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Original Article

Outcomes with Palliative Weekly Paclitaxel in Advanced, Recurrent, and Metastatic Esophageal Cancer - Real World Experience

Abstract

Background: In advanced esophageal cancer, combination chemotherapy regimens provide effective palliation but result in substantial toxicity. **Aim:** The aim of the study was to evaluate outcomes of recurrent and metastatic esophageal carcinoma treated with weekly paclitaxel. **Objectives:** The objective of the study was to determine the clinical and laboratory factors predicting response and affecting overall survival (OS) in patients receiving palliative chemotherapy for advanced esophageal/gastroesophageal cancer. **Materials and Methods:** Retrospective analysis of patients with advanced esophageal cancer, not amenable to definitive intent therapy that was treated with intravenous weekly paclitaxel was done. Progression-free survival (PFS) and OS were calculated with Kaplan–Meir analysis while factors affecting outcome were subjected to log rank test and multivariate analysis. **Results:** Between September 2010 and October 2014, 350 patients were included in analysis. Median follow-up is 8 months. Median age was 55 years, with a male:female ratio of 2.4:1. Nearly 34.5% were mid esophageal and 51% were lower third and gastroesophageal junction tumors. Almost 58% of the tumors had squamous histology. Performance status was >2 in 25.4%. Almost 62% patients had received prior therapy. Median number of cycles of weekly paclitaxel delivered was 12 with median duration of 3 months. Nearly 51% of patients had improvement in dysphagia, with time to symptom improvement of 20 days. In 31% patients, feeding nasogastric tube could be removed. Overall response rate was 32% (complete remission, 2.5% + partial remission, 29.5%). Median PFS was 4.0 months (95% confidence interval [CI]: 3.6–4.3 months) and median OS was 10 months (95% CI: 8.5–11.4 months). Performance status and pretreatment albumin significantly affected OS. **Conclusion:** Metronomic weekly paclitaxel chemotherapy provides good palliative benefit in advanced unresectable/metastatic esophageal cancer with minimal toxicity. Eastern Cooperative Oncology Group Performance Status (PS 0 and 1) and baseline serum albumin level >3.7 g/dl significantly improved survival.

Keywords: *Advanced esophageal carcinoma, metronomic therapy, weekly paclitaxel*

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Introduction

Esophageal cancer is one of the most aggressive cancers with dismal outcomes despite surgery, radiotherapy, and chemotherapy.[1] In patients with advanced unresectable or metastatic disease, the prognosis is grim with an estimated median survival of 6–7 months, regardless of whether the patient is treated with single agent chemotherapy or aggressive three-drug combination chemotherapy.[2-4] Taxanes have demonstrated promising activity in patients with esophageal cancer.[4] Paclitaxel has been used in various schedules, ranging from 24 h infusion to short 1 h infusion; however, shorter infusions have similar efficacy and lesser toxicity.[5] Metronomic weekly paclitaxel in smaller studies has shown modest response in unresectable and metastatic esophageal carcinoma. We present largest patient data from tertiary cancer center regarding experience with metronomic weekly paclitaxel in patients with advanced unresectable, metastatic, or recurrent esophageal and esophagogastric carcinomas.

Materials and Methods

We retrieved data of patients prospectively collected in our esophageal cancer database of recurrent, unresectable, and metastatic esophageal carcinoma registered between September 2010 and October 2014. Only patients who had confirmed histology and subsite available, received weekly paclitaxel as palliative chemotherapy, and having at least one response evaluation done as per Response Evaluation Criteria in

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Solid Tumor (RECIST, version 1.1, European Organisation for Research and Treatment of Cancer (EORTC), National Cancer Institute of United States, National Cancer Institute of Canada Clinical Trialist group, revised in 2008) were selected for final analysis. This study was approved by the Institutional Ethics Committee.

All patients were evaluated at baseline including history and physical examination, laboratory parameters, upper endoscopy (if indicated), and imaging studies. Patients were treated with paclitaxel at 80 mg/m^2 as a 1 h infusion given weekly with standard premedications including antihistamines, antiemetic, H2 antagonists, and steroids. Each dose of chemotherapy was considered as one cycle. If there was no evidence of hypersensitivity in the first few cycles of chemotherapy, steroids were omitted in subsequent cycles. Complete blood count was checked weekly and patients were evaluated by a physician weekly before chemotherapy. Serum biochemistry (including fasting blood glucose, liver functions, and renal functions) and serum electrolytes were checked once a month.

Response was calculated using standard response evaluation criteria in solid tumor (RECIST version 1.1) definitions, with the measurements including the maximum esophageal thickness added to other measurable lesions. Follow-up was taken from the case records, electronic medical records, and telephonic conversation with a patient or their relatives. Progression-free survival (PFS) was calculated from the date of receiving first dose of paclitaxel chemotherapy to the date of radiological progression, symptomatic deterioration in the absence of progressive disease (PD) on scan, start of next line of therapy due to any reason (logistic reasons, financial constraints, or unacceptable toxicity), or death from any cause. Overall survival (OS) was calculated from the date of first chemotherapy to the date of death from any cause. Toxicity was graded according to common terminology criteria for adverse events (Common terminology criteria for adverse events. CTC v 4.03 (National Cancer Institute Common Terminology Criteria for Adverse Events v4.0). Imaging studies were repeated approximately every eight cycles. Statistical Package for the Social Sciences version 18 (IBM Corp. Released 2011. IBM SPSS Statistics for Windows, Version 20.0. Armonk, NY: IBM Corp.) was used for statistical analysis. For OS and PFS, Kaplan–Meier estimation curves were generated. Clinical factors and laboratory factors individually were tested with log-rank test. Those factors which prognosticated for OS were then tested in a Cox proportional Hazard method for multivariate analysis.

Results

Between September 2010 and October 2014, we selected data of 350 patients who were registered as recurrent/metastatic esophageal carcinoma in our prospectively maintained institutional database and received at least four doses of weekly paclitaxel with at least one response evaluation available. Median age at diagnosis is 55 years with a male:female ratio of 2.4:1 [Table 1]. Nearly 58% were squamous cell carcinoma whereas 42% had adenocarcinoma histology. Lower one-third was the most common subsite (51%,) followed by mid (35%) and upper esophagus (14%). Performance status was >2 in 25.4%. Nearly 205 (59%) had baseline metastatic disease at presentation, whereas 218 (62%) had received previous therapy such as surgery, radiotherapy, or chemotherapy for definitive or palliative purpose. Among patients who received previous chemotherapy, 50% patients were platinum pretreated and 39% had received prior 3 weekly paclitaxel. Median number of cycles of weekly paclitaxel delivered was 12 with median total duration of 3 months. About 51% of patients had improvement in dysphagia on weekly paclitaxel, with a median time to symptom improvement of 20 days. In 31% of feeding tube-dependent patients, the nasogastric tube could be removed successfully.

Table 1: Distribution of baseline factors of patients with recurrent/metastatic esophageal carcinoma (*n*=350)

Baseline factors	Groups	Values (%)
Age (median 55 years)	<55	211 (60.3)
	>55	139 (39.7)
Sex	Male	247 (70.5)
	Female	103 (29.4)
Histology	Squamous	203 (58)
	Adenocarcinoma	147 (42)
Subsite	Upper	50 (14.3)
	Mid	121 (34.6)
	Lower	179 (51.1)
Performance status	0-1	261 (74.6)
	2	60 (17.1)
	3	29 (8.28)
Comorbidities	None	224 (64)
	Any*	126 (36)
At presentation disease	Metastatic	205 (58.6)
	Non metastatic	145 (41.4)
Previous treatment	Any#	218 (62.3)
	None	132 (37.7)

*Hypertension, diabetic, ischemic heart disease, active asthma, COPD; #Surgery, radiotherapy, chemotherapy. COPD – Chronic obstructive pulmonary disease

Median follow-up is 8 months. Response to weekly paclitaxel includes complete remission (CR: 2.5%), partial remission (PR: 29.5%), stable disease (22.8%), and PD (40.6%). In 4.6% patients, the response was not assessable. Patients who had received platinum-based chemotherapy before weekly paclitaxel had a response rate (CR + PR) of 25.8%, whereas patients who were platinum naïve had a better response rate of 38.9% (P = 0.03). Median PFS was 4.0 months (95% confidence interval [CI]: 3.6–4.3 months) and

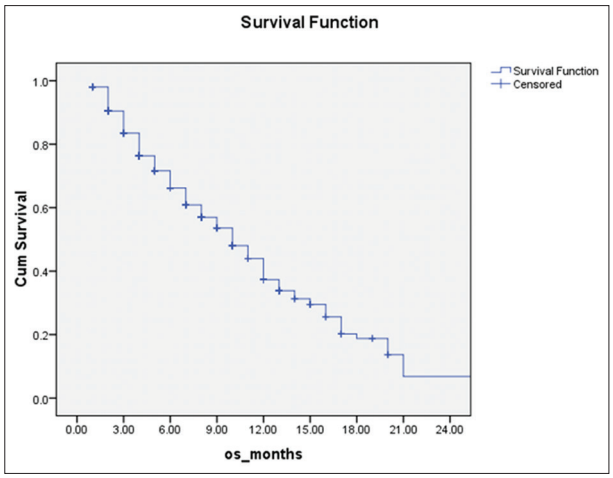

Figure 1: Overall survival of patients (*N* = 350) treated with weekly paclitaxel

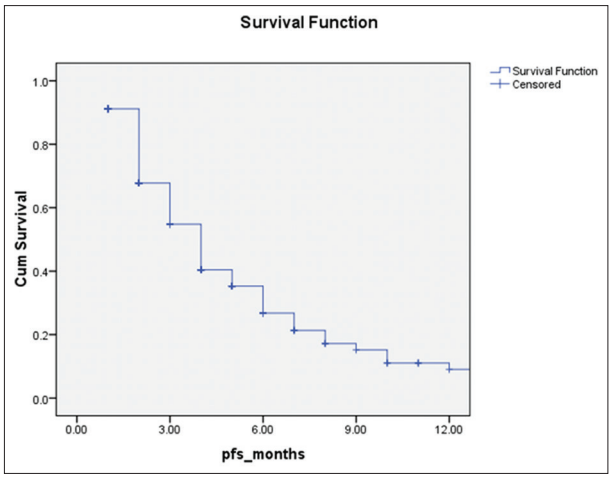

Figure 2: Progression-free survival of patients (*N* = 360) treated with weekly paclitaxel

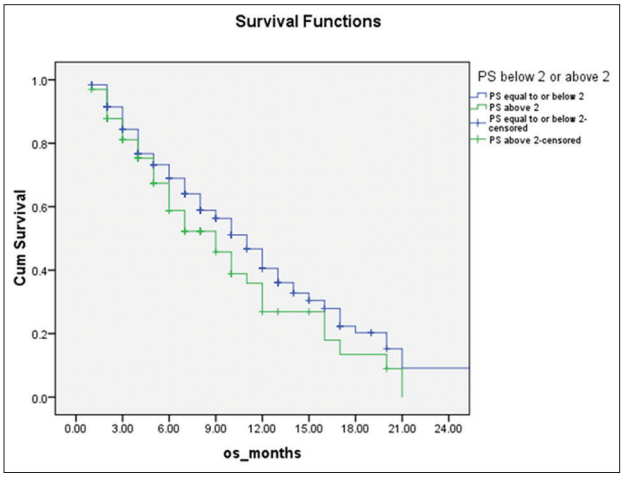

Figure 3: Overall survival of patients stratified with performance status 0–1 (blue line) and 2 or more (green line), 11 months versus 9 months, respectively (*P* = 0.007)

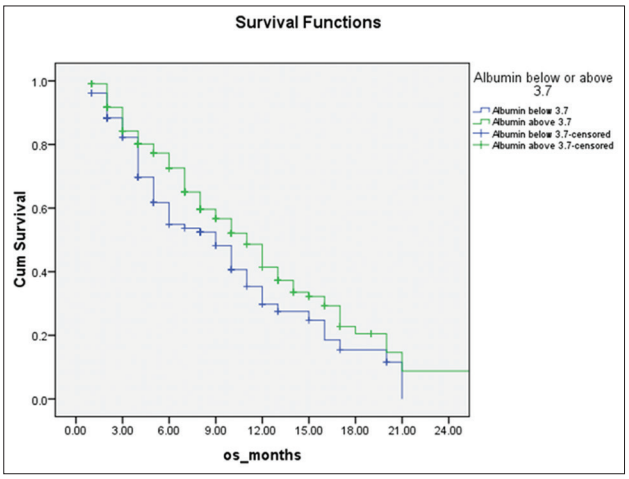

Figure 4: Overall survival of patients stratified with serum albumin above (green line) and below (blue line) 3.7 mg/dL, 11 months versus 9 months, respectively (*P* = 0.03)

median OS was 10 months (95% CI: 8.5–11.4 months) [Figures 1 and 2]. In univariate analysis, better performance status and pretreatment albumin significantly affected OS [Table 2]. However, multivariate analysis demonstrated good performance status (PS 0–1) as the sole prognostic factor affecting survival outcome [Figure 3 and 4].

The most common grade 3/4 toxicities included hyponatremia (14.8%), fatigue (6.3%), diarrhea (6.2%), anemia (27.4%), neutropenia (17.1%), and febrile neutropenia (4%). Two hundred and sixty-eight out of 350 (76.5%) patients underwent salvage therapy beyond weekly paclitaxel progression. Common salvage therapies included capecitabine alone in 153 patients (43.7%) followed by gefitinib/erlotinib in 48 (13.7%), single agent irinotecan in 23 (6.6%), palliative radiotherapy in 21 (6%), irinotecan with capecitabine in 13 (3.7%), and oral methotrexate with celecoxib in 10 patients (2.9%). Remaining patients had rapid deterioriation of performance status and were send for palliative care alone.

Discussion

Esophageal carcinomas are one of the most lethal malignancies with poor long-term outcomes.[6,7] In patients with locally advanced and metastatic esophageal carcinoma, the goal of treatment remains palliation of symptoms, improving quality of life, and attempt for prolongation of survival.[8] Systemic chemotherapy plays a pivotal role in inducing meaningful and early improvement in local and systemic disease-related symptoms.[4] Use of systemic chemotherapy improves response rates and survival irrespective of primary esophageal histology albeit with some toxicities.[9,10] Use of combination doublet/triplet chemotherapeutic agents compared to single agent have only produced marginal improvement in response rates with very modest survival benefit but at the cost of much higher toxicities.[2,11-13] Single agent weekly paclitaxel in unresectable, recurrent, and metastatic esophageal carcinomas has produced good response rates with median survival of 8–10 months with much better toxicity

Table 2: Factors affecting outcomes, progression-free and overall survival (log-rank test)

Factors	Groups	PFS (months)	*P*	OS (months)	*P*
Age (years)	<55	4	0.9	11	0.16
	>55	4		8	
Disease at presentation	Metastatic	3	0.01	9	0.17
	Nonmetastatic	5		11	
Extent at presentation	Distant	3	0.002	9	0.11
	Loco regional	6		12	
Hemoglobin (g/dL)	<11.4	4	0.78	10	0.98
	≥11.4	4		10	
Albumin (g/dL)	<3.7	4	0.78	9	0.03
	>3.7	4		11	
PS	0-1	6	0.007	11	0.007
	>2	4		9	
Platinum exposed	Yes	4	0.07	10	0.62
	No	4		10	
Previous treatment	Yes	4	0.736	10	0.53
	No	4		10	

PFS – Progression-free survival; OS – Overall survival

profile.[1,14,15] We report largest patient data of locally advanced and recurrent/metastatic esophageal carcinomas treated with single agent metronomic weekly paclitaxel.

Only a few studies have reported outcomes with the use of weekly palliative paclitaxel regime in advanced, metastatic esophageal carcinoma. In a phase II study, Kato *et al*. in a selected cohort of patients with good performance status (PS 0–1) with advanced and recurrent squamous esophageal carcinoma showed a substantial response of 44% with weekly paclitaxel.[15] In predominantly platinum pretreated patients, they demonstrated a PFS of 4.8 months and median survival of 10.8 months. Unlike Kato *et al*., Ilson *et al*. in a multicentric study, could only demonstrate a modest response rate of 13%, which failed to meet the anticipated response rate of 25%.[14] Having rigid selection criteria of including only patients of performance status 0–2, no comorbidities, and no prior chemotherapy for metastatic disease, they showed a better response rate for adenocarcinoma (15%) compared to squamous carcinoma (8%). The reason of lower response rates in Ilson *et al*. compared to Kato *et al*. could be due to its multicentric nature of study and lower dose of paclitaxel (80 mg/m^2) used in similar patient cohort. In a more contemporary study, Noronha *et al*. demonstrated response rate of 49% in a population which comprised 45% of patients with performance status 2 or more, 41% with comorbidities, 51% had previous platinum exposure, and 76% with distant metastasis.[1]

In our study population of 350 patients, 58% of patients had squamous cell carcinoma histology with 25.4% patients had performance status >2 before receiving weekly paclitaxel. Nearly 50% of them were platinum pretreated and 39% had history of receiving prior 3 weekly paclitaxel. Hence, our patient population was quite contrary to that reported by Ilson *et al*. (*N* = 102) where all patients had better PS (<2) and none had received previous chemotherapy.[14] Compared to Kato *et al*. study, in which all patients were Eastern Cooperative Oncology Group performance status of <1, our study had only 74.6% patients with PS <2., with 58% squamous histology compared to 98% reported by Kato *et al*.[15] Our reported patient profile is closer to that reported by Noronha *et al*. except only 25% patients had PS >2 in our study compared to 45% reported by them. Our response rates with weekly paclitaxel, 32% (CR + PR) were more modest compared to Kato *et al*.[15] and Noronha *et al*.[1] However, the median duration of response and PFS was similar across all studies.[1,14,15] Our median survival of 10 months is similar to that reported by others except for Noronha *et al*. where median OS was 7.5 months.[1,14,15] Ilson *et al*. and Noronha *et al*. both had shown higher responses in platinum naïve compared to platinum exposed population, 64% versus 35% and 15% versus 5%, respectively; however our result had similar responses irrespective of prior platinum exposure (32% vs. 37%). Our study showed no significant difference in PFS whether squamous or adenocarcinoma histology, unlike reported by Noronha *et al* [Table 3].

Progressive dysphagia and weight loss often lead to poor quality of life in patients with esophageal carcinoma, especially after disease progression. The efficacy of any intervention in such cases not only depends on the response rates but also in terms of resolution of dysphagia and independence from feeding tube requirements. Use of weekly paclitaxel in our study produced significant improvement of dysphagia in 51% of patients with median duration of 20 days from first dose. In 31% of patients, the feeding nasogastric tube could be successfully removed. Among several prognostic factors analyzed, only performance status 0–1 before starting chemotherapy and serum albumin >3.7 g/dL were significant. However, in multivariate analysis, performance status 0–1 was the sole prognostic factor with significant impact on OS. The merit of any systemic therapy is decided by its therapeutic index and toxicity profile. In our cohort of patients treated with weekly paclitaxel, most common grade 3/4 toxicities, beyond 10% incidence, were hyponatremia (14.8%), anemia (27.4%), and neutropenia (17.1%). Grade 3/4 motor-sensory neuropathy and febrile neutropenia were 6% and 4%, respectively, which is similar to that reported in other series.[1,14,15]

One of the remarkable findings in our study was that 76.5% of patients had received subsequent salvage chemotherapy after progression on weekly paclitaxel, probably having an impact on longer reported median OS of 10 months. Being retrospective, we do not rule out any selection bias and inadvertent omission of patients which might have inflated the overall outcome, as only patients entered in our prospective database were analyzed which might not have

Table 3: Comparison of demographic profiles, outcomes, and toxicity across several reported studies

Characteristics	Kato *et al.*	Ilson *et al.*	Noronha *et al.*	Present series
Number of patients (*n*)	53	95	51	350
Median age (years)	65	59	56	55
Male/female	6.6/1	12.5/1	2.9/1	2.4/1
Co-morbidities, *n* (%)	None	Excluded	21 (41)	126 (36)
PS, *n* (%)				
0-1	53 (100)	PS 0-2	28 (55)	261 (74.5)
2 or more	None	NR	23 (45)	89 (25.5)
Squamous versus (%)	52 (98)	32 (31)	33 (65)	203 (58)
Adenocarcinoma (%)	1 (2)	63 (62)	18 (35)	147 (42)
Previous platinum exposed (%)	47/53 (88.6)	22 (22)	26 (51)	175 (50)
Platinum naïve (%)			25 (49)	175 (50)
Median weekly paclitaxel doses	10	12	11	12
Paclitaxel dose per week (mg/m^2)	100	80	80	80
Response rates (CR+PR) (%)	43.5 (7.5+36)	13 (0+13)	49 (4+45)	32 (2.5+29.5)
Response platinum exposed versus naïve (%)	39.6 versus NR	5 versus 15	35 versus 64*	32 versus 37
PFS (median), months	4.8	5.7	4.7	4
OS (median), months	10.8	9	7.5	10
PFS				
Squamous versus adenocarcinoma	4.8 months$^{\$}$	NR	5.9 versus 3.6 months*	4 months versus 3 months
PS 0-1 versus 2 or more	4.8 months$^{\$}$	NR	10.6 versus 5.4 months*	6 months versus 4 months*
Previous platinum versus none	NR	NR	NR	4 months versus 4 months
Grade 3/4 neutropenia (%)	52.8	5	9.8	17
Grade 3/4 leucopenia (%)	45.3	-	7.4	10
Febrile neutropenia (%)	3.8	1	4	4
Grade 3/4 sensory neuropathy (%)	5.7	3	2	5.8

*Statistically significant; $^{\$}$Only squamous carcinoma and PS 0-1 were enrolled. NR – Not reported; OS – Overall survival; PFS – Progression-free survival

included all patients with locally advanced and metastatic esophageal carcinomas treated or referred in our institute.

Palliative systemic chemotherapy for locally advanced and metastatic esophageal carcinoma has shown very modest to no benefit in OS compared to best supportive care in different studies and systematic reviews.[4,16-20] After progression on doublet/triplet, first-line chemotherapy, single-agent chemotherapy with taxanes, or irinotecan provides modest survival benefit with good palliation.[21-24] Moreover, use of combination chemotherapy compared to single agent after disease progression has shown very modest improvement in responses with no clinically meaning full improvement in OS.[25-27] We propose single agent metronomic weekly paclitaxel as valid therapeutic option in locally advanced, recurrent, and metastatic esophageal carcinoma. This regimen when used ensures tolerable safety profile and early meaningful improvement in tumor-related symptoms with effective palliation.

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Nil.

Conflicts of interest

There are no conflicts of interest.

References

1. Noronha V, Patil V, Bhosale B, Joshi A, Purandare N, Prabhash K. Metronomic weekly paclitaxel in advanced unresectable esophageal cancer. Indian J Cancer 2013;50:128-34.
2. Van Cutsem E, Moiseyenko VM, Tjulandin S, Majlis A, Constenla M, Boni C, *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.
3. Webb A, Cunningham D, Scarffe JH, Harper P, Norman A, Joffe JK, *et al.* Randomized trial comparing epirubicin, cisplatin, and fluorouracil versus fluorouracil, doxorubicin, and methotrexate in advanced esophagogastric cancer. J Clin Oncol 1997;15:261-7.
4. Homs MY, v d Gaast A, Siersema PD, Steyerberg EW, Kuipers EJ. Chemotherapy for metastatic carcinoma of the esophagus and gastro-esophageal junction. The Cochrane database of systematic reviews 2006:Cd004063.
5. Williams C, Bryant A. Short versus long duration infusions of paclitaxel for any advanced adenocarcinoma. The Cochrane database of systematic reviews 2011:Cd003911.
6. Malkan G, Mohandas KM. Epidemiology of digestive cancers in India. I. General principles and esophageal cancer. Indian J Gastroenterol 1997;16:98-102.
7. Yeole BB, Kurkure AP, Sunny L. Cancer survival in Mumbai (Bombay), India, 1992-1999. IARC scientific publications. 2011:133-42.
8. Grünberger B, Raderer M, Schmidinger M, Hejna M. Palliative

chemotherapy for recurrent and metastatic esophageal cancer. Anticancer Res 2007;27:2705-14.

9. Chau I, Norman AR, Cunningham D, Oates J, Hawkins R, Iveson T, *et al.* The impact of primary tumour origins in patients with advanced oesophageal, oesophago-gastric junction and gastric adenocarcinoma – Individual patient data from 1775 patients in four randomised controlled trials. Ann Oncol 2009;20:885-91.
10. Wang K, Johnson A, Ali SM, Klempner SJ, Bekaii-Saab T, Vacirca JL, *et al.* Comprehensive genomic profiling of advanced esophageal squamous cell carcinomas and esophageal adenocarcinomas reveals similarities and differences. Oncologist 2015;20:1132-9.
11. Ilson DH. Docetaxel, cisplatin, and fluorouracil in gastric cancer: Does the punishment fit the crime? J Clin Oncol 2007;25:3188-90.
12. Muro K, Hamaguchi T, Ohtsu A, Boku N, Chin K, Hyodo I, *et al.* A phase II study of single-agent docetaxel in patients with metastatic esophageal cancer. Ann Oncol 2004;15:955-9.
13. Wagner AD, Grothe W, Haerting J, Kleber G, Grothey A, Fleig WE. Chemotherapy in advanced gastric cancer: A systematic review and meta-analysis based on aggregate data. J Clin Oncol 2006;24:2903-9.
14. Ilson DH, Wadleigh RG, Leichman LP, Kelsen DP. Paclitaxel given by a weekly 1-h infusion in advanced esophageal cancer. Ann Oncol 2007;18:898-902.
15. Kato K, Tahara M, Hironaka S, Muro K, Takiuchi H, Hamamoto Y, *et al.* A phase II study of paclitaxel by weekly 1-h infusion for advanced or recurrent esophageal cancer in patients who had previously received platinum-based chemotherapy. Cancer Chemother Pharmacol 2011;67:1265-72.
16. Murad AM, Santiago FF, Petroianu A, Rocha PR, Rodrigues MA, Rausch M. Modified therapy with 5-fluorouracil, doxorubicin, and methotrexate in advanced gastric cancer. Cancer 1993;72:37-41.
17. Pyrhönen S, Kuitunen T, Nyandoto P, Kouri M. Randomised comparison of fluorouracil, epidoxorubicin and methotrexate (FEMTX) plus supportive care with supportive care alone in patients with non-resectable gastric cancer. Br J Cancer 1995;71:587-91.
18. Glimelius B, Ekström K, Hoffman K, Graf W, Sjödén PO, Haglund U, *et al.* Randomized comparison between chemotherapy plus best supportive care with best supportive care in advanced gastric cancer. Ann Oncol 1997;8:163-8.
19. Thuss-Patience PC, Kretzschmar A, Bichev D, Deist T, Hinke A, Breithaupt K, *et al*. Survival advantage for irinotecan versus best supportive care as second-line chemotherapy in gastric cancer--a randomised phase III study of the Arbeitsgemeinschaft Internistische Onkologie (AIO). European journal of cancer (Oxford, England: 1990). 2011;47:2306-14.
20. Wagner AD, Unverzagt S, Grothe W, Kleber G, Grothey A, Haerting J, *et al*. Chemotherapy for advanced gastric cancer. Cochrane Database Syst Rev 2010;Cd004064.
21. Kang JH, Lee SI, Lim DH, Park KW, Oh SY, Kwon HC, *et al.* Salvage chemotherapy for pretreated gastric cancer: A randomized phase III trial comparing chemotherapy plus best supportive care with best supportive care alone. J Clin Oncol 2012;30:1513-8.
22. Thuss-Patience PC, Kretzschmar A, Bichev D, Deist T, Hinke A, Breithaupt K, *et al.* Survival advantage for irinotecan versus best supportive care as second-line chemotherapy in gastric cancer – A randomised phase III study of the Arbeitsgemeinschaft Internistische Onkologie (AIO). Eur J Cancer 2011;47:2306-14.
23. Ford HE, Marshall A, Bridgewater JA, Janowitz T, Coxon FY, Wadsley J, *et al.* Docetaxel versus active symptom control for refractory oesophagogastric adenocarcinoma (COUGAR-02): An open-label, phase 3 randomised controlled trial. Lancet Oncol 2014;15:78-86.
24. Janowitz T, Thuss-Patience P, Marshall A, Kang JH, Connell C, Cook N, *et al.* Chemotherapy vs. supportive care alone for relapsed gastric, gastroesophageal junction, and oesophageal adenocarcinoma: A meta-analysis of patient-level data. Br J Cancer 2016;114:381-7.
25. Higuchi K, Tanabe S, Shimada K, Hosaka H, Sasaki E, Nakayama N, *et al.* Biweekly irinotecan plus cisplatin versus irinotecan alone as second-line treatment for advanced gastric cancer: A randomised phase III trial (TCOG GI-0801/BIRIP trial). Eur J Cancer 2014;50:1437-45.
26. Nishikawa K, Fujitani K, Inagaki H, Akamaru Y, Tokunaga S, Takagi M, *et al.* Randomised phase III trial of second-line irinotecan plus cisplatin versus irinotecan alone in patients with advanced gastric cancer refractory to S-1 monotherapy: TRICS trial. Eur J Cancer 2015;51:808-16.
27. Sym SJ, Hong J, Park J, Cho EK, Lee JH, Park YH, *et al.* A randomized phase II study of biweekly irinotecan monotherapy or a combination of irinotecan plus 5-fluorouracil/leucovorin (mFOLFIRI) in patients with metastatic gastric adenocarcinoma refractory to or progressive after first-line chemotherapy. Cancer Chemother Pharmacol 2013;71:481-8.