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Docetaxel and irinotecan as second-line therapy for advanced oesophagogastric cancer

Eliza Hawkes [a], *Alicia F.C. Okines* [a], *Demetris Papamichael* [b], *Sheela Rao* [a], *Sue Ashley* [a], *Haris Charalambous* [b], *Alona Koukouma* [b], *Ian Chau* [a], *David Cunningham* [a,*]

[a] *The Royal Marsden Hospital, London and Surrey, UK*
[b] *Bank of Cyprus Oncology Centre, Nicosia, Cyprus*

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ABSTRACT

Introduction: Systemic chemotherapy improves survival in oesophagogastric cancer however no standard second-line regimen exists due to a paucity of randomised data. Docetaxel combined with irinotecan (DI) provides a suitable option due to the lack of cross-reactivity with first-line therapeutics and a tolerable toxicity profile.

Methods: We retrospectively reviewed a cohort of patients with advanced oesophagogastric cancer in two institutions treated with the combination of docetaxel 35 mg/m^2 plus irinotecan 60 mg/m^2 day 1 and day 8 every 21 days, following progression with first-line platinum-based therapy.

Results: Between January 2000 and September 2009, 41 eligible patients were identified. Median age was 58 years, male:female 25:16, adenocarcinoma:squamous cell carcinoma 37:4, oesophageal:oesophagogastric junction:gastric 7:10:24. Locally advanced:metastatic disease 6:35. Previous radical surgery:radiotherapy:both 6:4:7. 27/41 had progressed within 90 days of receiving platinum-based therapy. Median number of chemotherapy cycles: 3 (range 1–12). Eight patients required dose reductions due to DI toxicity. 10/28 evaluable patients had a response, median progression-free survival (PFS) was 11 weeks (95% confidence intervals (CI): 9–13 weeks) with median overall survival 24 weeks (95%CI: 12–35 weeks). No significant prognostic factors were identified.

Conclusion: Weekly docetaxel combined with irinotecan has acceptable safety and modest efficacy in the second-line treatment of advanced oesophagogastric cancer. Further prospective evaluation of this regimen is warranted.

1. Introduction

Oesophagogastric (OG) cancer accounts for 1.2 million new cancer diagnoses per annum worldwide and 12,500 cancer deaths per year in the United Kingdom alone.[1] Despite global disparity in the incidence, natural history and outcomes of this disease, the majority of patients present with advanced or inoperable disease and thus prognosis is poor. For patients with advanced disease, systemic chemotherapy improves both quality of life[2] and duration of survival.[3] First-line treatment of advanced OG cancer with combination chemotherapy has demonstrated a survival benefit compared to monotherapy in a large meta-analysis (HR 0.82; 95%CI: 0.74–0.90).[3] Whilst geographical variability in choice of first-line therapy is evident, most regimens are based on a platinum and fluoropyrimidine backbone, with an anthracy-

* *Corresponding author:* Address: GI and Lymphoma Unit, Royal Marsden Hospital, Downs Rd., Sutton, Surrey SM2 5PT, UK. Tel.: +44 208 661 3156; fax: +44 208 643 9414.
E-mail address: David.Cunningham@rmh.nhs.uk (D. Cunningham).
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cline commonly added in the UK and Europe and combination with docetaxel more frequently used in the US. In the second-line setting, no standard regimen exists. Most regimens used in pre-treated advanced gastric cancer patients have not been evaluated beyond the phase II setting. Activity has been demonstrated with regimens such as single agent paclitaxel,[4] docetaxel[5] and irinotecan,[6] combination FOLFIRI (5-fluorouracil and irinotecan)[7] and CAPIRI (capecitabine plus irinotecan).[8] Response rates range from 16% to 29%. Recently, a small phase III study evaluating single agent irinotecan, which closed early due to poor accrual, demonstrated a statistically significant overall survival benefit over best supportive care alone.[9]

A Korean phase II study has evaluated 3-weekly docetaxel (50–65 mg/m^2) and irinotecan (120–160 mg/m^2) in 49 patients with previously treated metastatic or recurrent advanced gastric cancer. However while demonstrating a median time to progression (TTP) of 2.7 months and an impressive median overall survival of 8.9 months, toxicity was high.[10] Although data from Western studies demonstrate single agent activity for each drug, the combination has not been previously evaluated in Western, platinum and fluoropyrimidine pre-treated population which includes patients with both oesophageal and gastric cancer. This retrospective study examines the role of irinotecan in combination with docetaxel (DI) in both advanced oesophageal and gastric cancer patients pre-treated with platinum-based chemotherapy.

2. Methods

2.1. Patients

Patients were identified from an electronic pharmacy database at two institutions; all information was obtained from patient records. Patients of at least 18 years of age with documented histologically confirmed metastatic or inoperable adenocarcinoma, undifferentiated or squamous cell carcinoma of the oesophagus or stomach were deemed eligible. All patients had received prior treatment with one platinum-fluoropyrimidine based chemotherapy regimen and undergone at least one cycle of docetaxel 35 mg/m^2, irinotecan 60 mg/m^2 day 1 and day 8, every 21 days. Patients had received treatment between January 2000 and September 2009. Data were collected on gender, age, site of primary tumour, histopathological sub-type, previous radical surgery or radiotherapy, previous chemotherapy regimens, date of last chemotherapy, date of commencing DI, performance status, number of cycles of DI, best response, symptomatic response, number of admissions for toxicity and type of toxicity, date of progression, any further treatment and date of death or last follow-up.

2.2. Statistical design

The primary end-point of this study was overall survival. Secondary end-points were progression-free survival (PFS), response rate, symptomatic response and number and duration of hospital admissions for toxicity. PFS was measured from day 1 of treatment to disease progression or death from any cause. OS was measured from day 1 of treatment to death or last documented follow-up. Kaplan Meier survival curves were generated and median PFS and OS were calculated with 95%CI. Radiological review of baseline and on-treatment imaging was undertaken by a radiologist to determine response rate. Response was not assessable in 11 patients due to lack of measurable disease or no confirmatory imaging being undertaken. The only indices of toxicity were dose reductions and hospital admissions for treatment related

Table 1 – Patient characteristics.

	Number (%) N = 41
Median age	58 years (range 34–73)
Male:female	25:16
Site of disease	
Oesophagus	7 (17)
GOJ	10 (24)
Stomach	24 (59)
Histological subtype	
Adenocarcinoma	37 (90)
Squamous cell carcinoma	4 (10)
Disease distribution	
Locally advanced	6 (15)
Metastatic	35 (85)
Performance status	
0	1 (2)
1	34 (83)
2	6 (15)
Prior radical treatment	17 (41)
Radical surgery	6 (15)
Radical chemoirradiation	4 (10)
Both	7 (17)
Prior chemotherapy regimen	
EOX	21 (51)
ECX	12 (29)
CapeOx	3 (7)
FOLFOX	4 (10)
MMC, gem + cis	1 (2)
Progressed within 90 days of platinum therapy	27 (66)
Progressed >90 days after platinum therapy	14 (34)
Additional treatment	6 (15)
Bevacizumab	1 (2)
RFA	1 (2)
Cetuximab	2 (5)
Radical radiotherapy	1 (2)
Surgery	1 (2)
Third-line chemotherapy	23 (56)
Rechallenge with DI	2 (5)
DI plus targeted agents	1(2)
Rechallenge with EOX	2 (9)
Other chemotherapy regimen	10 (24)
Other chemo + targeted agent	2 (5)
Palliative RT	5 (17)
RFA to liver	1 (2)

EOX = epirubicin, oxaliplatin and capecitabine; ECX = epirubicin, cisplatin and capecitabine; CapeOX = capecitabine and oxaliplatin; MMC, gem + cis = mitomycin C, gemcitabine and cisplatin; RFA = radiofrequency ablation.

causes as the data were collected outside the context of a clinical trial.

3. Results

3.1. Patient characteristics

Forty-one eligible patients were identified between January 2000 and September 2009, 22 from the Royal Marsden Hospital and 19 from Bank of Cyprus Oncology Centre. The median age was 58 years (range 34–73). 25/41 (61%) were male. The primary site of disease was oesophagus in 7, oesophagogastric junction (OGJ) in 10 and gastric in 24 patients respectively, with histological diagnosis of adenocarcinoma in 90% (37/41), and squamous cell carcinoma in 10% (4/41). Metastatic disease was present in 35 patients (85%) at commencement of DI chemotherapy, whereas only 6 (15%) had locally advanced disease. ECOG performance status (PS) ranged from 0 to 2, with 83% (34/41) being PS 1. Full patient characteristics can be found in Table 1. At time of analysis, 32 (78%) patients had died, 6 (15%) remained alive and 3 (7%) were lost to follow-up.

All patients had received prior systemic chemotherapy with a triplet platinum-based regimen and 41% had undergone previous radical treatment with surgery (6/41), radical intent radiotherapy (RT) (4/41) or both (7/41). 34 (83%) of these patients subsequently received additional first-line chemotherapy for metastatic disease prior to undergoing second-line DI, with only 7 patients proceeding directly from radical intent treatment to DI, most commonly due to a disease-free interval of less than six months. The majority of patients (27/41 or 66%) had progressed within 90 days of their last cycle of platinum chemotherapy (see Table 1).

A total number of 173 cycles of DI chemotherapy were administered (median 3 cycles per patient, range 1–12). Six patients received concurrent treatments with DI: 2 patients received concurrent cetuximab; 1 concurrent bevacizumab; 1 patient underwent radiofrequency ablation to liver lesions; 1 received radical radiotherapy after 4 cycles of therapy and 1 patient treated with initial palliative intent had an excellent response to 4 cycles of second-line DI converting their locally advanced unresectable disease to potentially resectable disease, which permitted radical gastrectomy. This patient received an additional 4 cycles as adjuvant therapy and remained disease free at the time of analysis.

Overall, 23/41 patients went on to receive further treatment after completing DI which comprised rechallenge with docetaxel/irinotecan (2), rechallenge with epirubicin/oxaliplatin/capecitabine (2), DI plus bevacizumab plus cetuximab (1), palliative radiotherapy (5) other chemotherapy (10), other chemotherapy with targeted agent (2) and radiofrequency ablation to the liver (1).

3.2. Safety

Dose reductions to docetaxel, irinotecan or both were required in 15 patients (37%), 7 of whom received dose reductions from cycle 1 due to toxicity from prior regimens. 15/41 patients were hospitalised for a total number of 20 admissions with a median duration of 5 days (range 1–34) secondary to treatment related toxicities. Reasons for admission can be found in Table 2.

There were two treatment-related deaths. One occurred during cycle 3, following an episode of severe respiratory sepsis complicated by a fatal cardiac arrhythmia. The second, a case of sudden death during radical radiotherapy delivered following cycle 1, where the post-mortem report was a 'ruptured artery' with no further details.

3.3. Efficacy

The median overall survival was 24 weeks (95%CI 12–35 weeks) with a median progression-free survival of 11 weeks (95%CI 9–13 weeks) (Figs. 1a and 2). 48% of patients remained alive at six months (95%CI 32–62%), with a six month PFS of 20% (95%CI 9–33%). No significant prognostic factors for overall survival were identified.

Radiological response was assessable on 30 patients as 5 patients had no measurable disease, and 6 did not have available on-treatment confirmatory scans (2 due to early treatment-related death, 4 had documented clinical PD). Single radiologist imaging review by RECIST was possible for 12/30 assessable patients, with 75% concordance with the original report. The overall response rate was 33% (10/30). There were 10 partial responses (PR). No complete responses were seen. Seven patients had stable disease (SD) for a minimum of 8.3

Table 2 – Toxicity.

Toxicity requiring hospital admission (any grade)	Number of patients $N = 41$	Number of admissions	Median days in hospital (range)
All	15	18	5 (1–34)
Nausea and vomiting	2	2	3.5 (3–4)
Febrile neutropenia	4	5	6.5 (3–19)
Diarrhoea	4	6	7 (4–11)
Infection with normal ANC	3	5	5 (1–7)
VTE	1	1[a]	4
Acute respiratory distress syndrome	1	1	34
Treatment-related deaths	2[b]		

[a] Admitted for intravenous heparin after failure of low molecular weight heparin.
[b] 1 due to sepsis-related rapid atrial fibrillation, 1 post mortem 'ruptured artery'.

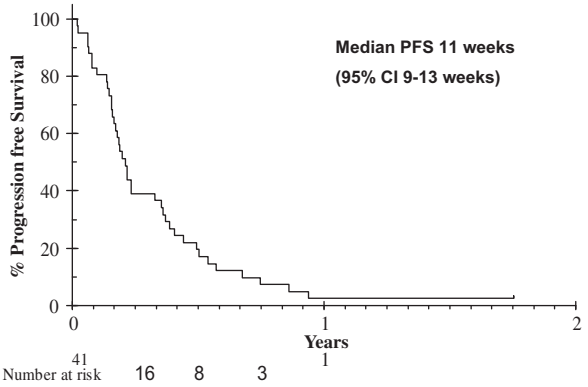

Fig. 1a – Progression-free survival overall population.

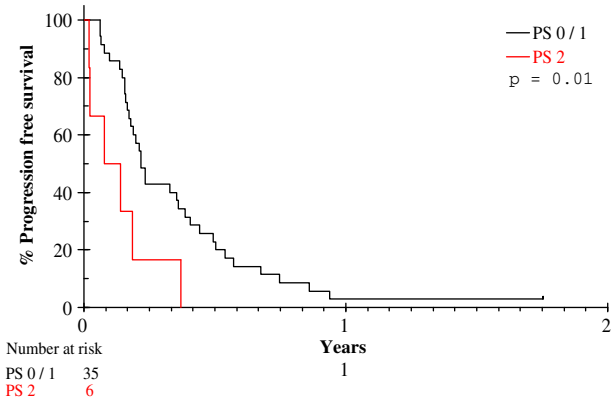

Fig. 1b – Progression-free survival by performance status.

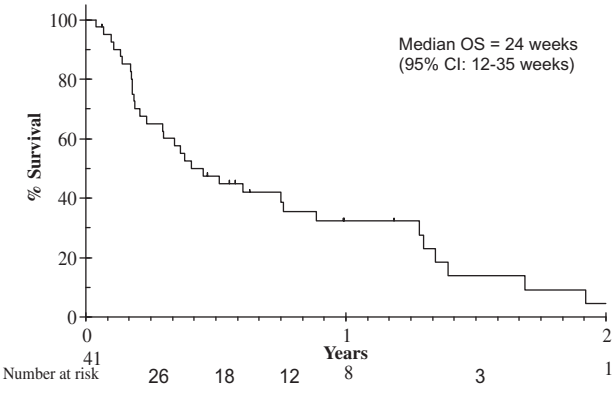

Fig. 2 – Overall survival.

weeks (median 12 weeks, range 8.3–25.1 weeks), leading to a disease control rate (PR + SD) of 57%. Progressive disease was documented radiologically in 13 patients and clinically in 4 patients (Table 3). Major (7) or minor (11) symptomatic response was documented in 18/41 (44%) patients.

Prognostic factors examined included gender, age, performance status (PS), histology (SCC or adenocarcinoma), primary site (oesophagus, OGJ or gastric), previous radical surgery, previous radical chemoradiation and time from previous treatment (<90 days or ⩾90 days). Patients of PS 2 had

Table 3 – Efficacy.

	n (%)
Symptomatic response	N = 41
Major	7 (17)
Minor	11 (27)
None	19 (46)
Not documented	4 (10)
Radiological response	N = 30
Partial response	10 (34)
Stable disease	7 (24)
Progressive disease	13 (46)
Disease control rate (PR + SD)	16 (59)
Not evaluable for radiological response	N = 11
No measurable disease	5
No confirmatory scan performed	6
On treatment death	2
Clinical PD	4
Median progression-free survival (95%CI)	11 weeks (9–13 weeks)
Median overall survival (95%CI)	24 weeks (12–35 weeks)

a poorer PFS ($p = 0.01$) (Fig. 1b) but no other factors significantly affected PFS or OS.

There was a trend towards improved survival in patients age ⩽58 (the median age) compared to >58 years old ($p = 0.04$).

4. Discussion

This retrospective, international collaboration analysing 41 patients is the largest study, to our knowledge, evaluating a weekly docetaxel–irinotecan combination in a Western population with platinum pre-treated advanced OG cancer. Our reported overall survival of 24 weeks and PFS of 11 weeks are comparable to published second-line studies.

Standard first-line therapeutic options for advanced OG cancer are based on a platinum and fluoropyrimidine doublet, regardless of histology, or site of the primary tumour. A triplet regimen, with the addition of epirubicin to oxaliplatin and the oral fluoropyrimidine, capecitabine is a standard of care for advanced OG cancer in Europe, due to the efficacy and safety profile of the EOX regimen in the REAL-2 study.[12] Both docetaxel and irinotecan have no cross-reactivity with these first-line agents and have proven efficacy in advanced OG cancer. In one phase III study of previously untreated patients, the addition of 3-weekly docetaxel to cisplatin and 5FU increased survival compared to the doublet regimen but with significant toxicity, notably complicated and uncomplicated neutropenia, compared to the doublet regimen.[13] However, weekly docetaxel regimens are much better tolerated.[14] Irinotecan also has demonstrated efficacy in phase II trials of first-line treatment however is not an established standard in previously untreated metastatic OG cancer.[15,16]

Additive and synergistic activity *in vitro* and *in vivo* has been demonstrated with docetaxel and irinotecan leading to the phase I dose-escalation study which confirmed tolerable, non-overlapping toxicities and promising efficacy with the weekly schedule used in our cohort.[17] Docetaxel and

irinotecan have subsequently been combined in three small phase II trials in previously treated patients with oesophageal cancer. The first one, a study of patients who had received perioperative chemotherapy but no treatment in the metastatic setting, closed early due to a rate of 71% Grade 4 haematological toxicity and 43% experiencing febrile neutropenia from the 3-weekly regimen ($n = 15$).[18] In a second study of 29 oesophageal cancer patients who were pre-treated with cisplatin, the 3-weekly regimen was modified to a 4-weekly schedule after the first 4 recruited patients experienced febrile neutropenia.[19] The third aimed to test DI as a first-line metastatic regimen however included 15 radically treated patients who had relapsed, and cytotoxic details were not reported.[11] Again the pre-treated group closed early due to poor accrual. Response rates were 12–30% in these studies. One Korean phase II study of 49 patients with advanced gastric cancer evaluated second-line DI in an entirely Eastern population. The authors reported an ORR of 60% (95%CI, 29.6–90.3%) in 10 patients treated at the starting doses of irinotecan 160 mg/m^2 and docetaxel 65 mg/m^2 every 3 weeks. These doses were reduced due to toxicity, but this also appeared to reduce efficacy as the response rate was only 10.3% (95%CI, 0.7–19.8%) in the remaining 39 patients treated at the reduced doses (irinotecan 120 mg/m^2 and docetaxel 50 mg/m^2). Median time to progression in all patients was 2.7 months (95%CI, 1.7–3.8 months) with an encouraging overall survival of 8.9 months (95%CI, 6.6–11.3 months).[10] Haematological toxicity was the principal toxicity, as is common to 3-weekly docetaxel-based regimens, with grade 3/4 neutropenia in 90% and febrile neutropenia in 50% of patients before the dose reductions and 71% and 11% respectively after the adjustment. Based on these data, a weekly regimen of docetaxel and irinotecan is used for selected patients at our institutions.

Symptom development on disease progression during or after first-line chemotherapy for advanced OG cancer is often rapid, with an associated deterioration in performance status rendering patients unfit for systemic treatment. Hence, there is a paucity of prospective data in the second-line setting due to poor trial accrual. The only phase III randomised control trial of second-line therapy that has been conducted closed prematurely due to slow recruitment and assessed a total of 40 patients. The investigators randomised previously treated advanced OG cancer patients to single agent irinotecan 250–300 mg/m^2 q 21 days or Best Supportive Care (BSC) following progression within 6 months of first-line chemotherapy. Despite early closure, a significant improvement in overall survival was demonstrated (median 4.0 versus 2.4 months $n = 40$) although no radiological responses were reported in either arm.[9] This study although too small to be practice changing, confirms that second-line chemotherapy is feasible and confers a modest overall survival benefit compared to supportive care alone. Second-line chemotherapy is not routinely delivered in many countries, largely due to the lack of evidence from randomised control trials. This paucity of data results in limited recommendations from current guidelines and, particularly in the UK, an absence of government funding. In the UK REAL2 trial[12] only 14% of patients received further chemotherapy after progression. In contrast, in the international ToGA trial[20] 42% received second-line treatment, in the US V325 trial, 32% and 41% of patients received further chemotherapy in the triplet and doublet arms, respectively[13] and in the entirely Eastern population in SPIRITS[6] 75% underwent further treatment after disease progression. Clearly, these data suggest that the potential benefits of second-line therapy are recognised in clinical practice. There is a current research focus on incorporating targeted agents in this pre-treated population and the results of randomised trials are awaited. However, it appears increasingly unlikely that further phase III data will emerge defining the optimal chemotherapeutic backbone.

The efficacy in our cohort is comparable to prospective data. The response rate of 34% we observed, albeit unconfirmed, is higher than that of the phase III study of irinotecan alone[9] despite 68% of our patients fitting the same definition of platinum-refractory. The median PFS of 11 weeks that we report is similar to the 2 months described with 3-weekly irinotecan however the 24-week overall survival is higher than the 4 months observed by Thuss-Patience et al. for single agent irinotecan,[9] yet compared to the Korean phase II data,[10] median PFS is similar but OS is much lower. This could be attributed to the difference in natural history between Eastern and Western populations, but also differing numbers of patients offered additional lines of therapy and the majority of our patients being platinum-refractory at time of treatment.

In addition to the retrospective nature of this study, a limitation is that response was not consistently measured radiologically, due to a number of patients having no measurable disease or no on-treatment scan but documented clinical progression. Therefore the response rate presented herein is less reliable than the objective measure of overall survival.

Of the prognostic factors evaluated, performance status 2 was predictive of a poorer PFS ($p = 0.01$), however only age demonstrated a trend towards predicting improved overall survival, yet was not statistically significant. No other factor was associated with a significant difference in progression-free or overall survival. However this analysis was limited by the small numbers in the study.

The focus of palliative therapy must be a balance of symptom control and toxicity, aiming to maintain or improve quality of life. In our study, toxicity was manageable with the majority of admissions resulting in early discharge and only 8 dose reductions as a result of DI. The high percentage (56%) of patients in our cohort who went on to receive third-line treatment highlights the careful patient selection in this study.

In conclusion, weekly docetaxel plus irinotecan is a tolerable and promising second-line combination in the treatment of advanced oesophagogastric cancer in a select Western population, especially in platinum-refractory patients that requires evaluation within a prospective randomised study.

Conflict of interest statement

All conflicts of interest declared are in the 2 years prior to submission: Dr. Sheela Rao has received an honorarium from Roche. Dr. Ian Chau has received honoraria from Roche and Sanofi-Aventis as well as research funding Novartis and

Merck-Serono and serves on uncompensated advisory boards for Roche, Merck-Serono, Imclone, Novartis and OSI. Prof. David Cunningham has received research funding from Merck Serono, Roche and Amgen and serves on uncompensated advisory boards for Roche and Amgen. Dr. Eliza Hawkes, Dr. Alicia F.C. Okines, Dr. Demetris Papamichael serves on the Novartis advisory board, Dr. Sue Ashley, Dr. Haris Charalambous, Dr. Alona Koukouma all have no conflicts of interest to declare.

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REFERENCES

1. Cancer Research, UK. http://info.cancerresearchuk.org/cancerstats/incidence/index.htm. London, UK; 2010.
2. Glimelius B, Ekstrom K, Hoffman K, et al. Randomized comparison between chemotherapy plus best supportive care with best supportive care in advanced gastric cancer. *Ann Oncol* 1997;**8**:163–8.
3. Wagner AD, Unverzagt S, Grothe W, et al. Chemotherapy for advanced gastric cancer. *Cochrane Database Syst Rev* 2010;**3**:CD004064.
4. Kodera Y, Ito S, Mochizuki Y, et al. A phase II study of weekly paclitaxel as second-line chemotherapy for advanced gastric Cancer (CCOG0302 study). *Anticancer Res* 2007;**27**:2667–71.
5. Lee JL, Ryu MH, Chang HM, et al. A phase II study of docetaxel as salvage chemotherapy in advanced gastric cancer after failure of fluoropyrimidine and platinum combination chemotherapy. *Cancer Chemother Pharmacol* 2008;**61**:631–7.
6. Chun JH, Kim HK, Lee JS, et al. Weekly irinotecan in patients with metastatic gastric cancer failing cisplatin-based chemotherapy. *Jpn J Clin Oncol* 2004;**34**:8–13.
7. Assersohn L, Brown G, Cunningham D, et al. Phase II study of irinotecan and 5-fluorouracil/leucovorin in patients with primary refractory or relapsed advanced oesophageal and gastric carcinoma. *Ann Oncol* 2004;**15**:64–9.
8. Leary A, Assersohn L, Cunningham D, et al. A phase II trial evaluating capecitabine and irinotecan as second-line treatment in patients with oesophago-gastric cancer who have progressed on, or within 3 months of platinum-based chemotherapy. *Cancer Chemother Pharmacol* 2009;**64**:455–62.
9. Thuss-Patience PKA, Deist T, Hinke A, Bichev D, Lebedinzew B, Gebauer B, Schumacher G, Reichardt P. Survival advantage for irinotecan versus best supportive care (BSC) as 2nd-line chemotherapy in gastric cancer – a randomized phase III study of the Arbeitsgemeinschaft Internistische Onkologie (AIO). Eur J Cancer vol. 7, No. 2, Joint ECCO 15–34th ESMO Multidisciplinary Congress; 2009.
10. Sym SJ, Chang HM, Kang HJ, et al. A phase II study of irinotecan and docetaxel combination chemotherapy for patients with previously treated metastatic or recurrent advanced gastric cancer. *Cancer Chemother Pharmacol* 2008;**63**:1–8.
11. Burtness B, Gibson M, Egleston B, et al. Phase II trial of docetaxel–irinotecan combination in advanced esophageal cancer. *Ann Oncol* 2009;**20**:1242–8.
12. Cunningham D, Starling N, Rao S, et al. Capecitabine and oxaliplatin for advanced esophagogastric cancer. *N Engl J Med* 2008;**358**:36–46.
13. Van Cutsem E, Moiseyenko VM, Tjulandin S, et al. Phase III study of docetaxel and cisplatin plus fluorouracil compared with cisplatin and fluorouracil as first-line therapy for advanced gastric cancer: a report of the V325 Study Group. *J Clin Oncol* 2006;**24**:4991–7.
14. Tebbutt NC, Cummins MM, Sourjina T, et al. Randomised, non-comparative phase II study of weekly docetaxel with cisplatin and 5-fluorouracil or with capecitabine in oesophagogastric cancer: the AGITG ATTAX trial. *Br J Cancer* 2010;**102**:475–81.
15. Kohne CH, Catane R, Klein B, et al. Irinotecan is active in chemonaive patients with metastatic gastric cancer: a phase II multicentric trial. *Br J Cancer* 2003;**89**:997–1001.
16. Farhat FS. A general review of the role of irinotecan (CPT11) in the treatment of gastric cancer. *Med Oncol* 2007;**24**:137–46.
17. Bleickardt E, Argiris A, Rich R, et al. Phase I dose escalation trial of weekly docetaxel plus irinotecan in patients with advanced cancer. *Cancer Biol Ther* 2002;**1**:646–51.
18. Govindan R, Read W, Faust J, et al. Phase II study of docetaxel and irinotecan in metastatic or recurrent esophageal cancer: a preliminary report. *Oncology (Williston Park)* 2003;**17**:27–31.
19. Lordick F, von Schilling C, Bernhard H, et al. Phase II trial of irinotecan plus docetaxel in cisplatin-pretreated relapsed or refractory oesophageal cancer. *Br J Cancer* 2003;**89**:630–3.
20. Van Cutsem EKY, Chung H, Shen L, et al. Efficacy results from the ToGA trial: a phase III study of trastuzumab added to standard chemotherapy (CT) in first-line human epidermal growth factor receptor 2 (HER2)-positive advanced gastric cancer (GC). *J Clin Oncol* 2009;**27**:LBA4509.