

Quality of life with biweekly docetaxel and capecitabine in advanced gastro-oesophageal cancer

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Abstract

Purpose This study aimed to evaluate the feasibility and tolerability of biweekly docetaxel with capecitabine as first-line treatment in advanced gastro-oesophageal cancer.

Methods Fifty-three patients at median age of 61 years with advanced gastric cancer were included in this prospective, non-randomized, multicentre phase II trial to receive intravenous docetaxel 50 mg/m² on days 1 and 15, and oral capecitabine 1250 mg/m² every 12 h, on days 1–7 and 15–21 of each 28-day cycle. QOL was assessed using EORTC QLQ-C30, together with the gastric module (QLQ-STO 22).

Results Forty-six patients were evaluable for QOL analyses. No deterioration in global health status was found. Social functioning scores improved, and eating difficulties and pain were alleviated during treatment. The most common grade 3 or 4 toxicity was neutropenia (47%), whereas neutropenic fever was uncommon (6%). The clinical benefit rate was 60%, including complete and partial responses as well as stabilized disease. Median overall survival was 8.8 months (95%

CI 5.8–11.9 months), and median time to progression was 6.2 months (95% CI 4.9–7.5 months).

Conclusions Biweekly docetaxel with capecitabine is a feasible treatment in AGC, delivered on an outpatient basis, with no need for central venous access device. No deterioration of global health status was reported. In addition, pain and eating difficulties were alleviated during study treatment. This trial is registered at [ClinicalTrials.gov](https://clinicaltrials.gov), number NCT00669370.

Keywords Quality of life · Advanced gastro-oesophageal cancer · Chemotherapy · Palliative treatment

Introduction

The incidence of distal gastric cancer is decreasing, whereas cancers of the distal oesophagus and gastro-oesophageal junction tend to increase in the Western world [1]. Worldwide, these cancers cause substantial morbidity and mortality. Nearly one million new cases and more than 700,000 deaths due to gastric cancer were estimated to have occurred in 2012, setting gastric cancer the fifth most common cancer and the third most common cause of cancer death [2]. The prognosis of advanced gastro-oesophageal cancer (AGC) remains poor [1, 2]. A substantial proportion of patients presents with or ends up having metastatic disease after initial treatment [3, 4].

Systemic chemotherapy is shown to improve disease outcome in AGC, as compared to best supportive care, with median survival rates reaching 6–9 months [5–7]. During the past decade, several new-generation cytotoxic agents, including capecitabine, irinotecan, oxaliplatin and docetaxel, have been investigated in the treatment of metastatic gastric cancer [7–10]. Two previous large phase III trials demonstrated an oral fluoropyrimidine capecitabine not to be inferior to 5-FU in the setting of a platinum-containing doublet or triplet for

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AGC [8, 9]. Adding docetaxel into the combination of cisplatin and fluorouracil (DCF) was studied in a randomized phase III trial in first-line therapy for AGC. The final results showed improved survival, response rate, and health-related QOL, albeit increased toxicity with DCF [10]. Further, in a phase III open-label, randomized controlled trial in HER2-positive AGC, trastuzumab in combination with chemotherapy significantly improved median overall survival as compared to chemotherapy alone [11]. Recently, VEGFR-2 antagonist ramucirumab was found to improve survival as monotherapy or in combination with paclitaxel in AGC after first-line treatment [12, 13]. However, so far, no survival benefit has been reported in the first-line setting with other novel targeted agents in AGC, in addition of trastuzumab.

In advanced cancer, the primary treatment goals are to prolong survival, relieve symptoms and sustain or improve the quality of life. Thereby, chemotherapy-related toxicity is an important issue when determining the true value of treatment. Patients with AGC are generally elderly and exhibit poor general performance status, which emphasizes the need for effective treatment options and improved control of side effects. On the basis of these considerations, we conducted a phase II trial to determine the feasibility and tolerability of biweekly docetaxel in combination with capecitabine as first-line treatment of patients with AGC.

Patients and methods

Study design and patient population

This prospective, non-randomized, multicentre phase II trial included patients over 18 years of age with histologically confirmed, locally advanced (inoperable) or metastatic adenocarcinoma of the stomach or gastro-oesophageal junction. Disease lesions could be either evaluable or measurable. No previous chemotherapy for advanced or metastatic disease was allowed, and a time interval of ≥ 6 months after adjuvant chemotherapy was imperative. Patients were required to have adequate haematological (neutrophils $>1.5 \times 10^9/l$, haemoglobin ≥ 100 g/l after transfusion when needed and platelets $\geq 100 \times 10^9/l$), renal (serum creatinine $\leq 1.25 \times$ upper normal limit) and liver function (total serum bilirubin $\leq 1.25 \times$ upper normal limit or alanine aminotransferase $\leq 3 \times$ upper normal limit, alkaline phosphatase $\leq 2.5 \times$ upper normal limit, unless bone metastases; in case of liver metastasis total serum bilirubin $\leq 1.5 \times$ upper normal limit and alanine aminotransferase $\leq 5 \times$ upper normal limit). Prophylactic use of granulocyte colony-stimulating factor (G-CSF) was not allowed.

Exclusion criteria included pregnancy or breast feeding, metastatic disease to the central nervous system, unresolved bowel obstruction or dysmotility, chronic diarrhoea, clinically significant malabsorption syndrome, inability to swallow

tablets, known dihydropyrimidine dehydrogenase deficiency, peripheral neuropathy \geq grade 2, concurrent severe and/or uncontrolled co-morbid medical condition such as uncontrolled infection, hypertension, ischemic heart disease, myocardial infarction within previous 6 months or congestive heart disease. Patients with previous serious hypersensitive reactions, history of allergy to drugs containing the excipient TWEEN 80® or 5-fluorouracil, major surgery within 4 weeks prior to study treatment or passage disorder were also excluded from the participation in the study.

Study treatment

Patients received intravenous docetaxel 50 mg/m^2 on days 1 and 15 and oral capecitabine 1250 mg/m^2 every 12 h, starting on days 1 and 15 in the evening and continuing on days 2–7 and 16–21. One cycle consisted of 28 days. Premedication with 7.5 mg of oral dexamethasone or methylprednisolone 40 mg was given the evening prior to docetaxel infusion and continuing thereafter every 12 h three times. Dose reduction was based on the most severe grade of toxicity in the previous cycle. A planned cycle could be delayed up to 21 days due to toxicity. If a patient had not recovered from toxicities within 21 days, he/she was withdrawn from the study. In case either

Table 1 Patient characteristics ($n = 53$)

Median age (range) (years)	61 (28–79)
Sex, n (%)	
Male	36 (68)
Female	17 (32)
ECOG performance status, n (%)	
0	10 (19)
1	39 (74)
2	4 (7)
Location of primary tumour, n (%)	
Oesophagogastric junction	21 (40)
Gastric	32 (60)
Resection of primary tumour, n (%)	
Yes	19 (36)
No	34 (64)
Previous adjuvant chemotherapy, n (%)	10 (19)
Previous radiotherapy, n (%)	8 (15)
Organ involvement, n (%)	
Stomach	34 (64%)
Lymph nodes	25 (47%)
Liver	12 (33%)
Peritoneum	11 (21%)
Number of disease sites, n (%)	
1	20 (38)
2	26 (49)
≥ 3	7 (13)

of the test docetaxel or capecitabine was discontinued due to an adverse event, the patient could continue in the study taking only one test drug.

Efficacy and safety assessments

Before study inclusion, patients underwent complete physical examination, blood analysis (haematology and biochemistry), electrocardiogram and computerized tomography (CT) scan of the abdomen and pelvis as well as CT of the thorax or chest x-ray. Blood samples were taken for haematology tests prior to each treatment on days 1 and 15 of each cycle. Biochemistry tests were performed before the start of each cycle. During treatment, imaging of target and non-target lesions was repeated every three cycles (every 12 weeks) or as clinically indicated. Tumour response was classified according to RECIST [14]. Toxicity was evaluated before every cycle using National Cancer Institute-Common Terminology Criteria for Adverse Events [15].

Quality of life assessments

Quality of life (QOL) was assessed using European Organization for Research and Treatment of Cancer Quality-of-Life Questionnaire (EORTC QLQ-C30) [16], together with the gastric module (QLQ-STO 22) [17]. QLQ assessment was performed at baseline, on day 1 of the second and subsequent

cycles (prior to the infusion), at the end-of-study visit, during follow-up until progression or the start of second-line treatment or death. Prerequisites for inclusion in the analyses of (a change in) physical functioning score consisted of at least one given treatment cycle as well as QLQ-questionnaire filled at baseline and after the first treatment cycle. The physical functioning score was measured using the EORTC QLQ-C30 and QLQ-STO 22 [16, 17].

Statistical analysis

The primary end point of the study was physical functioning score, measured by the EORTC QLQ-C30 and QLQ-STO 22 instruments, comparing the scores received at baseline with those obtained after one treatment cycle, using a paired *t* test. Secondary end points were time to progression (TTP), overall response rate (ORR) and overall survival (OS).

Summary measurements are presented as mean and standard deviation (SD) or as median with 25th–75th percentile, unless otherwise stated. The change from baseline for continuous variables was analysed by paired samples *t* test. The Kaplan-Meier curve was created to show overall survival from recruitment to the end of follow-up (i.e. death or end of the study). All analyses were performed using SPSS for Windows (IBM Corp. Released 2011. IBM SPSS Statistics for Windows, version 20.0. Armonk, NY: IBM Corp.)

Table 2 The main results of QoL-C30 and STO-22 questionnaires

Variable	Baseline <i>n</i> = 46	Cycle 1 <i>n</i> = 45	Cycle 2 <i>n</i> = 37	Cycle 3 <i>n</i> = 30	Cycle 4 <i>n</i> = 27	Cycle 5 <i>n</i> = 20
Global health status	62 (SD19)	64 (SD19) <i>p</i> = 0.002	67 (SD18) <i>p</i> = 0.018	66 (SD17)	62 (SD16)	62 (SD16)
Physical functioning	77 (SD18)	76 (SD17)	78 (SD17)	77 (SD16)	77 (SD17)	77 (SD18) <i>p</i> = 0.012
Social functioning	83 (SD20)	82 (SD19)	84 (SD22)	87 (SD18)	91 (SD15) <i>p</i> = 0.005	87 (SD16)
Emotional functioning	76 (SD20)	84 (SD17) <i>p</i> = 0.004	86 (SD14) <i>p</i> = 0.011	87 (SD12) <i>p</i> = 0.004	85 (SD20) <i>p</i> = 0.025	84 (SD17)
Cognitive functioning	87 (SD14)	89 (SD14)	90 (SD13)	86 (SD16)	88 (SD14)	89 (SD17)
Role functioning	68 (SD31)	74 (SD24)	79 (SD25)	80 (SD23)	80 (SD16)	77 (SD29)
Fatigue	33 (SD19)	32 (SD17)	31 (SD20)	30 (SD20)	30 (SD18)	28 (SD20)
Pain	26 (SD16)	20 (SD15) <i>p</i> = 0.01	15 (SD11) <i>p</i> < 0.001	14 (SD12) <i>p</i> = 0.001	13 (SD14) <i>p</i> = 0.001	1 (SD12) <i>p</i> = 0.002
Eating restrictions	29 (SD23)	22 (SD20) <i>p</i> = 0.001	15 (SD17) <i>p</i> = 0.005	19 (SD18)	16 (SD19)	15 (SD12)
Dysphagia	31 (SD31)	26 (SD24)	21 (SD25)	20 (SD23)	18 (SD16)	22 (SD29)
Taste	16 (SD25)	27 (SD28) <i>p</i> = 0.004	37 (SD28) <i>p</i> < 0.001	36 (SD33) <i>p</i> = 0.007	30 (SD21) <i>p</i> = 0.003	38 (SD25) <i>p</i> = 0.030
Anxiety	46 (SD23)	38 (SD21) <i>p</i> = 0.001	34 (SD19) <i>p</i> = 0.006	33 (SD31) <i>p</i> = 0.001	31 (SD21) <i>p</i> = 0.002	32 (SD18) <i>p</i> = 0.011

The values are presented as mean with standard deviation (SD). The scores of each cycle as compared to the baseline score

Results

Patients and treatment

This prospective phase II trial was conducted at four university hospitals and one central hospital in Finland. A total of 53 patients were registered between June 2006 and December 2009. One patient was withdrawn from the study after the first cycle due to detected HER2-positivity, necessitating the start of trastuzumab treatment. Altogether, 46 patients were eligible for the QOL analyses. The patient characteristics are summarized in Table 1.

The total number of chemotherapy cycles administered was 220. The median number of treatment cycles per patient was 4 (range, 0.5–16), and the median time on study treatment was 4.8 months (range, 0.1–17.6 months). The main reasons for treatment discontinuation were progressive disease or deteriorating general condition ($n = 31$, 58%). Altogether, 26 patients (49%) received second-line chemotherapy.

Effect of treatment on quality of life

The number of patients with assessable QOL questionnaires at baseline was 46 (45 for global health status and STO 22 questionnaires), after the first and subsequent four cycles, the number of patients was 45, 37, 30, 27 and 20, respectively. Detailed results QOL analyses are shown in Table 2. Pain and eating restrictions were common at baseline (Fig. 1a). During treatment, clinically relevant alleviation was detected both in pain and in eating restrictions. No deterioration in global health status or in social or physical functioning occurred (Fig. 1a–c).

Clinical benefit

One of the 53 patients (2%) achieved complete response (CR), and 8 patients (15%) had partial response (PR). Of the patients, 23 (43%) showed stable disease (SD) and 5 (9%) had progressive disease (PD). The clinical benefit rate was 60%. The response was not evaluable among 18 patients (30%), due to early discontinuation of the study treatment. Median time to progression was 6.2 months (95% CI 4.9–7.5 months) and median overall survival 8.8 months (95% CI 5.8–11.9 months) (Fig. 2a, b).

Safety

During study treatment, 25 (47%) patients were hospitalized. Fifty percent of the hospitalizations were caused by a treatment-related adverse event. The most common grade 3 or 4 toxicity was neutropenia, detected in 25 patients (47%). However, only three patients (6%) experienced neutropenic fever. One patient had a

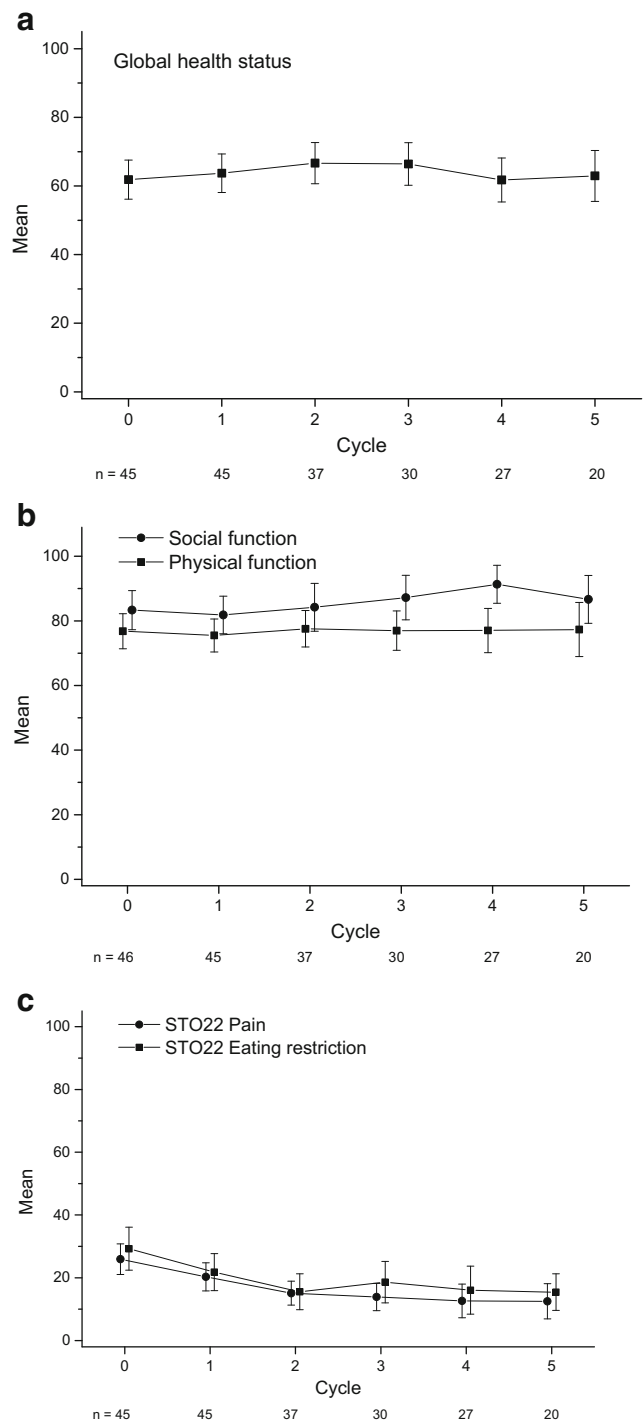
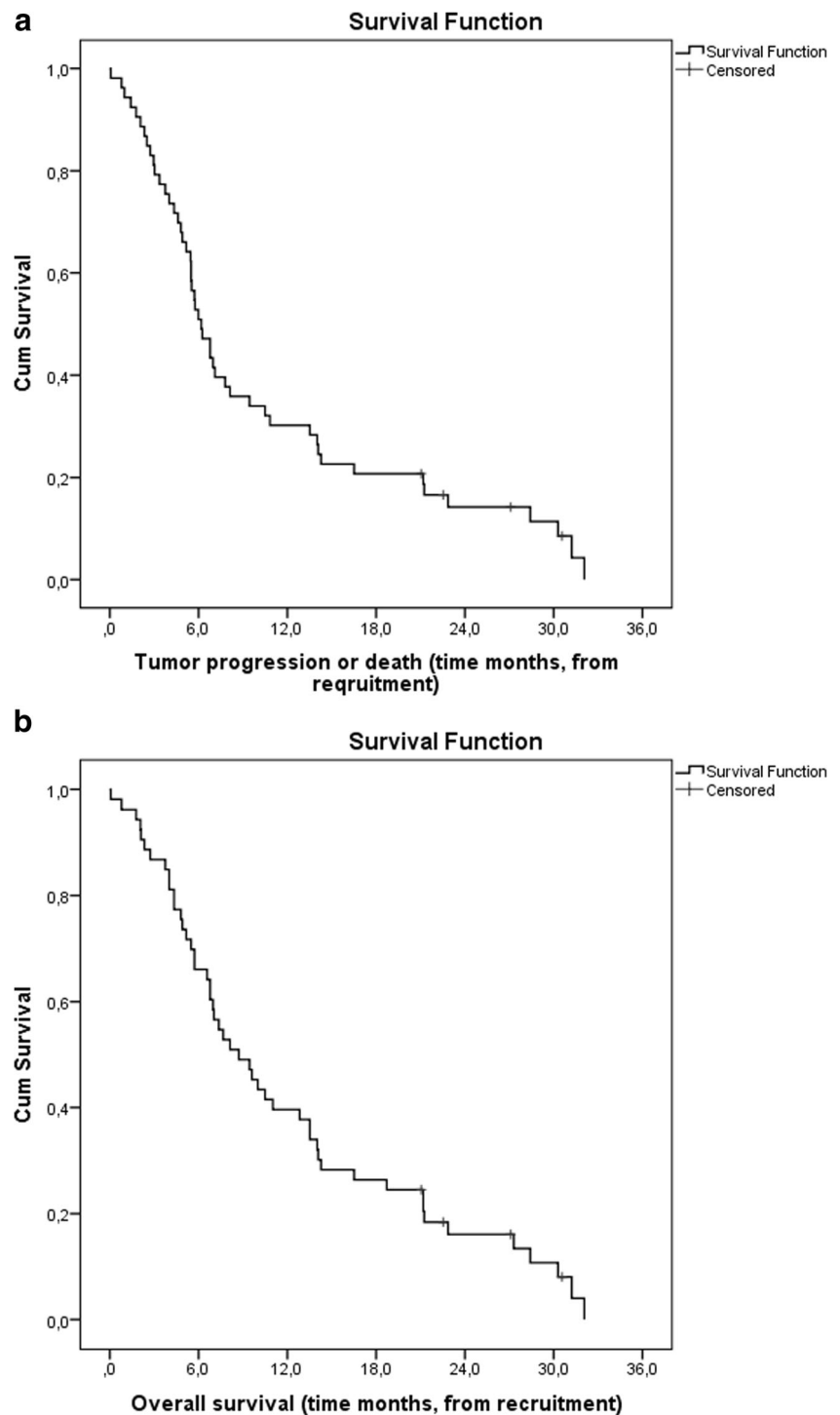


Fig. 1 Effect of treatment on quality of life: **a** global health status, **b** social and physical function, and **c** pain and eating restrictions presented as mean values per cycle

grade 3 allergic reaction during docetaxel infusion, precluding further treatment. There were no direct treatment-related deaths. One sudden death occurred during the first treatment cycle. According to the autopsy report, the cause of death was metastatic gastric cancer and no evidence of cardiac-related death could be detected. The common adverse events are listed in Table 3.

Fig. 2 **a** Median time to progression. **b** Median overall survival



Discussion

This prospective phase II trial with a combination of biweekly docetaxel and capecitabine in AGC showed no deterioration of global health status or either physical or social functioning. Importantly, the patients' quality of life was not compromised during treatment. Moreover, disease-associated symptoms, including eating restrictions and dysphagia, as well as pain and

anxiety, were alleviated during study treatment. The regimen was also conveniently delivered on an outpatient setting without a need for central venous access device.

Docetaxel in various combinations has previously been studied in the treatment in AGC, also including QOL assessments [18–21]. A recent prostate cancer trial reported better time to treatment failure and fewer serious adverse events with two weekly than with three weekly dosing of docetaxel [22].

Table 3 Adverse events, according to grade

	Grades 1 and 2 <i>n</i> (%)	Grades 3 and 4 <i>n</i> (%)
Non-haematological toxicity		
Asthenia	26 (49)	11 (21)
Alopecia	42 (79)	0 (0)
Anorexia	31 (59)	6 (11)
Nausea	31 (59)	4 (8)
Vomiting	12 (23)	2 (4)
Diarrhoea	20 (38)	3 (6)
Hand-foot syndrome	24 (45)	0 (0)
Nail changes	29 (55)	0 (0)
Paraesthesia	18 (34)	0 (0)
Fluid retention	14 (26)	0 (0)
Cardiac arrhythmia	8 (15)	1 (2)
Non-neutropenic fever	13 (24)	10 (19)
Haematological toxicity		
Anaemia	28 (72)	1 (2)
Leukopenia	18 (34)	8 (15)
Neutropenia	11 (21)	25 (47)
Thrombocytopenia	4 (8)	0 (0)
Neutropenic fever	0 (0)	3 (6)

In AGC, docetaxel combined to cisplatin and fluorouracil resulted in better symptom palliation and improved QOL, as compared to treatment with epirubicin, cisplatin and fluorouracil. Unfortunately, treatment toxicity data for this combination were not readily provided [19]. Previous trials have generally demonstrated improved QOL accompanied with improved efficacy in AGC, despite increased toxicity with docetaxel triplet combinations [10, 18, 19, 21], i.e. treatment efficacy rather than toxicity tends to affect QOL [23]. Importantly, in the current study, the patients' QOL was not compromised during treatment. Eating difficulties were alleviated during chemotherapy but started deteriorating along with disease progression. Similarly, after commencing therapy, pain was experienced to relieve but intensify again as cancer progressed. Physical functioning remained stable during chemotherapy, while social functioning improved, even despite disease progression. The global health status was maintained or slightly improved during therapy.

Gubanski and colleagues investigated the effect of sequential treatment on QOL. Patients were randomized to start treatment with either docetaxel or irinotecan combined to fluorouracil and leucovorin. After four cycles, the treatment was switched. Chemotherapy was not found to affect the average QOL scores. Instead, patients with a radiological response were able to sustain better QOL as compared to patients with no radiological response [24]. A patient's perception of expected treatment efficacy might also influence on QOL scores: a substantial

proportion of patients may not comprehend their disease unlikely to be curable [25]. Thus, they may be ready to tolerate even serious side effects and yet experience QOL to be maintained.

The results of this study showed the clinical benefit rate to be 60%, including complete (CR) and partial (PR) responses and stabilized disease (SD), and median overall survival of 8.8 months. These findings are parallel to a previous trial of weekly docetaxel together with capecitabine on days 1–14 of a 21-day cycle, showing a comparable response rate of 29%, stable disease of 44% and overall survival reaching 10.7 months [26]. Another study investigating dose-dependent efficacy of docetaxel and capecitabine resulted in improved overall response rates with full dosing of these agents. However, two patients in each cohort experienced grade 3–4 cardiac arrhythmia, one patient pulmonary oedema, and three patients grade 3–4 thrombosis/pulmonary embolism, one of them leading to death [27]. In the current study, no death was directly associated to study treatment. One patient died after the very first infusion of chemotherapy due to rapidly progressing cancer, without any signs of cardiac complications in the autopsy. However, ventricular fibrillation cannot entirely be ruled out, despite of a negative autopsy report. In the current study, only one patient experienced grade 3–4 cardiac arrhythmia.

Our study shows a moderate incidence of grade 3–4 neutropenia, resulting only rarely in neutropenic fever. Nevertheless, infection was the main reason for treatment-related hospitalization. These results are comparable with earlier studies, reporting even higher rates of grade 3–4 neutropenia, in up to 23–80% of patients, febrile neutropenia among 2–12% and grade 3–4 non-neutropenic fever among 2–41% of patients, while hospitalization data are not readily available [19, 26, 27]. The incidence of mild palmo-plantar dysesthesia or hand-foot syndrome (HFS) was previously reported to be 9–42% and that of severe HFS 3–20% [19, 26, 27]. Even though the incidence of HFS in the current study was 45%, no grade 3–4 symptoms were detected. Likewise, mild diarrhoea was frequent but severe diarrhoea a rare event. On the whole, haematologic and non-haematologic toxicities were considered tolerable.

In conclusion, no treatment combination has been proven superior as compared to others in AGC in the palliative setting. Biweekly docetaxel, together with capecitabine is a feasible, outpatient-based, well-tolerated treatment that enables sustaining QOL and alleviating disease-associated symptoms.

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Compliance with ethical standards

Ethical approval This study was conducted in accordance with the ethical standards of the institutional and/or national research committee

and with the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards. The protocol was approved by the Ethics Committee of the Hospital District of Southwest Finland and by Finnish Medicines Agency (Fimea). The study was registered in www.clinicaltrials.gov (NCT00669370).

Informed consent All patients provided written informed consent before the study entry.

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