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Capecitabine, epirubicin and cisplatin in the treatment of oesophagogastric adenocarcinoma

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ABSTRACT

Background: Inoperable or metastatic oesophagogastric adenocarcinoma has a poor prognosis. From the many different chemotherapeutic regimens used in the past, a combination of epirubicin, cisplatin and continuous 5-fluorouracil infusion (ECF) showed a consistent response rate of ± 50% with acceptable toxicity. Continuous 5-FU infusion may be replaced by oral fluoropyrimidines. Here we evaluate treatment with epirubicin and cisplatin combined with oral capecitabine (ECC), replacing intravenous 5-FU infusion.

Methods: Retrospectively, we analysed 23 consecutive patients who were treated with epirubicin, cisplatin and oral capecitabine for inoperable or metastatic oesophagogastric adenocarcinoma during 2002 and 2003.

Results: The overall response rate was 57%; another 26% achieved stable disease and only 17% had progressive disease. The median duration of response was 6.4 months; the median survival was 9.0 months. Previously treated patients (n=10) had a significantly worse overall response rate (20%) compared with previously untreated patients (85%). A nonsignificant difference in median survival was found between these groups (3.9 *vs* 9.8 months in previously treated *vs* untreated patients). An acceptable incidence of grade 3 and 4 toxicity was found.

Conclusion: Capecitabine in combination with epirubicin and cisplatin is an effective and safe alternative to ECF, without the risks of a continuous venous access.

KEYWORDS

Capecitabine, chemotherapy, inoperable, metastatic oesophagogastric carcinoma

INTRODUCTION

Adenocarcinoma of the distal oesophagus and stomach often presents at a late stage with locally advanced or metastatic disease, which explains the poor prognosis. The incidence of oesophageal adenocarcinoma and cancer originating at the gastro-oesophageal junction is rising, in contrast to oesophageal squamous cell carcinoma and the even declining incidence of distal gastric cancer.[1-3]

The tumour readily spreads to adjacent, mediastinal and supraclavicular lymph nodes, peritoneum, liver, lungs and pleura. Only a minority of patients with oesophageal or gastric cancer is considered for curative resection and even then, there is high rate of local or metastatic recurrence, resulting in an overall five-year survival of less then 10%.[1,2] The local extension of the disease can be measured with CT scan and endoscopic ultrasound. Chemotherapy with single agents has a limited response rate in advanced oesophagogastric cancer. Many former reference regimens such as FAM (5-FU, adriamycin and mitomycin) and FAMTX (5-FU, adriamycin and methotrexate) have fallen into disregard, as the initial response rates of 40 to 50% were only 10 to 20% in confirmatory phase III trials.[4-6] A general phenomenon in comparative studies is a survival of 9 to 11 months for the 'best' regimen *vs* six to seven months for the 'former best' regimen, but a mere three to five months with best supportive care only.[7] This story has been somehow repeated with the ECF regimen, although this regimen has consistently shown a response rate of ± 50% and limited toxicity.

The ECF regimen was developed because of the single-agent activity of epirubicin, cisplatin and 5-FU and the synergy between 5-FU and cisplatin in experimental models.[8] An anthracycline was added to enhance cytotoxicity; epirubicin was preferred to minimise side effects in terms of mucositis and cardiac toxicity. The

choice for continuous venous infusion of 5-fluorouracil was based on the data of an enhanced response rate and less bone marrow toxicity in colorectal cancer.[9] The first phase II results showed an impressive response rate of 71%.[10] In a multicentre phase III study response rate was 45%, but still significantly superior to the 'reference' FAMTX regimen that showed only a 21% response rate. Toxicity data, time to progression and survival (8.9 months *vs* 5.7 months) were also all significantly in favour of the ECF regimen.[6,11] The high response rates and manageable toxicity, also with the venous access system, have been confirmed by others.[10,12-14]

With the introduction of oral 5-FU analogues an alternative for prolonged or continuous administration of intravenous 5-FU has become available. The oral fluoropyrimidine capecitabine has proven to be at least as effective as 5-FU with leucovorin in the treatment of metastatic colorectal and breast carcinoma.[15-17] The drug is absorbed rapidly from the intestine as an intact molecule and converted to 5-FU in the liver and tumour cells. Patients with colorectal cancer treated with capecitabine as compared with intravenous bolus of 5-FU showed significantly less grade 3-4 mucositis and neutropenia, but significantly more grade 3 hand-foot syndrome and uncomplicated grade 3-4 hyperbilirubinaemia.[15,16] A dose-finding study of epirubicin, cisplatin and capecitabine replacing infusional 5-fluorouracil has already been performed in patients with inoperable oesophagogastric cancer.[18]

We started to treat patients with locally advanced or metastatic adenocarcinoma of the oesophagogastric region with epirubicin and cisplatin in combination with oral capecitabine (ECC) instead of the previously used intravenous 5-FU (ECF-regimen). In this paper we describe the side effects as assessed by Common Toxicity Criteria (CTC), the efficacy or response rate of this treatment regimen, as well as the duration of response and the overall survival.

MATERIALS AND METHODS

We analysed retrospectively all the patients in our hospital who had started treatment with ECC for inoperable or metastatic oesophagogastric adenocarcinoma from January 2002 to December 2003. The ECC regimen was repeated every three weeks. Epirubicin and cisplatin were both given intravenously at day one at a dose of 50 mg/m^2 and 60 mg/m^2, respectively. Capecitabine was given at a dose of 1000 mg/m^2 twice daily for 14 days. Standard supportive care with an HT-3 antagonist plus dexamethasone as well as pre- and posthydration to prevent cisplatin-induced nephrotoxicity were used and required hospital admission for two days.

Data were collected concerning doses and dose adjustments, response to therapy, side effects, duration of response, and survival. Response to therapy was measured after every second or third cycle and at the end of treatment by means of CT, ultrasound, or X-rays. If the lesion could not be measured by X-ray, endoscopy was used. Response was defined according to RECIST criteria.[19] Toxicity was graded according to the USA National Cancer Institute CTC scale version 2.0. Nausea and vomiting, hand-foot syndrome, neuropathy, anaemia, leucopenia, thrombocytopenia, hyperbilirubinaemia, transfusions, infections, and hospital admissions were evaluated.

Duration of response was defined as the period from the first day of treatment until documented progression, while the duration of overall survival was defined as the period from the first day of treatment until death or end of follow-up.

Statistics

Survival data were examined using the Kaplan-Meier method. The log-rank test was used to test for between-group differences in survival. Between-group differences in proportions were compared using the χ^2 test.

RESULTS

Patient characteristics

During 2002 and 2003, 23 patients (19 men and 4 women) with inoperable or metastatic oesophagogastric adenocarcinoma were treated with ECC in our hospital. All patients had a World Health Organisation performance score of 0 to 2. A median of 5.5 courses (range 1 to 8) was delivered. Clinical data are presented in *table 1*. There was a male

Table 1. *Patient characteristics*

	Patients (n)	%
Male	19	83
Female	4	17
Median age (range), years	61 (42-71)	
Primary tumour site		
Distal oesophagus	6	26
Gastro-oesophageal junction	2	9
Gastric	15	65
Metastatic disease	20	87
Histology (differentiation)		
Adenocarcinoma		
Poor	7	30
Intermediate	7	30
Good	1	4
Unclassified	7	30
Nonspecified carcinoma	1	4
Previous treatment		
None	13	57
Resection	6	26
Radiation	1	4
Radiation with chemotherapy	3	13

predominance (83%). Twenty of 23 patients had metastatic disease. The six patients who had undergone previous resection, five with curative intent, presented from one month until 13 years (median 12 months) after operation.

Efficacy and survival

The response results are presented in *table 2*. Three patients had a complete response (CR) and ten patients a partial response (PR), resulting in an overall response rate of 57%. Another six patients (26%) had stable disease. Three patients could not be evaluated for response; two of them died shortly after their first course, and a third patient chose not to continue because his physical condition declined rapidly after the first cycle of chemotherapy. The median duration of response was 6.4 months; the median survival was 9.0 months (*figure 1*).

No relation between response and tumour location, or differentiation grade was found. However, there were differences in outcome in the previously treated group compared with the previously untreated group. In ten patients who had received treatment for their oesophagogastric carcinoma in the past (resection, brachytherapy or radiation plus cisplatin therapy in six, one and three patients, respectively), only two patients (one with a resection and the other with radiation plus chemotherapy in the past) achieved a partial response (20%). Compared with an overall response of 85% (3 CRs and 8 PRs) in the group of 13 patients who had not received previous therapy, this is a significant difference in response rate ($p<0.01$). Also a difference in median survival was found between the previously treated group (3.9 months) and the previously untreated group (9.8 months), however this difference was not significant ($p=0.39$), probably due to the small number of patients.

Adverse events

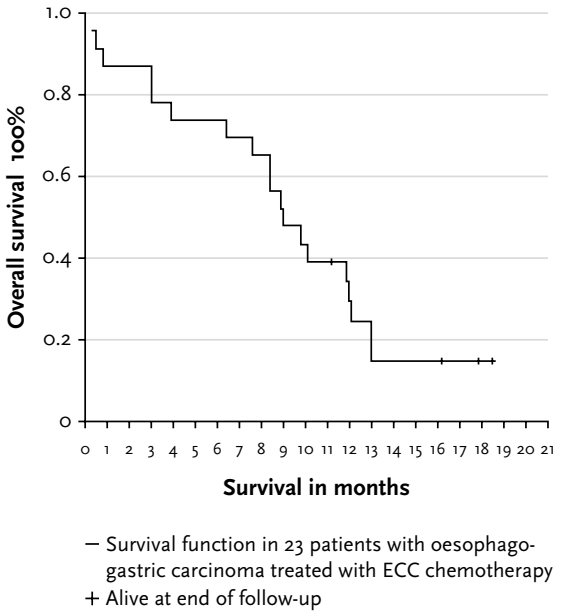
The adverse reactions are presented in *table 3*. Most side effects were mild, grade 1 or 2. Nausea was the most common side effect (n=15), but only one patient had grade 3-4 vomiting. Also, most haematological toxicity was of grade 1-2 severity. Serious haematological side effects were limited to grade 3-4 anaemia in two and leucopenia in four patients. The latter resulted in one period of febrile neutropenia. Erythrocyte transfusions were given to nine patients. Erythropoietin was not used. Miscellaneous infections (herpes simplex infection, rhinitis, bronchitis, wound infection, jaw abscess, and streptococcal bacteraemia) were reported in six patients, requiring hospitalisation in three of them. The wound infection developed during a period of grade 4 leucopenia; the abscess and bacteraemia with grade 1 leucopenia. Three other patients were admitted for treatment-related problems (nausea, dehydration and a brachial vein thrombosis).

Table 2. *Response rates in 23 patients with oesophagogastric carcinoma treated with ECC chemotherapy*

Response	Patients (n)	%
Overall response (CR and PR)	13	57
Complete response	3	13
Partial response	10	43
Stable disease	6	26
Progressive disease	4	17
Documented progression	1	4
Not evaluable	3	13
Total	*23*	*100*

ECC = a combination of epirubicin, cisplatin and oral capecitabine; CR = complete response; PR = partial response.

Figure 1. *Survival in 23 patients with oesophagogastric carcinoma treated with ECC chemotherapy*



ECC = a combination of epirubicin, cisplatin and oral capecitabine.

Shortly after the first course one patient died of a massive ischaemic cerebrovascular accident and another patient died probably due to massive pulmonary embolism.

Dose adjustments

Dose reduction was considered necessary in eight patients. In three this was due to hand-foot syndrome, in four because of nausea and/or vomiting, and in one because of neuropathy. Reductions were made after a median of three courses (range 3 to 6) resulting in administration of 96, 95 and 87% of intended epirubicin, cisplatin and capecitabine doses, respectively. Dose interruption took place in two patients for one and two weeks, because of nausea and hand-foot syndrome, respectively.

Table 3. *Adverse events in 23 patients with oesophagogastric carcinoma treated with ECC chemotherapy*

Toxicity*	Grade 1-2		Grade 3-4	
Nonhaematological	**Patients (n)**	**%**	**Patients (n)**	**%**
Nausea	15	65	1	4
Vomiting	4	17	1	4
Stomatitis	1	4	0	0
Diarrhoea	1	4	0	0
Hand-foot syndrome	5	22	2	9
Neuropathy	5	22	2	9
Hyperbilirubinaemia	1	4	0	0
Haematological				
Anaemia	7	30	2	9
Leucopenia	12	52	4	17
Thrombopenia	6	26	0	0
Red cell transfusion	7	30	2	9

*Toxicity was scored according to the NCI-CTC criteria. ECC = a combination of epirubicin, cisplatin and oral capecitabine.

DISCUSSION

Patients with locally advanced or metastatic adenocarcinoma of the distal oesophagus or stomach have a poor prognosis. Overall response rates of chemotherapeutic 'reference' regimens used in the past were 9 to 41%.[4,12,20] The ECF regimen is currently considered by many oncologists as the 'new reference' regimen, as the response rate in several phase II and phase III studies is consistently about 50% with acceptable toxicity.[6,10-14] However, because the continuous infusion of 5-FU by a port-a-cath may result in infection or thrombosis of the venous access, we changed the continuous 5-FU (200 mg/m²/day = 4200 mg/m²/cycle) into 14 days of capecitabine (1000 mg/m² twice daily = 14 x 2000 mg/m² per cycle), based on a phase I and pharmacokinetic study.[18]

Our results with the ECC regimen, showing a response rate of 57%, including a complete response rate of 13%, are well in line with previous results obtained with the ECF regimen. In two studies in 111 and 220 evaluable patients, the overall response rates were 45 and 61% with CR rates of 6 and 11%.[6,21] Apart from the overall response rate of 57%, a stable disease rate of 26% may also be of significance provided symptomatic benefit and a low rate of toxicity is observed. In our six patients with stable disease symptomatic benefit was observed in four and significant toxicity was seen in two. Only 17% of patients had progressive disease during treatment.
The median duration of response in this retrospective analysis was 6.4 months and comparable with the data obtained with the ECF regimen.[6,21] This was measured once patients were again symptomatic and not by routine imaging examination. The median survival time of nine months, on the other hand, could be determined accurately, showing a similar survival, compared with studies using the ECF regimen. The study by Bamias *et al.* reported an overall survival of 8.4 months with 6.2 months failure-free survival.[21] Webb *et al.* found a median survival time of 8.9 months with ECF and median failure-free survival duration of 7.4 months.[6] From trials from the early 1990s, the median survival in untreated patients has shown to be three months.[7]

An acceptable incidence of grade 3 and 4 toxicity was found. The primary toxicity was nausea with mainly grade 1-2 severity. More severe nausea and vomiting was reported in just one patient. Most patients suffering from nausea and/or vomiting had these side effects every first week of a treatment cycle. In the future the incidence of severe nausea can possibly be lowered further by administration of new antiemetics such as the NK-1 antagonist aprepitant.[22]
In studies comparing intravenous 5-FU with capecitabine in the treatment of colorectal cancer, 5-FU bolus treatment showed significantly more stomatitis (grade 3-4: 12 to 13.3% *vs* 1.3 to 2%) and grade 3-4 leucopenia (9.7 to 26% *vs* 2 to 2.4%), with leucopenic fever and sepsis (1 to 3% *vs* 0 to 0.3%). On the other hand capecitabine-treated patients suffered significantly more grade 3 hand-foot syndrome (16.2 to 18% *vs* 0.3 to 0.6%) and hyperbilirubinaemia (18.6 to 28.3% *vs* 5.9 to 6.6%).[15,16]
Our data also show a low incidence of stomatitis reported in only one patient. Seven patients developed hand-foot syndrome of which two (9%) severe (grade 3). In all cases it responded to interruption or dose reduction. Overall the doses given were only slightly limited. Remarkably, we did not find hyperbilirubinaemia in our patient group. A possible explanation is the lower capecitabine dose used in ECC: 1000 mg/m² twice daily *vs* 1250 mg/m² twice daily in monotherapy for colorectal carcinoma.

Haematological toxicity grade 3-4 occurred in 17% of patients. In four patients (17%) grade 3-4 leucopenia was found. Only one episode of febrile neutropenia occurred. Two possible treatment-related deaths occurred. Both were due to a thromboembolic event, which has a higher incidence in patients undergoing chemotherapy, especially cisplatin-based.[23,24] Our toxicity data are comparable to the literature.[18]

If equal response rate is to be expected, 89% of patients prefer oral therapy.[25] Considering the fact that the treatment is mostly palliative, patient comfort is of high value. With the ECF regimen a continuous intravenous access was necessary. Apart from the possible complications this is highly uncomfortable since patients, even though treated at home, are hindered. Potential disadvantages of oral administration are patient noncompliance, unpredictable gastrointestinal absorption, and not being able to take the tablets due to stenosis, for example. Our patient compliance was not investigated. Pharmacokinetic studies have shown good absorption profiles, but no separate data for patients with or without gastric resection were provided.[18,26] Although problems in taking oral medication are of special concern in patients with tumours of the oesophagus or cardia, in clinical practice this hardly ever occurs. One patient at first took only smaller 150 mg tablets during the first two courses, until after response he could continue with the 500 mg tablets.
A difference in response with regard to previously treated patients compared with untreated patients was found. Although the numbers are small, untreated patients had significantly better results and also seem to have a (nonsignificantly) better survival. A possible explanation could be a difference in performance status at the time of detection of the recurrence, because a worse performance status is associated with a poor response to chemotherapy. In our patient group we could not confirm this, nor did we find other prognostic factors, but it is likely that the number of patients was too small for a significant difference to be found.
A median survival over 12 months is still a major obstacle in chemotherapeutic regimens in locally advanced and metastatic oesophagogastric cancer, despite an initial response rate of ±50% in various regimens. Symptomatic benefit of symptoms due to metastatic or recurrent disease occurs in over 90% of patients within one or two cycles of chemotherapy, enabling appropriate selection of patients in which continuation of palliative chemotherapy is worthwhile.

With ECF treatment Bamias *et al.* and Webb *et al.* found a higher response rate in patients with locally advanced disease. A potential curative resection was performed in 66 to 75% of responders undergoing surgery.[6,21] This interesting development is gaining more support. Other studies have described preoperative chemotherapy using the ECF regimen where some of the patients with locally advanced disease underwent resection with curative intent if a good tumour response occurred with chemotherapy.[14] In our patient group three patients had locally advanced disease, all located in the oesophagus. Two achieved a partial response; the other had stable disease. The former underwent surgery. A potential curative resection was performed in both. After follow-up of 16.2 and 18.5 months no sign of recurrence has been found. Thus, for a select group of patients ECC can be considered as down-staging chemotherapy. The role of neoadjuvant chemotherapy is not yet established, but an increased disease-free survival has recently been reported.[27]

In conclusion, capecitabine in combination with epirubicin and cisplatin (ECC) appears to be an effective, safe and more comfortable alternative to ECF considering the high response rate and few complications, without the need of a continuous intravenous access with the risk of infection and thrombosis. A larger, phase 2 study is currently being executed to further analyse these results.

REFERENCES

1. Blot WJ, Devesa SS, Kneller RW, Fraumeni JF. Rising incidence of adenocarcinoma of the oesophagus and gastric cardia. JAMA 1991;265:1287-9.
2. Schroy P. Gastric cancer: pathology, pathogenesis, and risk factors. ©2004 UpToDate® version 12.3.
3. Bonis PA, Sampliner RE. Epidemiology, pathobiology, and clinical manifestations of oesophageal cancer. ©2004 UpToDate® version 12.3.
4. Wils JA, Klein HO, Wagener DJ, et al. Sequential high-dose methotrexate and fluorouracil combined with doxorubicin – a step ahead in the treatment of advanced gastric cancer: a trial of the European Organization for Research and Treatment of Cancer Gastrointestinal Tract Cooperative Group. J Clin Oncol 1991;9:827-31.
5. Kelsen D, Atiq OT, Saltz L, et al. FAMTX versus etoposide, doxorubicin, and cisplatin: a random assignment trial in gastric cancer. J Clin Oncol 1992;10:541-8.
6. Webb A, Cunningham D, Scarffe JH, et al. Randomized trial comparing epirubicin, cisplatin, and fluorouracil versus fluorouracil, doxorubicin, and methotrexate in advanced oesophagogastric cancer. J Clin Oncol 1997;15:261-7.
7. 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.
8. Etienne MC, Bernard S, Fischel JL, et al. Dose reduction without loss of efficacy for 5-fluorouracil and cisplatin combined with folinic acid. In vitro study on human head and neck carcinoma cell lines. Br J Cancer 1991;63:372-7.
9. Lokich JJ, Ahlgren JD, Gullo JJ, Philips JA, Fryer JG. A prospective randomized comparison of continuous infusion fluorouracil with a conventional bolus schedule in metastatic colorectal carcinoma: a Mid-Atlantic Oncology Program Study. J Clin Oncol 1989; 7:425-32.
10. Findlay M, Cunningham D, Norman A, et al. A phase II study in advanced gastro-oesophageal cancer using epirubicin and cisplatin in combination with continuous infusion 5-fluorouracil (ECF). Ann Oncol 1994;5:609-16.
11. Waters JS, Norman A, Cunningham D, et al. Long-term survival after epirubicin, cisplatin and fluorouracil for gastric cancer: results of a randomized trial. Br J Cancer 1999;80:269-72.

12. Kyoto Research Group for Chemotherapy of Gastric Cancer. A randomized, comparative study of combination chemotherapies in advanced gastric cancer: 5-fluorouracil and cisplatin (CP) versus 5-fluorouracil, cisplatin, and 4'-epirubicin (FPEPIR). Anticancer Res 1992;12:1983-8.

13. Zaniboni A, Barni S, Labianca R, et al. Epirubicin, cisplatin, and continuous infusion 5-fluorouracil is an active and safe regimen for patients with advanced gastric cancer. An Italian Group for the Study of Digestive Tract Cancer (GISCAD) report. Cancer 1995;76:1694-9.

14. Geh JI, Glynne-Jones R, Kwok QS, et al. Preoperative ECF chemotherapy in gastro-oesophageal adenocarcinoma. Clin Oncol 2000;12:182-7.

15. Scheithauer W, McKendrick J, Begbie S, et al. Oral capecitabine as an alternative to i.v. 5-fluorouracil-based adjuvant therapy for colon cancer: safety results of a randomized phase III trial. Ann Oncol 2003;14:1735-43.

16. Van Cutsem E, Twelves C, Cassidy J, et al. Oral capecitabine compared with intravenous fluorouracil plus leucovorin in patients with metastatic colorectal cancer: results of a large phase III study. J Clin Oncol 2001;19(21):4097-106.

17. O'Shaughnessy J, Miles D, Vukelja S, et al. Superior survival with capecitabine plus docetaxel combination therapy in anthracycline-pretreated patients with advanced breast cancer: phase III trial results. J Clin Oncol 2002;20:2812-23.

18. Evans TR, Pentheroudakis G, Paul J, et al. A phase I and pharmacokinetic study of capecitabine in combination with epirubicin and cisplatin in patients with inoperable oesophago-gastric adenocarcinoma. Ann Oncol 2002;13(9):1469-78.

19. Therasse P, Arbuck S, Eisenhauer E, et al. New guidelines to evaluate the response to treatment in solid tumors. J Nat Cancer Inst 2000;92(3):205-16.

20. Vanhoefer U, Rougier P, Wilke H, et al. Final results of a randomized phase III trial of sequential high-dose methotrexate, 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;18:2648-57.

21. Bamias A, Hill M, Cunningham D, et al. Epirubicin, Cisplatin and protracted venous infusion of 5-fluorouracil for oesophagogastric adenocarcinoma: response, toxicity, quality of life, and survival. Cancer 1996;77:1978-85.

22. De Wit R, Herrstedt J, Rapoport B, et al. Addition of the oral NK1 antagonist aprepitant to standard antiemetics provides protection against nausea and vomiting during multiple cycles of cisplatin-based chemotherapy. J Clin Oncol 2003;21:4077-80.

23. Shlebak AA, Smith DB. Incidence of objectively diagnosed thromboembolic disease in cancer patients undergoing cytotoxic chemotherapy and/or hormonal therapy. Cancer Chemother Pharmacol 1997;39:462-6.

24. Czaykowski PM, Moore MJ, Tannock IF. High risk of vascular events in patients with urothelial transitional cell carcinoma treated with cisplatin based chemotherapy. J Urol 1998;160:2021-4.

25. Liu G, Franssen E, Fitch MI, Warner E. Patients preferences for oral versus intravenous palliative chemotherapy. J Clin Oncol 1994;12:14-20.

26. Malet-Martino M, Martino R. Clinical studies of three oral prodrugs of 5-fluorouracil (capecitabine, UFT, S-1): a review. Oncologist 2002;7(4):288-323.

27. Allum W, Cunningham D, Weeden S, et al. Perioperative chemotherapy in operable gastric and lower oesophageal cancer: A randomised, controlled trial (the MAGIC trial). J Clin Oncol 2003;22:249 abstr 998.