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Epirubicin, taxotere and fluorouracil modulated by folinic acid in the treatment of advanced gastric cancer: A phase II study of the Gruppo Oncologico dell' Italia Meridionale (GOIM)

F. Giuliani[a,*], *S. Romito*[b], *E. Maiello*[c], *A. Capobianco*[d], *F. Carrozza*[b], *I. Nugnes*[a], *A. Misino*[a], *M.R. Valerio*[e], *L. Manzione*[f], *G. Colucci*[a]

[a]*Medical Oncology Department, NCI, Bari, Italy*
[b]*Medical Oncology Unit, Cardarelli Hospital, Campobasso, Italy*
[c]*Medical Oncology Unit, San Giovanni Rotondo Hospital, Italy*
[d]*Medical Oncology Unit, Oncology Hospital, Rionero in Vulture (PZ), Italy*
[e]*Medical Oncology Unit, University, Palermo, Italy*
[f]*Medical Oncology Unit, S. Carlo Hospital, Potenza, Italy*

ARTICLE INFO

Article history:
Received 6 June 2008

Keywords:
Gastric cancer
Epirubicin
Taxotere

ABSTRACT

Introduction: Despite the large number of drugs active in AGC, no combination can be considered as the gold standard treatment. Modest increase have been obtained in overall survival with the most widely employed regimens such as CF or ECF, often obtained at expense of increased toxicity. So there is a strong need to develop new active drugs to improve the clinical outcome. Taxotere showed to be effective in preclinical studies and some phase II trials confirmed its clinical efficacy. Recently, the addition of TXT to CDDP + FU (TCF regimen), obtained, in a large randomised phase III trial, better survival than CF alone. However the toxicity of this combination was relevant and mainly due to the association with CDDP. Considering these data the GOIM started a phase II study aiming to evaluate efficacy and safety of a three drugs combination, employing EPI instead of CDDP.

Materials and methods: Forty-one histologically proven untreated gastric cancer patients, with advanced measurable disease, age between 18 and 75 years, performance status $\geqslant 70$ (Kfsky scale) and available to sign written informed consent, were enrolled. They received the following treatment: Epirubicin at 60 mg/m^2 on day 1, Taxotere at 50 mg/m^2 on day 1, Folinic Acid at 100 mg/m^2 on days 1–2, Fluorouracil bolus at 400 mg/m^2 on days 1–2 and Fluorouracil 22 h continuous infusion on days 1–2 every three weeks.

Results: Amongst the 38 evaluable patients we observed 5 CR (13%), 9 PR (24%), 9 SD (24%) and 15 PD (39%) for an ORR of 37% (95% CI: 22–52) and a tumor growth control rate of 61%. The median time to progression was 4 months and the median survival was 9 months. The treatment was well tolerated. The main grade III–IV haematologic toxicities were leucopenia 7%, neutropenia 5% and anemia 5% while non-haematologics were diarrhoea 2%, alopecia 2% and cardiac 2%.

Conclusion: The three drugs combination of Taxotere, Epirubicin and Fluorouracil is active and well tolerated first-line treatment in advanced gastric cancer patients.

* *Corresponding author:* Tel.: +39 080 5555241; fax: +39 080 5555232.
E-mail address: giuliani_daniela@libero.it (F. Giuliani).
1359-6349/$ - see front matter
doi:10.1016/j.ejcsup.2008.06.017

1. Introduction

Despite a decline in its incidence, gastric cancer remains one of the leading causes of cancer death worldwide.[1] More than 80% of the patients still die either because they have an advanced tumour at the time of diagnosis or because of incurable recurrences after resection. In advanced disease, chemotherapy is the most effective treatment in order to improve median survival and quality of life. Several randomised trials demonstrated the superior efficacy of fluorouracil (FU)-based regimens when compared to the best supportive care,[2–5] but despite the large number of drugs employed in association, no chemotherapy combination is accepted as the gold standard. Between the two drug regimens the combination of cisplatin (CDDP) plus FU (CF regimen) is considered a reference, mainly in United States of America (USA), on the basis of the results of a randomised trial that compared CF versus FU plus adriamycin (ADM) and mitomycin-c (MMC) (FAM regimen) or FU alone.[6] In Europe, a randomised phase III trial employing epirubicin (EPI), CDDP and FU (ECF regimen) showed superior response rate and significantly prolonged survival compared with the historical reference combination of FU plus ADM and methotrexate (MTX) (FAMTX regimen).[7] The same results were reproduced in another randomised phase III trial comparing ECF to MMC plus CDDP and FU (MCF regimen).[8] So ECF is considered one of the reference regimens in the treatment of advanced gastric cancer (AGC) and is widely employed.

The results of a recent meta-analysis demonstrated a survival advantage of about 2 months with the three-drug combination of FU/anthracyclines and cisplatin compared with regimens, containing either FU and cisplatin without anthacyclines or FU and anthacyclines without cisplatin.[9]

Since the increase in terms of survival is modest and achieved at the expense of increased toxicity, a particular attention to chemotherapy-related side-effects has to be considered.

So there is a strong need to develop new active regimens to improve the outcome for AGC patients and to reduce the toxicity. Taxotere (TXT), a semisynthetic taxoid developed in eighties, showed to be effective in human gastric cell lines[10] and active against a broad spectrum of human solid tumours[11,12]; besides, preclinical data demonstrated the synergism of TXT with FU, anthacyclines and cisplatin.[13,14] In advanced gastric cancer, several phase II trials employing TXT at dosage ranging from 60 mg/m^2 to 100 mg/m^2 every three weeks reported an interesting response rate of about 20% in AGC both as first[15–18] and second-line therapy [19–21] with acceptable toxicity profile. Subsequently, two studies explored the activity of the combination of TXT plus CDDP (TC regimen) without or with FU (TCF regimen) and reported a response rate of about 50% with median overall survival of 9.0 and 9.3 months.[22,23] A randomised phase II trial comparing head-to-head, the two regimens demonstrated the superiority of the three-drug combination in terms of response rate (43% versus 26%).[24] In the large phase III randomised trial named V325 comparing TCF and CF, the triple-drug combination obtained better results in terms of time to progression (5.6 versus 3.7 months) and overall survival (9.2 versus 8.6 months).[25] However, the toxicity of TCF regimen seemed to be relevant and to be mainly due to the association with CDDP.

Considering these data, the GOIM started a multicentre phase II study aiming to evaluate the activity and safety of a combination of taxotere and fluorouracil with the addition of EPI instead of CDDP.

2. Patients and methods

2.1. Patients selection

The following eligible criteria were required: hystologically proven metastatic or locally inoperable gastric cancer, at least one measurable lesion, age between 18 and 75 years, performance status $\geqslant$70 (K.fsy scale), life expectancy $\geqslant$3 months, adequate bone marrow reserve (neutrophils $\geqslant$ 2.000/mm^3, platelets $\geqslant$ 100.000 mm^{-3} and haemoglobin level $\geqslant$ 10 g/dl), renal (creatinine $\leqslant$ 1.2 mg/dl) and hepatic function (bilirubin < 2.0 upper normal limit, thransaminase $\leqslant$ 2.5 upper normal level in the absence of liver metastases or $\leqslant$5 if liver involvement was present) and no cardiovascular impairments. No prior chemotherapy was permitted. Patients had to be available to sign written informed consent; fertile women had to use an adequate contraceptive method. Exclusion criteria were the absence of measurable disease, previous chemotherapy, congestive heart failure, angina pectoris even if medically controlled, myocardial infarction, neurological or psychiatric disorders, past history of cancer (except adequately treated in situ cervical cancer and basal cell carcinoma), the presence of brain metastases and history of allergy. The presence of bone metastase as single site of disease was not permitted.

2.2. Study design and treatment regimen

This was a multicentre prospective phase II study conducted in six Italian centres.

The study protocol was approved by the Ethics Committee of each participating site.

The enrolled patients received the following treatment:

Epirubicin at 60 mg/m^2 in 100 ml saline solution on day 1.
Taxotere at 50 mg/m^2 in 500 ml saline solution on day 1.
Folinic acid at 100 mg/m^2 in 500 ml saline solution on days 1–2.
Fluorouracil at 400 mg/^{2} bolus on days 1–2.
Fluorouracil at 600 mg/m^2 continuos infusion on days 1–2.

Cycles were repeated every three weeks.

Prophylactic medication with dexhametasone 20 mg plus an anti-HT3 receptor inhibitor was administered before the infusion of chemotherapy.

Due to the expected haematologic toxicity, granulocyte-colony stimulating factor from day 6 to 10 was planned.

2.3. Efficacy parameters

The primary end-point of the study was the evaluation of the activity of the combination through the determination of the objective response (complete plus partial) rate according to Recist criteria.

The secondary end-points were time to progression (TTP), overall survival (OS) and safety of the combination.

2.4. *Dose-adjustment*

All adverse events were graded using NCI-CTC score (version 2).

In case of insufficient haematologic function at recycle, treatment was delayed for up to two weeks, until resolution and the drug dose was reduced at 40 mg/m^2 for epirubicin and 50 mg/m^2 for taxotere.

If there was no recovery, the treatment was discontinued.

In case of grade 3 non-haematologic toxicity, treatment was delayed for up to two weeks until resolution and the dose was reduced at 40 mg/m^2 for epirubicin and 50 mg/m^2 for taxotere.

If there was no recovery, the treatment was discontinued.

In case of grade 4 non-haematologic toxicity, treatment was permanently discontinued.

2.5. *Study visits and procedures*

Consenting patients were initially screened during the 15 days before starting treatment. During this period the following were recorded: complete medical history, physical examination with vital signs, weight, body surface and performance status, laboratory tests including blood cell count, serum creatinine level, hepatic function and marker (CEA and Ca19-9) values, concomitant medications. A complete cardiac evaluation (ECG and bi-dimensionally echocardiography) was performed during this period. Appropriate measurement of the tumour size by CT scan or MRI was realised at least 28 days before registration.

Before each cycle, a physical examination and a complete haematologic evaluation were conducted, and the toxicities occurring between the cycles were recorded.

Every three cycles, response to treatment was evaluated according to the same criteria as for the baseline evaluation.

At least three cycles were required to consider patients evaluable for activity whilst at least one cycle has to be performed for the evaluation of safety.

2.6. *Statistical analysis*

The statistical analysis was performed according to Simon's optimal two stage design.

At least three responses had to be observed amongst the first 14 enrolled patients to continue the enrollment up to 36 patients.

Time to progression was calculated from the start of treatment to the time of progression of disease, while overall survival was determined from the start of treatment to death.

Response rate was described with the confidence interval (CI) of 95%. All tests were a two-side formulation with an error of 5%.

3. Results

Forty-one patients were enrolled. Their main characteristics are listed in Table 1.

Table 1 – Main characteristics of patients

Enrolled	41
Sex M/F:	26/15
Age median	63
Range	44–73
PS median	80
Range	70–100
Site of disease	
T	17 (41%)
Liver	22 (54%)
Lymphonodes	13 (32%)
Other	24 (59%)
Histology	
Adenocarcinoma G2	7 (17%)
G3	23 (56%)
Gx	2 (5%)
Signet ring	6 (15%)
Carcinoma	3 (7%)
Single site	16 (39%)
Multiple site	25 (61%)

Table 2 – Response

Enrolled	41
Evaluable	38*
CR	5 (13%)
PR	9 (24%)
SD	9 (24%)
PRO	15 (39%)
ORR	14/38 (37%)
TGCR	23/38 (61%)

* One refused to continue after the 1st cycle not for toxicity; one excluded for haematologic toxicity; one excluded for IMA.

There were 26 males and 15 females; the median age was 63 yrs (range 44–73); the median performance status was 80 (range 70–100). With regard to hystology, there were 23 poorly differentiated and seven moderately differentiated adenocarcinomas, six signet ring cells and five undefined carcinoma. The main sites of disease were liver 22 (54%), primary tumour 17 (41%) and lymph-nodes 13 (32%); multiple sites were 25 (61%) while 16 (39%) patients had only one site of disease.

Thirty-eight patients were evaluable for activity. Three patients were not evaluable: one because refused to continue not for toxicity, one was excluded for haematologic toxicity (neutropenia G4) and one for the appearance of an acute myocardial ischaemia.

Amongst the 38 evaluable patients, five CR (13%) (95% CI: 0–24%) and nine PR (24%) (95% CI: 10–38%) were observed for an ORR of 14/38 (37%) (95% CI: 22–52%). Additionally, nine SD (24%) and 15 PRO were observed for a tumour growth control rate (TGCR) of 23/38 (61%) (Table 2).

The median time to progression was 4 months (Fig. 1) while the median overall survival was 9 months (Fig. 2).

The treatment was well-tolerated (Table 3). The main grade III–IV haematologic toxicities were leucopenia 7%, neutropenia 5% and anaemia 5%, while non-haematologics were diarrhoea 2%, alopecia 48% and cardiac 2%. Mild nausea/vom-

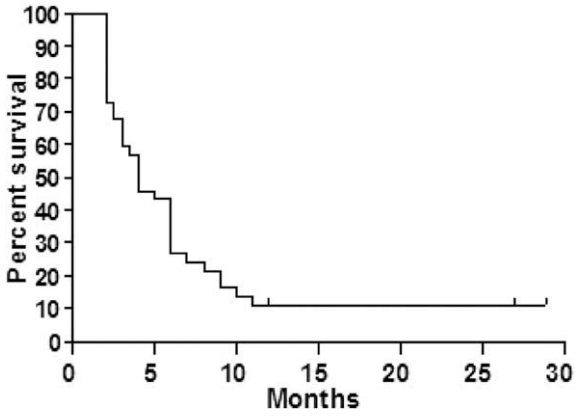

Fig. 1 – Time to progression.

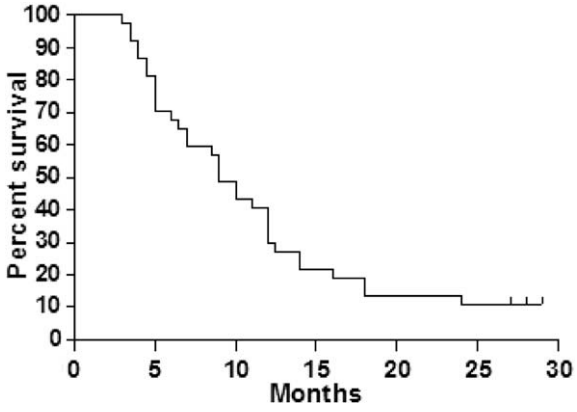

Fig. 2 – Overall survival.

Table 3 – % main toxicity

Toxicity	Grade	
	I–II (%)	III–IV (%)
Nausea/vomiting	61	–
Diarrhoea	44	2
Mucositis	36	–
Aneamia	41	5
Leukopenia	29	7
Neutropenia	15	5
Thrombocytopenia	10	–
Alopecia	36	48
Fever	10	–
Cardiac	–	2

NB: Use of GCS-F from day 6 to 10.

iting, mucositis and diarrhoea were observed in 61%, 36% and 44%, respectively.

4. Discussion

Gastric cancer is considered a chemo-responsive tumour. Many regimens have been employed in the treatment of advanced disease but none of them can be considered as standard. In the past years, different combinations, such as FAM or FAMTX, were considered as reference but in well conducted phase III trials their activity in terms of response rate was less than 30% with no impact on overall survival.[6,26]

Regimens containing cisplatin such as ECF or CF obtained, also in a recent experience,[27,28] higher percentage of responses and are now widely employed in USA and Europe. The recent introduction of taxotere in the clinical practice increased the armamentarium of medical oncologists and phase II and III trials employing taxotere-based regimens obtained about 50% of responses. In a randomised phase II trial comparing TCF versus TF versus ECF, TCF obtained better response rate than the others (36.6% versus 18.5% versus 25%, respectively) and a slightly better survival than ECF (10.4 versus 8.3 months).[29] So also TCF is considered one of the standard treatments in advanced disease. Hovewer this combination is characterised by a substantial toxicity mainly haematologic, due to the combination of TXT and CDDP, and is considered a treatment requiring a selection of patients' population to treat. [30,31]

In our study, we explored the activity and safety of a taxotere-based three-drug combination with the substitution of CDDP instead of epirubicin. The observed response rate of 37% is interesting especially if we consider the unfavourable characteristics of the enrolled patients with respect to the histologic pattern of poorly differentiated or signet ring cell carcinomas, two kinds traditionally considered poorly responsive to treatment, involving more than 70% of patients, the presence of primary tumour in about 40% and multiple sites of disease in about 60% of population.

Another interesting aspect is the high percentage of complete responses, one of the best reported in the literature. If this high rate of complete response will be confirmed in future phase III trials, this combination could be considered as a good option in the adjuvant setting.

The median TTP of 4 months was similar to that reported in a phase II trial that employed epirubicin and taxotere without fluorouracil[32] with an OS slightly inferior (9 versus 12 months); however, in our study the response rate was better (37% versus 19.4%) and similar to the 34% reported in another trial employing the same combination of TXT + EPI + FU,[33] so emphasising the role of FU in the treatment of AGC.

At the time when our study was designed, few data were reported about second-line treatments in advanced disease. Only recently, it has been stated that metastatic disease can be treated with a large choice of regimens and that patients with good performance status can be treated with the effective second-line treatment.[34] Our previous experience with the combination of irinotecan (CPT-11) plus MMC as salvage therapy in advanced gastric cancer confirms this consideration.[35] So future trials should be conducted, planning effective second-line options.

With regard to the toxicity profile, the combination was well-tolerated. No toxic death was observed and only two patients were not evaluable due to toxicity: one cardiac event and one severe neutropenia. Globally, grade III–IV haematologic toxicities were observed in less than 10% of patients' population and limited to neutropenia (5%) and anaemia (5%). These side-effect rates are inferior to those reported in a similar experience employing TXT plus EPI plus FU The low rate of neutropenia was certainly due to the prophylactic

use of colony-stimulating factors. Also grade III–IV non-haematologic toxicities were low and limited to diarrhoea (2%), hair-loss (48%) and cardiac event (2%).

In conclusion, the triple-drug combination of taxotere, epirubicin and fluorouracil is active and well-tolerated first-line combination in AGC patients. However, more studies need to better clarify its role in the treatment of this carcinoma.

Conflict of interest statement

None declared.

REFERENCES

1. Hisarnishi S. Screening for gastric cancer. *World J Surg* 1989;**13**:31–7.
2. Murad AM, Santiago FF, Petroianu A, et al. Modified therapy with 5-fluorouracil, doxorubicin and methotrexate in advanced gastric cancer. *Cancer* 1993;**72**:37–41.
3. Pyrhonen S, Kuitunen T, Nyandoto P, et al. 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.
4. Scheithauer W, Kornek G, Hejna M, et al. Palliative chemotherapy versus best supportive care in patients with metastatic gastric cancer: a randomized trial. *Ann Hematol* 1994;**73**(Suppl. 2) [abstract A181].
5. 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**:1–6.
6. Kim NK, Park YS, Heo DS, et al. A phase III randomized study of 5-fluorouracil and cisplatin versus 5-fluorouracil, doxorubicin and mitomycin-c versus 5-fluorouracilo alone in the treatment of advanced gastric cancer. *Cancer* 1993;**71**(12):3813–8.
7. Webb A, Cunningham D, Scarffe JH, et al. Randomized trial comparing epirubicin, cisplatin and fluorouracil versus fluorouracil, doxorubicin and methotrexate in advanced esophagogastric cancer. *J Clin Oncol* 1997;**15**(1):261–7.
8. Ross P, Nicolson M, Cunningham D, et al. Prospective randomized trial comparing mitomycin, cisplatin and protracted venous-infusion fluorouracil (PVI 5-FU) with epirubicin, cisplatin and PVI 5-FU in advanced esophagogastric cancer. *J Clin Oncol* 2002;**20**(8):1996–2004.
9. Wagner AD, Grothe W, Haerting J, et al. Chemotherapy in advanced gastric cancer: a systematic review and meta-analysis based on aggregate data. *J Clin Oncol* 2006;**24**(18):2903–9.
10. Tanaka M, Obata T, Sasaki K, et al. Evaluation of antitumor effects of docetaxel (Taxotere) on human gastric cancers in vitro and in vivo. *Eur J Cancer* 1996;**32A**:226–30.
11. Francis PA, Rigas JR, Kris MG, et al. Phase II trial of docetaxel in patients with stage III and IV non-small cell lung cancer. *J Clin Oncol* 1994;**12**:1232–7.
12. Verweij J, catimel G, Sulkes A, et al. Phase II studies of docetaxel in the treatment of various solid tumors. EORTC Soft Tissue and Bone Sarcoma Group. *Eur J Cancer* 1995;**31A**(Suppl. 4):S21–24.
13. Maeda S, Sugiura T, Saikawa Y, et al. Docetaxel enhances the cytotoxicity of cisplatin to gastric cancer cells by modification of intracellular platinum metabolism. *Cancer Sci* 2004;**95**(8):679–84.
14. Egawa T, Kubota T, Suto A, et al. Docetaxel enhances the cytotoxicity of anthracyclines by increasing intracellular drug accumulation. *Oncol Rep* 2002;**9**(4):777–81.
15. Sulkes A, Smyth J, Sessa C, et al. Docetaxel (taxotere) in advanced gastric cancer: results of a phase II clinical trial. EORTC Early Clinical Trials Group. *Br J Cancer* 1994;**70**:380–3.
16. Einzing AI, Neuberg D, Remick SC, et al. Phase II trial of docetaxel (taxotere) in patients with adenocarcinoma of the upper gastrointestinal tract previously untreated with cytoxic chemotherapy: the Eastern Cooperative Oncology Group (ECOG) results of protocol E1293. *Med Oncol* 1996;**13**: 87–93.
17. Mavroudis D, Kourousis C, Androlakis N, et al. Frontline treatment of advanced gastric cancer with docetaxel and granulocyte colony-stimulating factor (G-CFS): a phase II trial. *Am J Clin Oncol* 2000;**23**:341–4.
18. Bang YJ, Kang WK, Kang YK, et al. Docetaxel 75 mg/m^2 is active and well tolerated in patients with metastatic or recurrent gastric cancer: a phase II trial. *Jpn J Clin Oncol* 2002;**32**:248–54.
19. Vanhoefer U, Wilke H, Harstrick A, et al. Phase II study of docetaxel as second line chemotherapy (CT) in metastatic gastric cancer. *Proc Am Soc Cklin Oncol* 1999;**18**:1163 [abstract].
20. Taguchi T, Sakata Y, Kanamuru R, et al. Late phase II clinical study of RP56976 (docetaxel) in patients with advancer/ recurrent gastric cancer: a Japanese Cooperative Study Group Trial (Group A). *Gan To Kagatu Ryoho* 1998;**25**:1915–24.
21. Giuliani F, Gebbia V, De Vita F, et al. Docetaxel as salvage therapy in advanced gastric cancer: a phase II study of the Gruppo Oncologico Italia Meridionale (GOIM). *Anticancer Res* 2003;**23**(5b):4219–22.
22. Roth A, Mainbach R, Martinelli G, et al. Docetaxel (taxotere)-cisplatin (TC): an effective drug combination in gastric carcinoma. Swiss Group for Clinical Cancer Research (SAKK) and the European Institute Oncology (EIO). *Ann Oncol* 2000;**11**(3):301–6.
23. Roth A, Mainbach R, Falk S, et al. 5-Fluorouracil as protracted continuous intravenous infusion can be added to full-dose docetaxel (taxotere)-cisplatin in advanced gastric carcinoma: a phase I–II trial. *Ann Oncol* 2004;**15**(5):759–64.
24. Ajani JA, Fodor MB, Tjulandin SA, et al. Phase II multi-institutional randomized trial of docetaxel plus cisplatin with or without fluorouracil in patients with untreated, advanced gastric or gastroesophageal adenocarcinoma. *J Clin Oncol* 2005;**23**(24):5660–7.
25. 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**(31):4991–7.
26. Vanhoefer U, Rougier P, Wilke H, et al. Final results of a randomized phase III trial os sequential high-dose metotrexate, fluorouracil and doxorubicin versus etoposide, leucovorin and fluorouracil versus infusional fluorouracil and cisplatin in advanced gastric cancer: a trial of the European Organization for Research and Treatment of Cancer Gastrointestinal Tract Cancer Cooperative Group. *J Clin Oncol* 2000;**18**(14):2648–57.
27. Lutz M, Wilke H, Wagener T, et al. Weekly infusional high-dose fluorouracil (HD-FU), HD-FU plus folinic acid (HD-FU/FA), or HD-FU/FA plus biweekly cisplatin in advanced gastric cancer: randomized phase II trial 40953 of the European Organisation for Research and the Treatment of Cancer Gastrointestinal Group and the Arbeitgemeinschaft Internistiche Onkologie. *J Clin Oncol* 2007;**25**:2580–5.
28. Ohtsu A, Shimada Y, Shirao K, et al. Randomized phase III trial of fluorouracil alone versus fluorouracile plus cisplatin versus uracil and tegafur plus mitomycin in patients with

unresectable, advanced gastric cancer: the Japan Clinical Oncology Group Study (JCOG9205). *JCO* 2003;**21**:54–9.
29. Roth A, Fazio N, Stupp R, et al. Docetaxel, cisplatin and fluorouracil; docetaxel and cisplatin; and epirubicin, cisplatin, and fluorouracil as systemic treatment for advanced gastric carcinoma: a randomized phase II trial of the Swiss Group for Clinical Cancer Research. *J Clin Oncol* 2007;**25**(22):3217–23.
30. Ilson DH. Docetaxel, cisplatin and fluorouracil in gastric cancer: does the punishment fit the crime? *JCO* 2007;**25**(22):3188–90.
31. van Cutsem E, van de Velde C, Rothe A, et al. Expert opinion on management of gastric and gastro-oesophageal junction adenocarcinoma on behalf of the European Organisation for Research and Treatment of Cancer (EORTC) – Gastrointestinal Cancer Group. *Eur J Cancer* 2008;**44**:182–94.
32. Nguyen S, Rebischung C, van Ongeval, et al. Epirubicin-docetaxel in advanced gastric cancer: two phase II studies as second and first line treatment. *Bull Cancer* 2006;**93**(1).. E1-6.
33. Murad AM, Ninholas J, Skare M, et al. A phase II multicentric trial of docetaxel (taxotere), 5-fluorouracil (5-FU) and epirubicin (EPI) in previously untreated advanced gastric cancer: a novel and effective regimen. *Proc Asco*:21. [abstract 650].
34. Roth AD. Multimodal management of metastatic gastric and oesophageal cancer. In: ASCO 40th annual meeting, educational book; 2004. p. 199–204.
35. Giuliani F, Molica S, Maiello E, et al. Irinotecan (CPT-11) and Mitomycin-C (MMC) as second-line therapy in advanced gastric cancer: a phase II study of the Gruppo Oncologico dell' Italia Meridionale (prot. 2106). *Am J Clin Oncol* 2005;**28**(6):581–5.