2 days 1 + 8, Capecitabine 825 mg/m^2 bid days 1–14 q3w	?	GAC (8)	12.5%	4.2 months		10.4 months	Lo *et al.* [2010]
Docetaxel 60 mg/m^2 day 1, Capecitabine 825 mg/m^2 bid days 1–14 q3w	Cisplatin + 5FU	SEC (30)	23%	3 months		8.3 months	Li *et al.* [2013]
Docetaxel 75 mg/m^2 day 1, Capecitabine 1000 mg/m^2 bid days 1–14 q3w	Cisplatin ± 5FU ± RT	SEC, EAC (8)	25%			6.2 months	Lorenzen *et al.* [2005]
Docetaxel 25 mg/m^2 days 1 + 8 + 15, Irinotecan 55 mg/m^2 days 1 + 8 + 15 q4w	Cisplatin ± 5FU ± RT	SEC (11), EAC (13)	12.5%		9 weeks	26 weeks	Lordick *et al.* [2003]
Docetaxel 35 mg/m^2 days 1 + 8, Irinotecan 50 mg/m^2 days 1 + 8 q3w	? (chemotherapy as part of radical treatment)	EAC, EGJAC (12), SEC (3)	20%		3.5 months	11.4 months	Burtness *et al.* [2009]
Docetaxel 65 mg/m^2 day 1, Irinotecan 160 mg/m^2 day 1 q3w	Cisplatin + 5FU	GAC (49)	20%	2.7 months		8.9 months	Sym *et al.* [2008]
Docetaxel 75 mg/m^2 day 1, Epirubicin 60 mg/m^2 day 1 q3w	Cisplatin + 5FU	GAC (50)	15.5%	2.4 months		5 months	Nguyen *et al.* [2006]
Docetaxel 50 mg/m^2 day 1, Epirubicin 50 mg/m^2 day 1 q3w	5FU ± Cisplatin	GAC (22)	0%		16 weeks	30 weeks	Yi *et al.* [2014]
Docetaxel 35 mg/m^2 days 1 + 8, Gemcitabine 1000 mg/m^2 days 1 + 8 q3w	5FU ± Cisplatin	SEC (33)	30%		6 months	9 months	Lee *et al.* [2014]

(Continued)

Table 2. (Continued)

Docetaxel schedule	Previous treatment	Study population (patient numbers)	ORR	TTP	PFS	OS	Reference
DCF or Docetaxel 75 mg/m^2 day 2, Capecitabine 1000 mg/m^2 bid days 2–15 q3w plus Trastuzumab 6 mg/kg day 1 q3w	?	GAC (22)	59%		6.8 months	16 months	Dai *et al.* [2012]
Docetaxel 30 mg/m^2 day 1 + 8, Cetuximab 250 mg/m^2 days 1 + 8 + 15 q3w	Docetaxel + 5FU ± Cisplatin	SEC (4), EAC, EGJAC, GAC (33)	6%		2.1 months	5.4 months	Tebbutt *et al.* [2013]

5FU, 5-fluorouracil; bid, twice daily; DCF, docetaxel, cisplatin, 5FU; EAC, esophageal adenocarcinoma; ECF, epirubicin, cisplatin, 5FU; EGJAC, esophagogastric junction adenocarcinoma; GAC, gastric adenocarcinoma; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; q2w, every 2 weeks; q3w, every 3 weeks; q4w, every 4 weeks; RT, radiotherapy; SEC, squamous esophageal cancer; TTP, time-to-progression.

in pretreated GAC. Park and colleagues [Park *et al.* 2004] treated 43 patients with GAC relapsing within 1 year of receiving 5FU with docetaxel and cisplatin, both at 60 mg/m^2 q3w. ORR was 17% and median OS 5.8 months and the authors concluded that this regimen was feasible and merited further study. The same regimen was used to treat 30 patients with relapsed, pretreated GAC in a Japanese study [Kunisaki *et al.* 2005]. A total of 20 of these patients had previously received single agent S-1, whereas 10 had received cisplatin and infusional 5FU, and it is not clear from the study report how many were initially treated with a curative intent. Results were encouraging with ORR 27%, median TTP 4.5 months and median OS 13 months. However, the encouraging OS results were driven primarily by platinum-naïve patients who exhibited a median OS of 20 months compared with 8 months for platinum-pretreated ones. A similar pattern was seen in a study enrolling 32 Greek patients with GAC of which 20 were platinum-naïve (previous treatment mostly with mitomycin–epirubicin–5FU or methotrexate–epirubicin–5FU) and 12 had previously received ECF [Polyzos *et al.* 2006]. In that study, ORR was 25% for platinum-naïve but 0% for platinum-pretreated patients. Median OS in the whole study population was 6 months, in line with most studies in European patients but, unfortunately survival by previous platinum exposure status was not provided in the report.

The combination of docetaxel and oxaliplatin has also been evaluated in GAC. Choi and colleagues reported the results of a prospective study of docetaxel 35 mg/m^2 on days 1 and 8 in addition to oxaliplatin 100 mg/m^2 on day 1 q3w in 34 Korean patients with relapsed GAC [Choi *et al.* 2012]. All had previously received chemotherapy in the adjuvant setting, 22 with cisplatin–5FU combinations and the rest with single agent fluoropyrimidine. ORR was 56%, median PFS 5.3 months and median OS 13.8 months, reflecting the fact that these patients were treated in essentially the first-line advanced setting. In accordance with this, docetaxel 60 mg/m^2 and oxaliplatin 130 mg/m^2 q3w showed more modest activity with ORR 23%, median TTP 4.4 months and median OS 7.2 months in 48 Chinese patients with more advanced disease and previous platinum and fluoropyrimidine chemotherapy [Zhong *et al.* 2008]. These results were replicated in a European population [Barone *et al.* 2007]. In that study, docetaxel 75 mg/m^2 and oxaliplatin 80 mg/m^2 q3w

Table 3. Randomized studies of docetaxel in pretreated esophagogastric cancer.

Study arms (patient numbers)	Previous treatment	Study population (patient numbers)	ORR	TTP	PFS	OS	Reference
Docetaxel 75 mg/m^2 day 1 q3w (84) *versus* BSC (84)	Platinum + 5FU	EAC (33), EGJAC (59), GAC (76)	7% *versus* NA	12.2 weeks *versus* NA		5.2 months *versus* 3.6 months (HR 0.67, $p = 0.01$)	Ford *et al.* [2014]
Docetaxel 60 mg/m^2 day 1 q3w or Irinotecan 150 mg/m^2 day 1 q2w (126) *versus* BSC (62)	Platinum + 5FU	GAC	9.5% *versus* 0%			5.3 months *versus* 3.8 months (HR 0.66, $p = 0.007$)	Kang *et al.* [2012]
Docetaxel 75 mg/m^2 day 1 (44) *versus* Irinotecan 300 mg/m^2 day 1 (44) *versus* PEP02 120 mg/m^2 day 1 (44) q3w	1 prior course – no details available	EGJAC (30) GAC (102)	16% *versus* 7% *versus* 14%		2.7 months *versus* 2.6 months *versus* 2.7 months	7.7 months *versus* 7.8 months *versus* 7.3 months	Roy *et al.* [2013]
Docetaxel 60mg/m^2 day 1 + Sunitinib 37.5 mg od days 1–21 q3w (56) *versus* Docetaxel 60 mg/m^2 day 1 q3w (49)	Platinum + 5FU	GAC	41% *versus* 14% ($p = 0.002$)	3.9 months *versus* 2.6 months (HR 0.77, $p = 0.21$)		8 months *versus* 6.6 months (HR 0.94, $p = 0.8$)	Yi *et al.* [2012]
Docetaxel 36 mg/m^2 days 1 + 8 + Oxaliplatin 80 mg days 1 + 8 q3w (25) *versus* Docetaxel 36 mg/m^2 days 1 + 8 q3w (27)	Cisplatin ± 5FU	GAC	20% *versus* 15%		4.9 months *versus* 2 months ($p = 0.007$)	8.1 months *versus* 11.6 months ($p = 0.65$)	Kim *et al.* [2012]

5FU, 5-fluorouracil; BSC, best supportive care; EAC, esophageal adenocarcinoma; EGJAC, esophagogastric junction adenocarcinoma; GAC, gastric adenocarcinoma; HR, hazard ratio; NA, not available; od, once daily; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; q2w, every 2 weeks; q3w, every 3 weeks; RT, radiotherapy; TTP, time-to-progression.

were administered to 38 patients with GAC and EGJAC, the majority of whom had previously received ECF, resulting in an ORR of 10.5% and a median OS of 8.1 months.

The activity of docetaxel capecitabine combinations in relapsed pretreated esophageal cancer has been evaluated in two phase II studies [Li *et al.* 2013; Lorenzen *et al.* 2005]. The study by Li and colleagues enrolled patients with SEC exclusively, whereas Lorenzen and colleagues enrolled 8 patients with either SEC or EAC and reported 25% ORR and 6.2 months median OS with a regimen of docetaxel 75 mg/m^2 and capecitabine 1000 mg/m^2 twice daily (bid) days 1–14 q3w. However, results by histological subtype were not provided in the report. A fractionated docetaxel regimen (30 mg/m^2 days 1 and 8) combined with capecitabine 825mg/m^2 bid days 1–14 q3w was evaluated in a mixed population of chemotherapy-naïve and pretreated GAC patients [Lo *et al.* 2010]. No details of prior treatments were provided for the 8 pretreated patients who showed an ORR of 12.5% and median OS of 10.4 months in this study.

Irinotecan has shown activity as a single agent in relapsed gastric cancer [Farhat, 2007]. The combination of docetaxel and irinotecan q3w was evaluated in 49 patients with GAC, of which 59% had received palliative chemotherapy and a further 59% adjuvant treatment (18% had received both), consisting of fluoropyrimidine and platinum combinations in the majority [Sym *et al.* 2008]. The ORR in the whole study population was 20% and median OS 8.9 months. However, excessive grade 3/4 toxicity, mainly febrile neutropenia (FN) necessitated a change in protocol after 10 patients were enrolled, reducing the dose of docetaxel from 65 to 50 mg/m^2 and that of irinotecan from 160 to 120 mg/m^2. Patients receiving the lower, tolerable dose had lower ORR (10% *versus* 60%) but not shorter median OS (8.8 *versus* 9.5 months). Utilizing fractionated weekly schedules for both docetaxel and irinotecan was associated with less toxicity and similar efficacy (ORR 12.5–20%, median PFS 2.1–3.5 months) in a further 2 studies enrolling patients with SEC and EAC [Burtness *et al.* 2009; Lordick *et al.* 2003].

Docetaxel–anthracycline combinations could be an option for relapsed EGAC if not used in the first line. Nguyen and colleagues enrolled 50 patients with GAC, all of whom had received previous platinum and fluoropyrimidine-based chemotherapy in a phase II study of docetaxel 75 mg/m^2 and epirubicin 60 mg/m^2 q3w [Nguyen *et al.* 2006]. It was found that 40% of patients experienced FN, including 1 treatment-related death and efficacy was underwhelming with an ORR of 15.5% and median OS of 5 months. Haematological toxicity remained troublesome, leading to early treatment discontinuation in 5 of 22 patients in a second study that reduced the dose of both drugs to 50 mg/m^2 [Yi *et al.* 2014]. Efficacy remained disappointing with no objective responses and a median survival of 30 weeks.

In the only published study of docetaxel-based second-line chemotherapy in docetaxel-pretreated patients, Tebbutt and colleagues treated 37 patients with EGAC or SEC with docetaxel 30 mg/m^2 on days 1 and 8 q3w and cetuximab 250 mg/m^2 weekly after an initial loading dose of 400 mg/m^2 [Tebbutt et al. 2013]. All enrolled patients had received weekly docetaxel plus either capecitabine or cisplatin–5FU in an earlier study by the same group [Tebbutt *et al.* 2010]. The ORR with docetaxel cetuximab was only 6%, implying that the addition of cetuximab cannot overcome docetaxel resistance in this setting.

Following the publication of the ToGA study, trastuzumab has been incorporated into first-line platinum–fluoropyrimidine regimens for HER2-overexpressing GAC [Bang *et al.* 2010]. Dai and colleagues reported on a study of docetaxel-based combination chemotherapy plus trastuzumab in 22 HER2-amplified or overexpressing GAC patients [Dai *et al.* 2012]. All patients had previously received chemotherapy and appear to have been trastuzumab-naïve, although details were not given. The addition of trastuzumab to docetaxel-based chemotherapy showed impressive efficacy in this small study with 59% ORR, median PFS 6.8 and median OS 16 months. Therefore, it appears that docetaxel–trastuzumab combinations warrant further investigation in larger studies. It is not yet known whether continuation of trastuzumab with a different chemotherapy backbone beyond progression after first-line chemotherapy, a strategy with proven benefit in metastatic breast cancer [von Minckwitz *et al.* 2009], is beneficial in EGAC.

In summary, promising activity has been shown by docetaxel–platinum combinations but the benefit may be limited to patients not previously exposed to platinum analogues. Docetaxel–irinotecan combinations appear active but are associated with

significant toxicity, whereas docetaxel–epirubicin combinations show poor activity with excessive toxicity. The very limited data available preclude us from drawing any conclusions regarding the activity of docetaxel–capecitabine doublets in this population.

Randomized docetaxel studies in chemorefractory patients

Two studies, both published since 2012, have, for the first time, provided high quality evidence that docetaxel improves patient outcomes in the chemorefractory setting [Ford *et al.* 2014; Kang *et al.* 2012] (Table 3). Kang and colleagues enrolled 188 Korean patients who had received 1 or 2 prior courses of chemotherapy, including a fluoropyrimidine and a platinum analogue, and randomized them in a 2:1 ratio to 'salvage' chemotherapy or BSC. Choice of chemotherapeutic agent, either docetaxel 60 mg/m^2 q3w or irinotecan 150 mg/m^2 every 2 weeks (q2w), was left to the investigators resulting in 66 patients receiving docetaxel and 60 irinotecan. Approximately two-thirds of the patients had a chemotherapy-free interval <3 months. In the intent-to-treat (ITT) population, ORR to salvage chemotherapy was 9.5% compared with 0% for BSC and chemotherapy significantly prolonged OS (median 5.3 *versus* 3.8 months, HR 0.66, $p = 0.007$). ORR and median OS for docetaxel-treated patients were 11% and 5.2 months respectively, and were similar to the other active treatment arm (irinotecan ORR 8%, median OS 6.5 months).

The study by Ford and colleagues [Ford *et al.* 2014] provides further methodologically robust confirmation that docetaxel improves survival in relapsed EGAC. In this study, 168 patients, predominantly with GAC and EGJAC, but also EAC from 30 UK sites were randomized to docetaxel 75 mg/m^2 q3w or BSC in a 1:1 ratio (Table 3). Patients with both locally advanced and metastatic disease were allowed to participate provided they had received first-line treatment with a platinum–fluoropyrimidine combination and had relapsed or progressed within 6 months of that. Docetaxel significantly prolonged OS (median 5.2 *versus* 3.6 months, HR 0.67, $p = 0.01$). Patients treated with docetaxel had an ORR of 7% and median TTP of 12.2 weeks; these results were not reported for the BSC arm.

Although docetaxel and irinotecan efficacy appeared similar in the study by Kang and colleagues [Kang *et al.* 2012], this was not directly demonstrated. However, supporting evidence for similar outcomes is provided by a phase II study that randomized previously treated patients with EGJAC and GAC to either docetaxel 75 mg/m^2, irinotecan 300 mg/m^2 or a novel liposomal irinotecan formulation, PEP02, 120 mg/m^2 q3w [Roy *et al.* 2013]. It should be noted that, beyond stating that all patients had previously received chemotherapy, prior treatment details were not provided and that the study was not powered to directly compare outcomes among the three arms. Nevertheless, median PFS and OS were almost identical in the 3 arms, ranging from 2.6 to 2.7 and from 7.3 to 7.8 months, respectively (Table 3). ORR appeared similar for docetaxel (16%) and PEP02 (14%), but was numerically lower for irinotecan (7%).

Despite promising signs from single arm studies, whether docetaxel efficacy in the chemorefractory setting can be improved by the addition of a second agent is unclear at present. In a study only available in abstract form at present, Kim and colleagues randomized 52 GAC patients with previous exposure to cisplatin-based chemotherapy to fractionated docetaxel 36 mg/m^2 days 1 and 8 with or without oxaliplatin 80 mg/m^2 again on days 1 and 8 q3w [Kim et al. 2012]. Although PFS was significantly longer with combination treatment (median 4.9 *versus* 2 months, $p = 0.007$), OS was not prolonged and was actually shorter in the doublet arm (median 8.1 *versus* 11.6 months, $p = 0.65$). Similarly, the addition of continuous oral sunitinib to docetaxel 60 mg/m^2 q3w did not significantly improve PFS or OS compared with single agent docetaxel in a randomized study enrolling 107 platinum and fluoropyrimide-pretreated patients with GAC [Yi *et al.* 2012]. Although ORR was significantly higher with the combination (41% *versus* 14%, $p = 0.002$), this was accompanied by increased grade 3/4 toxicity rates (46% *versus* 31%, $p = 0.11$).

Docetaxel in patients previously exposed to platinum, fluoropyrimidines and irinotecan

Irinotecan has been frequently used in chemorefractory EGAC, although RCT evidence supporting improved outcomes in pretreated patients did not emerge until the publication of the study by Kang and colleagues [Kang *et al.* 2012] and a smaller study by Thuss-Patience and colleagues [Thuss-Patience *et al.* 2011]. No prospective clinical trial data exist at present with regards to the

role of docetaxel in even more heavily pretreated patients who have received a platinum analogue, a fluoropyrimidine and irinotecan previously. In a retrospective series, 33 patients with GAC, previously treated with FOLFOX and FOLFIRI, received docetaxel 75 mg/m^2 [Lee *et al.* 2013]; ORR was 15%, median TTP 2.1 months and median OS 4.7 months. Similar results were reported in a second series that included 35 patients treated with either single agent docetaxel or docetaxel cisplatin combinations in the third-line setting [Lee *et al.* 2012]. In that series, ORR was 14%, median PFS 1.9 months and median OS 3.6 months. Given the modest activity shown in these series, prospective investigation is needed to clarify whether third-line treatment is superior to BSC in GAC.

Toxicity of docetaxel treatment in refractory EGAC

Patients with relapsed EGAC frequently present with significant tumour-related morbidity [Wesolowski *et al.* 2009], making it difficult to differentiate between treatment-related toxicities and disease-related morbidity in single arm studies. Therefore, the best estimates for docetaxel toxicity in this setting come from the two randomized studies by Ford and colleagues [Ford *et al.* 2014] and Kang and colleagues [Kang *et al.* 2012]. In the former study, docetaxel was associated with more grade 4 toxicity (21%) than BSC (4%), particularly neutropenia, infections and FN. However, and despite the fact that growth factor support was not routinely administered, the rate of grade 3/4 FN in docetaxel-treated patients was relatively low at 7%. Exemplifying the morbidity of advanced EGAC, constitutional and gastrointestinal symptoms were extremely common in both arms and, actually, more haemorrhage and pain were noted in the BSC arm. Overall, docetaxel treatment resulted in better patient-reported symptom scores for pain, nausea, vomiting and constipation than BSC, providing evidence that the benefits from tumour control outweigh the treatment toxicities. In an analysis limited to the 24-week treatment period, the authors reported that docetaxel provided an extra 2.8 quality-adjusted life weeks compared with BSC [Ford *et al.* 2014]. A similar picture emerges when patients who received docetaxel are compared with the BSC arm in the study by Kang and colleagues (Kang *et al.* 2012). There were more haematological toxicities recorded in the docetaxel arm, but similar levels of fatigue and actually less anorexia, nausea and diarrhoea. Therefore, it appears that docetaxel treatment prolongs survival and at the same time also results in relief of common gastrointestinal symptoms of advanced EGAC. However, this does not necessarily apply to docetaxel-based combination treatments since, as mentioned before, many of the single arm studies had to be modified due to excessive toxicity.

Predictive factors for docetaxel benefit in advanced EGAC

Understanding the mechanisms of taxane resistance and developing predictive biomarkers are subjects of intense research interest [Ahmed *et al.* 2007; Cui *et al.* 2013; Karki *et al.* 2013; Murray *et al.* 2012; Swanton *et al.* 2009; Vergara *et al.* 2012]. Despite this, no biomarkers have reached the level of validation that would allow clinical use in treatment decision making. In many cases, the identified biomarkers appear to be simply prognostic and not predictive as in the case of SPARC expression and outcomes of first-line docetaxel treatment [Jeung *et al.* 2011]. Another study identified single nucleotide polymorphisms (SNPs) in *GSTP1, XRCC1* and *5-10-MTHFR* that were associated with OS in advanced GAC patients treated with first-line DCF [Ji *et al.* 2013]. As all patients received DCF, it is impossible to conclude whether these SNPs are prognostic or predictive. Moreover, it is likely that the *XRCC1* SNP exerts its effect through modulation of cisplatin activity and the *5-10-MTHFR* one through 5FU, and therefore these biomarkers are not specific to docetaxel.

The randomized studies by Ford and colleagues [Ford *et al.* 2014] and Kang and colleagues [Kang *et al.* 2012] provide the opportunity to identify biomarkers and differentiate between prognostic and predictive ones. Performance status (PS) and metastatic *versus* locally advanced disease predicted shorter OS in the study by Ford and colleagues [Ford *et al.* 2014]. Similarly, PS, treatment-free interval and number of previous chemotherapy courses were associated with shorter OS in the study by Kang and colleagues [Kang *et al.* 2012]. Nevertheless, none of these factors were predictive of a differential docetaxel effect as shown by similar HRs for docetaxel *versus* BSC in stratified comparisons. Despite this limitation, these factors could be used to select patients with very poor prognosis and a correspondingly very small absolute benefit from docetaxel

treatment; such patients could be offered BSC or experimental agents.

The place of docetaxel in the treatment of advanced EGAC

Following the publication of the study by Ford and colleagues [Ford *et al.* 2014], there is now level I evidence for docetaxel benefit in pretreated EGAC, with further support provided by the study by Kang and colleagues [Kang *et al.* 2012]. Additionally, both irinotecan and ramucirumab, a novel vascular endothelial growth factor receptor 2 (VEGFR-2) targeting monoclonal antibody, improve OS in pretreated EGAC. Evidence for irinotecan benefit is provided by the Kang and colleagues [Kang *et al.* 2012] study as well as a small German study that randomized 40 patients with EGJAC and GAC to irinotecan 250–350 mg/m^2 q3w or BSC. Despite the small patient numbers, irinotecan significantly improved OS (median 4 *versus* 2.4 months, HR 0.48, $p = 0.03$) [Thuss-Patience *et al.* 2011]. Similarly, in a large phase III study, 355 patients with pretreated EGJAC and GAC were randomized in a 2:1 ratio to ramucirumab 8 mg/kg q2w or placebo, and showed that ramucirumab significantly improved OS (median 5.2 *versus* 3.8 months, HR 0.78, $p = 0.047$) [Fuchs *et al.* 2014]. Very recently, the RAINBOW study showed for the first time that the addition of a targeted agent to chemotherapy further improves outcomes [Wilke *et al.* 2014]. In RAINBOW, 665 patients with pretreated EGJAC and GAC were randomized to paclitaxel 80 mg/m^2 on days 1, 8 and 15 every 4 weeks (q4w) and ramucirumab 8 mg/kg q2w or placebo. OS was significantly prolonged by the combination (median 9.6 *versus* 7.4 months, HR 0.81, $p = 0.017$), as was PFS (median 4.4 *versus* 2.9 months, HR 0.64, $p < 0.0001$) and ORR (28% *versus* 16%, $p = 0.0001$).

In the studies referenced above, docetaxel, irinotecan and ramucirumab were all associated with a remarkably consistent survival benefit of approximately 6-weeks over BSC. In the 'Randomized docetaxel studies in chemorefractory patients' section we presented evidence suggesting that irinotecan and docetaxel have similar efficacy in pretreated EGAC. Taxane and irinotecan treatment in this setting was directly compared in a Japanese study that randomized 223 patients with GAC to paclitaxel 80 mg/m^2 on days 1, 8 and 15 q4w or irinotecan 150 mg/m^2 q2w [Hironaka *et al.* 2013]. The study was designed to show superiority of irinotecan over paclitaxel. However, no significant difference was seen in OS (median 9.5 *versus* 8.4 months, HR 1.13, $p = 0.38$), PFS (median 3.6 *versus* 2.3 months, HR 1.14, $p = 0.33$) or ORR (21% *versus* 14%, $p = 0.24$), with results numerically favouring the paclitaxel arm. Additionally, paclitaxel 100 mg/m^2 weekly was found to have similar efficacy to docetaxel 70 mg/m^2 q3w in a retrospective study of 110 relapsed esophageal cancers, almost all with squamous histology (median PFS 2.3 *versus* 2.8 months; median OS 6.1 *versus* 6.9 months, respectively) [Shirakawa et al 2013]. Further head-to-head studies of these older chemotherapeutic drugs are unlikely to happen and, therefore, the choice among docetaxel, paclitaxel and irinotecan will mostly depend on comorbidities, toxicities from previous treatments and physician preference. Given the results of the RAINBOW study, paclitaxel and ramucirumab combination is likely become the preferred option in the United States and parts of Europe (although cost considerations may limit its adoption in some jurisdictions)

Conclusion

Docetaxel has demonstrated activity in both early and advanced EGAC, and as first-line or second-line treatment. In particular, level I evidence shows that docetaxel improves survival in advanced EGAC patients that have previously been treated with a platinum analogue and a fluoropyrimidine. Moreover, treatment with docetaxel is associated with relief from cancer-related constitutional and gastrointestinal symptoms with manageable, predominantly haematological, toxicity. Irinotecan, paclitaxel and ramucirumab all show a similar level of activity in the second-line setting. However, in view of the short survival time for the majority of these patients, further research is necessary to identify, on the one hand, combinations with targeted agents that will further improve outcomes and, on the other, biomarkers that will allow selection of those patients most likely to benefit.

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Conflict of interest statement

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