

Original article

Phase II study of Epirubicin, Cisplatin and Capecitabine as Neoadjuvant chemotherapy for resectable gastric and gastroesophageal junction cancer

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article**INTRODUCTION**

Gastric cancer is the fourth most common cancer in the world with an annual incidence of approximately one million¹. In the UK, there are an estimated 7,700 new diagnoses and 5,200 deaths from the disease each year². Over the past two decades there has been a change in the anatomical subsite distribution of gastric cancer, with a trend for tumours to develop more in the proximal stomach, especially around the gastric cardiac area rather than the distal part of the stomach³. It is thought that the lower oesophageal tumours may also be associated with an increasing incidence of gastro-oesophageal reflux disease⁴. In spite of a

declining incidence of the distal stomach cancer in the Western countries over the past decades, the incidence of adenocarcinoma of the lower esophagus and the gastroesophageal junction has dramatically increased in the world⁵. Early-stage gastric and gastroesophageal cancers are curable with surgical treatment alone, with a 5-year overall survival rate of 90%. However, the majority of gastric and gastroesophageal cancer patients are diagnosed with advanced diseases (stages III or IV)⁶.

Despite advances in cancer management, gastric cancer continues to remain a challenging disease to

treat. Almost one million new cases and over 738,000 deaths occur from gastric cancer every year, making it the fourth most common malignancy and second most common cause of cancer related death in the world⁷. A marked geographical variation exists, with more than 70% of cases occurring in developing countries and majority being in Eastern Asia⁷. In the Western world gastric cancer is often diagnosed at an advanced stage, in contrast to Japan where patients are more commonly diagnosed at an early stage probably due to an established gastric cancer screening program⁸. Radical surgery is the only modality that can lead to potential cure for localised disease however most patients will relapse post curative resection with loco-regional or metastatic disease leading to poor overall survival^{9,10}. Various multimodality approaches using chemotherapy, radiation or a combination of both have been evaluated in the last few decades in an attempt to improve outcomes post surgery.

Although adjuvant chemotherapy has demonstrated improved survival from gastric cancer, it is challenging to use it in most patients. Often post major surgery such as total gastrectomy, there can be long delays before patients are fit enough to start adjuvant chemotherapy, thus a number of patients are unable to have any post operative treatment, potentially leaving behind untreated micro-metastatic disease. Therefore, neoadjuvant chemotherapy has also been evaluated in gastric cancer as in general, it is much better tolerated than adjuvant chemotherapy, leading to a greater proportion of patients being able to have systemic treatment¹¹. Additionally, the usage of neoadjuvant chemotherapy may lead to downsizing of the tumour which may facilitate a curative resection in a greater proportion of patients. With this in mind, the EORTC 40954 study (n = 144) evaluated the role of neoadjuvant chemotherapy in early gastric cancer however, the trial was closed early due to poor accrual¹². An increased rate of R0 resection was seen (81.9% versus 66.7%, $P = 0.036$) with the use of neoadjuvant chemotherapy but this did not translate into a benefit in overall survival (hazard ratio, 0.84; 95% CI, 0.52–1.35; $P = .466$). Given the lack of supporting data, at this stage a purely neoadjuvant chemotherapeutic strategy should not be used in early gastric cancer.

The TNM staging classification dictates the subsequent management of a gastric tumour. Primary resection of the malignant tumour is the standard treatment for operable disease. In the Western world, most patients with gastric cancer present with advanced stages of disease, leading to a low 5-year survival of around 25%^{7,8}. After surgical resection, the majority of patients will develop a locoregional recurrence⁹. Many different strategies have been evaluated to improve

the outcome of gastric cancer surgery. Randomized trials investigating the role of a more extended lymph node dissection (D2) in comparison with the standard D1 lymphadenectomy, found no difference in overall survival, while a D2 dissection was associated with increased postoperative mortality and morbidity^{10, 13-15}.

Two Western studies have changed current clinical practice in the treatment of resectable gastric cancer. The Intergroup 0116 study showed a significant benefit in overall survival with adjuvant chemoradiotherapy (CRT) consisting of 45 Gy of radiotherapy combined with fluorouracil (5-FU), and leucovorin, compared to surgery alone¹⁰. The phase III UK Medical Research Adjuvant Gastric Cancer Study (MAGIC) randomised 503 patients with resectable adenocarcinoma of the stomach, oesophago-gastric junction (OGJ), or lower oesophagus to either perioperative chemotherapy and surgery or surgery alone⁹. All patients were planned to receive three cycles of preoperative ECF (Intravenous epirubicin 50 mg/m² and cisplatin 60 mg/m² on day 1, and a continuous infusion of 5-fluorouracil 200 mg/m²day for 21 days) chemotherapy and three cycles of the same chemotherapy after surgery. At a median follow up of 4 years, the addition of perioperative chemotherapy demonstrated a significant improvement in progression-free survival (HR 0.66; 95% CI, 0.53–0.81; $P < 0.001$) and overall survival (HR, 0.75; 95% CI, 0.60–0.93; $P = 0.009$; five-year survival rate, 36% vs 23%). Importantly, the addition of preoperative chemotherapy did not increase complications from surgery and similar rates of postoperative morbidity and 30-day mortality were seen in both arms. In comparison to the surgery alone arm, a significantly higher proportion of patients treated with chemotherapy had curative resections (as deemed by the surgeon; 79.3% vs 70.3%; $P = 0.03$) and were also found to have significantly smaller tumours and lower nodal burden at surgery. There was no heterogeneity of treatment effect according to the site of primary tumour (stomach, GOJ or lower oesophagus). Although 91% of patients were able to complete 3 cycles of preoperative treatment, only 50% could complete all postoperative treatment, thereby highlighting the challenges involved in administering chemotherapy after radical gastric surgery.

In many countries neoadjuvant chemoradiotherapy is the standard of care for operable disease. The neoadjuvant therapy is used to decrease the tumour bulk and improve the rate of complete surgical clearance following resection, with the aim of improving survival and reducing risk of tumour recurrence. The evaluation of histological changes in the tumour resection specimen is a method of assessing response to neoadjuvant therapy, and there is evidence that histological response reflects on survival¹⁰.

PATIENTS AND METHODS

Patient population and Eligibility criteria:

Twenty five patients with resectable gastric or gastroesophageal junction cancer were enrolled in this study in the period between January 2012 and January 2013 with following inclusion criteria: Ib-III (no distant metastases) gastric cancer (histologically proven); tumor bulk has to be in the stomach but may involve gastro-esophageal junction, WHO < 2, age ≥ 18 yrs, no prior abdominal radiotherapy or chemotherapy, hematology: Hb ≥ 9.0 gm/l; leukocytes $\geq 3.0/\text{mm}^3$, neutrophils $\geq 1.5/\text{mm}^3$, thrombocytes $\geq 100/\text{mm}^3$, renal function: serum creatinine ≤ 1.25 ULN, creatinine clearance ≥ 60 ml/min (calculated by Cockcroft and Gault formula), liver function: total bilirubin ≤ 1.5 x ULN, Alkaline phosphatase and ASAT/ALAT ≤ 3 x ULN and Left ventricular ejection fraction > 50%. While patients with the following criteria were excluded: T1N0 disease (endoscopic ultrasound), distant metastases, inoperable patients; due to technical surgery-related factors or general condition, previous malignancy, except adequately treated non-melanoma skin cancer or in-situ cancer of the cervix uteri, uncontrolled infections, significant concomitant diseases preventing the safe administration of study drugs or likely to interfere with study assessments, uncontrolled angina pectoris; cardiac failure or clinically significant arrhythmias, continuous use of immunosuppressive agents, Hearing loss > CTC grade 1 (In case of subjective hearing loss an audiogram is advised), Neurotoxicity > CTC grade 1 and Pregnancy or breast feeding.

Treatment plan:

All patients planned to receive 3 cycles of epirubicin, cisplatin and capecitabine (ECC) at three-weekly intervals preoperatively.

The chemotherapy regimen:

Epirubicin was given in a dose of 50 mg/m² diluted in 250 cc normal saline 0.9% over half an hour on day 1 intravenously every 3 weeks immediate prior to the cisplatin.

Cisplatin was administered at a dose of 60 mg/m² diluted in 1000 cc normal saline 0.9% on day 1 intravenously every 3 weeks with good hydration.

Capecitabine was given orally in two equally divided doses, 1000 mg/m² bid with a meal or snack from day 1-14 every 3 weeks.

Hydration done using 1000 cc of normal saline 0.9% and glucose 5% to each we added 20 mmol Kcl, 500 mg MgSO₄ and 1000 mg calcium gluconat, to be followed by 20 mg furosemide.

All patients received standard premedication with i.v. dexamethasone (20 mg), antihistamine, ranitidine Hcl (Zantac) and antiemetic treatment (ondansetron 16mg or granisetron 3mg) 1 hour before the start of therapy.

Pre-treatment assessment and Post-treatment reassessment:

Required baseline investigations before starting treatment including: History and physical examination, Weight, length, performance status (WHO)¹⁶, upper gastrointestinal tract endoscopy, representative tumor biopsy samples, in case of malnutrition placement of feeding tube, Endoscopic Ultrasonography (EUS), staging laparoscopy, hemoglobin, WBC and neutrophils, platelets, creatinine and creatinine clearance (calculated), Na, K, Ca, P, Bilirubin, Alk. phosphatase, ASAT, ALAT, γ GT, albumin, magnesium and calcium, tumor markers (CEA, CA 19.9), CT-scan chest and abdomen and Cardiac ejection fraction. Tumor response was evaluated after the third cycle using the same evaluation methods.

Toxicity:

Toxicity will be measured according to NCI Common Toxicity Criteria, version 3.0.

Dose adjustments for toxicity:

Dose adjustments during treatment were made based on Absolute Neutrophil Count (ANC) and platelet counts performed within 24 hours prior to the start of therapy and clinical assessment of nonhematologic toxicities. The day-1 dose of each subsequent cycle depended on the toxicity seen in the previous cycle. The treatment was delayed until the ANC returned to 1500 and the platelet count to 100.000. Otherwise, full doses of both drugs were given, except in patients with grade 4 neutropenia lasting >1 week, grade 4 neutropenia associated with fever $\geq 38.5^\circ\text{C}$, or grade 4 thrombocytopenia. In these circumstances, after recovery, the doses of drugs were given at 75% of the dose given on day 1. The observed nonhematologic toxicities (except alopecia and vomiting) had to return to WHO grade 0 to 1, or baseline conditions, before resuming treatment by the drugs. Doses in subsequent cycles were reduced to 75% or held for any grade 3 nonhematologic toxicity (except nausea/vomiting and alopecia), and were reduced to 50% or held for any grade 4 nonhematologic toxicity. Patients were withdrawn from the study after 3 weeks of treatment delay due to any toxicity. If serum bilirubin was increased to $>1.5 \times \text{ULN}$ or AST/ALT increased to $>3 \times \text{ULN}$ in patients without liver metastasis and $>5.0 \times \text{ULN}$ in patients with liver metastasis at the start of the next cycle then the cycle was delayed until serum bilirubin returned to $\leq 1.5 \times \text{ULN}$ and AST/ALT returned to $\leq 3 \times \text{ULN}$ in patients without liver metastasis and ≤ 5.0

× ULN in patients with liver metastasis. If the values did not return to these limits within 42 days from Day 1 of the current cycle then the patient was discontinued from the study. Creatinine clearance (calculated by Cockcroft and Gault formula) prior to treatment should be more than 60 ml/min. Thereafter creatinine clearance was repeated before each course of cisplatin and its dose should be adjusted as follows:

Creatinine clearance > 60 ml/min Full dose, 40-60 ml/min Same dose of cisplatin in mg as the value of creatinine clearance in ml/min (for example of 45 ml/min give 45 mg/m² cisplatin), or < 40 ml/min Omit cisplatin.

Surgery:

After completion of neoadjuvant chemotherapy patients were restaged with a CT scan of the abdomen and chest. The radiological assessment of response was evaluated. In the absence of metastatic disease patients underwent partial or total gastrectomy depending upon the site of the tumor. If possible, a macroscopic proximal and distal margin of 5 cm was obtained with D1-D2 lymphadenectomy with a minimum of 15 lymph nodes. Surgery was planned 3-6 weeks after the last chemotherapy course. The definitive decision to proceed to surgery was taken based on the absence of signs of progressive disease and other contraindications for surgery.

Under general anesthesia supported by epidural anesthesia, a midline laparotomy was performed, followed by a complete exploration of the abdomen including peritoneal surfaces, liver, and in women, the ovaries. Any free abdominal fluid was aspirated for cytological examination. A curative resection was not possible in case of tumor infiltration into the head of the pancreas requiring a Whipple procedure, para-aortic lymph node metastases below the renal arteries, tumor positive cytology of free peritoneal fluid, or peritoneal metastases that could not be included in the planned local resection. If curative resection was not possible, the best palliative surgical option was to be decided upon by the surgeon.

Pathology:

The specimen was sent to the pathologist, preferably fresh and unopened to enable the collection of fresh frozen tissue, followed by processing and reporting of the specimen. The pathology report included a minimal dataset containing the following items: type of tumor, localization and size of tumor, invasion depth, surgical margins, number of (tumor positive) lymph nodes and histological response criteria following neoadjuvant chemotherapy according to Ninomiya criteria.

Definition of response:

Analysis of the response to preoperative treatment was defined clinically as well as pathologically. Down

Grade 0	No change ± neither necrosis nor cellular or structural change can be seen throughout the lesion
Grade 1	1(a) Necrosis or disappearance of the tumour is present in less than 1/3 of the whole lesion 1(b) Necrosis or disappearance of the tumour is present in no more than 2/3 of the whole lesion
Grade 2	Moderate change ± necrosis or disappearance of the tumour is present in more than 2/3 of the whole lesion, but viable tumour cells remain.
Grade 3	Marked change ± the whole lesion falls into necrosis and/or is replaced by fibrosis, with or without granulomatous changes. No viable tumour cells.

staging was considered when pathological T (pT) was less than ultrasound T (uT) by endoscopic US or clinical T (cT) by CT. No response was considered when pT and uT or cT were similar. Disease progression was considered when pT was > uT or cT or when metastases were observed during surgery. Resected tumors were classified pathologically according to the tumor-node-metastasis system (TNM)¹⁸.

Data analysis:

Descriptive statistics were used to characterize study subjects and response to treatment. The primary end point of the study was the response rate. The toxicity was the secondary end point which was assessed as mentioned above using the NCI Common Toxicity Criteria, version 3.0.

RESULTS

Patients, clinic-pathological criteria are shown in Table (1).

Toxicity and treatment adherence:

Preoperative treatment:

During preoperative treatment 100% of patients (25 patients) received full course of chemotherapy, while 12% of patients (3 patients) received chemotherapy with delay 1-2 weeks; one due to diarrhea grade 3, another one due to hand and foot syndrome grade 3 while the third one because of stomatitis grade 3. The toxicity observed in the 25 patients during

the preoperative part of treatment was mainly gastrointestinal, skin, and to some extent stomatitis (Table 2). There was only one patient (4%) complained of diarrhea which was grade 3, while grades 1-2 were recorded in 3 patients (12%). All of the patients were controlled with antidiarrheal medications and intestinal antiseptics. Hand and foot syndrome was noticed in 2 patients (8%) and one patient (4%) with grades 1 and 3 respectively. The main hematological toxicity was anemia with 1 patient (4%) presented with grade 3, while 2 patients (8%) were grade 2, followed by leucopenia and thrombocytopenia with 2 patients (8%) in both toxicity.

Surgery:

Of the 25 patients that completed the preoperative treatment, 22 patients were operated upon: one patient died by sudden cardiac arrest unrelated to treatment which developed at the 4th week after preoperative treatment, and before the scheduled surgery. Another

one patient refused surgery, while in the third one, tumor progressed with development of peritoneal nodules and liver metastases made it irresectable.

Of the 22 patients, 19 (86.3%) had gastric tumor while 3 patient (13.7%) with gastroesophageal tumor. Partial gastrectomy was performed in 11 patients (50%), while radical gastrectomy in 8 patients (36.3%), while three patients (13.7%) underwent partial gastrectomy with lower esophagectomy. D1 and D2 dissection were performed in 5 patients (22.7%) and 17 patients (77.3%) respectively. Delay in wound healing occurred in 23.8% of patients (5 patients). Pelvic abscess developed in 4.5% of patients (1 patient), Table (3).

Efficacy: Down staging and Pathologic complete response

Following the preoperative treatment, the pathological staging of the 22 patients operated upon according to TNM staging system is shown in Table (4).

Table 1: Clinicopathologic characteristics of study patients (n=25).

Clinicopathologic patients' characteristics	Number (25)	Percentages (100%)	
Sex	Male	18	72.0
	Female	7	28.0
Age	Median	54	
	Range	31 – 72	
Performance status	Zero	15	60.0
	One	10	40.0
Site of the tumor	Stomach	20	80.0
	Gastroesophageal junction	5	20.0
Pathologic type	Intestinal	18	72.0
	Diffuse	7	28.0
Grade	Moderately differentiated	22	88.0
	Poorly differentiated	3	12.0
Clinical stage (cTN)	T2 N0	10	40.0
	T2 N+	10	40.0
	T3 N0	3	12.0
	T3 N+	2	8.0
cT	T2	20	80.0
	T3	5	20.0
cN	N0	13	52.0
	N+	12	48.0

Table 2: Description of neoadjuvant treatment related complication among study patients.

Toxicity	Grade 1		Grade 2		Grade 3		Grade 4		G 3-4	
	No of patients	%	No of patients	%	No of patients	%	No of patients	%	No of patients	%
Anemia	-	-	2	8	1	4	-	-	1	4
Leucopenia	-	-	2	8	-	-	-	-	-	-
thrombocytopenia	1	4	1	4	-	-	-	-	-	-
Diarrhea	1	4	2	8	1	4	-	-	1	4
Nausea	-	-	4	16	4	16	-	-	4	16
Vomiting	-	-	3	12	3	12	-	-	3	12
Hand and foot syndrome	2	8	-	-	1	4	-	-	1	4
stomatitis	2	8	-	-	1	4	-	-	1	4

Table 3: Description of surgical treatment and its related complication among study patients (22 patients).

Description of surgical treatment among study patients		N (22)	%
Surgery	Radical gastrectomy	8	36.3
	Partial gastrectomy	11	50
	Partial gastrectomy with esophagectomy	3	13.7
Lymphadenectomy	D1	5	22.7
	D2	17	77.3
Surgical complications		N (22)	%
Delayed wound healing		2	9
Intestinal obstruction		1	4.5
Burst abdomen		1	4.5

Table 4: Description of postoperative data of study patients

Description of postoperative data of study patients		N (22)	%
Pathological stage (pTN)	pT0 N1	2	9
	pT0 N2	1	4.5
	pT1 N0	5	22.7
	pT1 N1	4	18.1
	pT2 N0	2	9
	pT2 N1	4	18.1
	pT3 N2	4	18.1
pT	pT0	3	13.6
	pT1	9	40.9
	pT2	6	27.2
	pT3	4	18.1
pN	pN0	7	31.8
	pN1	10	45.4
	pN2	5	22.7
Complete response		3	13.6
Down staging		10	45.4
Stationary disease		9	40.9

DISCUSSION

Gastric cancer remains to be an important health issue worldwide. Over the past two decades, the incidence of distal gastric cancer has been decreased, but the incidence of proximal and esophagogastric junction cancers has been increased significantly¹⁹. The treatment of the gastroesophageal and gastric cancer is dependent on the TMN staging of the tumor. The advanced gastroesophageal and gastric cancers (stage III-IVB) without evidence of distant metastasis are potentially curable, but these tumors usually present with a more advanced stage and are associated with a worse prognosis²⁰, and a combination therapy, including surgery, chemotherapy and radiotherapy, is often needed. Chemotherapy is an adjuvant treatment modality in the form of adjuvant chemotherapy, NAC and concomitant chemoradiotherapy [21]. NAC has several advantages: (1) it is well tolerated; (2) it can better control the micrometastasis²²; and (3) it might downstage the tumor to the greatest extent and increase the probability of R0 resection so as to facilitate the surgery²³, thus improving the survival rate of the patients with gastroesophageal and gastric cancer. However, it might delay the curative treatment if the tumor does not respond to the NAC, which is also costly and may be detrimental to the patients. Theoretically, NAC can increase the survival rate and improve the quality of life of the patients.

Complete surgical resection of gastric cancer with negative margin (that is, R0 resection) is the most effective treatment to date and is related to better outcome. Unfortunately, many gastric cancer patients admitted to hospital are at an advanced stage and unresectable. Strategies to increase the R0 resection rate and overall survival could include both early detection and downstaging of the lesions. Early detection has proved to be useful in Japan, which

leads to a large proportion of early stage lesions and better survival outcome. However, in countries with relatively low incidence of gastric cancer, large scale screening may be not cost effective. Despite much effort to treat advanced gastric cancer, such as extended lymphadenectomy, it has proved difficult to achieve much toward the goal of improved treatment leading to better patient outcome²⁴.

Although it is generally agreed that patients with inoperable tumours have a poorer prognosis than those who are resectable, some degree of controversy does exist. That is, that surgical resection, whether curative or not, may be associated with a longer survival and removes the risk of potential complications. In the West it is generally considered by that palliative resection is indicated for primarily obstruction, bleeding, and less frequently perforation. They also found that gastrectomy appeared to be linked with a better survival. Sasako stated that even for linitis plastica that donot cause obstruction, survival of resected patients was superior to that of non-resected (Sasako 1996)²⁵. Consequently, to downstage the tumor and improve R0 rate should be the primary goals, and to achieve this for gastric cancer, neoadjuvant chemotherapy may be a potential effective therapeutic strategy.

Neoadjuvant chemotherapy has achieved great success in the management of breast cancer, osteosarcoma, rectal cancer, and other malignancies such as cervical cancer. In fact, neoadjuvant chemotherapy of gastric cancer was first attempted some time ago, the first report being published in 1967 (Fujimoto 1969)²⁶. These data were updated later, in 1976 (Fujimoto 1976)²⁷. The study was later neglected because of high toxicity and low response rate. Another factor is that gastric adenocarcinoma is only moderately sensitive to cytotoxic agents such as 5-fluoracil, metrometrate, mitomycin, and cisplatin. However, even with continuing efforts made by surgeons, oncologists, and biomedical professionals, the outcome of gastric cancer has not demonstrated a great improvement for decades, especially for those in the advanced stages of the disease. Patients with locally advanced disease who have undergone an R0 resection constitute the best prognostic group, with an estimated 5-year survival of 25% in Western countries and approximately 30% in Japan. However, even in patients who have a curative resection, nearly two thirds suffer from local recurrence and distant metastasis.

Many studies have been performed with adjuvant chemotherapy in resectable gastric cancer. These studies have been part of several meta-analyses, which could demonstrate no, or at the most a modest survival benefit for adjuvant chemotherapy²⁸⁻³³. Newer chemotherapy schedules, with capecitabine and oxaliplatin, have

shown to be as least as effective as schedules with 5-FU and cisplatin, with respect to overall survival (REAL-2 study)³⁴.

The combination of adjuvant with neo-adjuvant chemotherapy has proven its value in two randomized studies. In the MAGIC study, perioperative chemotherapy resulted in a reduction of the tumour stage, a 10% higher resectability rate and a significant survival benefit of 13% at 5 years⁹. It should be noted that only 55% started postoperative chemotherapy and 42% of the patients completed the entire treatment. The major reasons for a premature treatment stop were tumour progression, postoperative complications, patients' refusal and toxicity. A French prospective trial showed comparable results with 48% of the patients completing the total regimen¹². The final report of this study has to be awaited.

Due to the strong position of perioperative chemotherapy with tumour downsizing and downstaging the CRITICS investigators were reluctant towards a randomization arm without preoperative chemotherapy. Therefore, both arms have the same preoperative chemotherapy schedule. This also leads to comparable resection rates thus eliminating the effect of surgery (and preoperative therapy) on a potential survival difference between the two treatment arms³⁵.

In our study we enrolled 25 patients with median age 54 years, with 60% of patients were PS WHO 0, 80% of tumors gastric in location, while 20% were in the gastroesophageal junction, most cases were stage 2 with 48% with positive lymph nodes. These patients characters were comparable with both MAGIC and CRITICS studies^{9,35}.

We recorded ORR 59% (13/22 patients); where 3/22 patients (13.6%) attained CR; 10/22 patients (45.4%) attained PR. Stable disease (SD) occurred in 9/22 patients and 1 patient had PD. These response rates are almost similar to that reported in the studies conducted by Cunningham and his colleagues and Dikken and his co-workers. In view of previously shown data PCR rate of 13.6% (3/22) was encountered. By comparing clinical T stage and pathological T stage down staging was found to be 45.4% (10/22) and no disease progression was observed in any of the operated patients. This pathological staging response confirmed by Niomiya grading, with patients with complete response were grade 3, while patients with down staging (partial response) were grades 1 and 2. Patients with stationary disease were grade 0.

The toxic effects of the combination chemotherapy in the present study were manageable and consisted

mainly of non-hematological toxicities. The toxicity observed in the 25 patients during the preoperative part of treatment was mainly gastrointestinal, skin, and to some extent stomatitis (table 2). Patients complained of diarrhea were one patient (4%) with grade 3, while 3 patients (12%) were graded grades 1/2. Hand and foot syndrome was noticed in 2 patients (8%) and in one patient (4%) with grades 1 and 3, respectively. The main hematological toxicity recorded was anemia with 1 patient (4%) with grade 3, while 2 patients (8%) were grade 2, followed by leucopenia and thrombocytopenia with 2 patients (8%) in each toxicity. While Cunningham and his colleagues⁹ documented that both hematological and non-hematological toxicities were similar with leucopenia grades 1/2 occurred in 88.5% and grades 3 or 4 11.5%, anemia grades 1/2 documented in 95.3% and grades 3 or 4 0.4%. Diarrhea as grades 1/2 documented in 97.4%, and as grades 3 or 4 2.6%; while stomatitis documented as 95.7% and 4.3% as grades 1/2 and 3/4, respectively.

CONCLUSION

In conclusion, Epirubicin in combination with cisplatin and capecitabine has demonstrated an acceptable activity as well as tolerable safety profile. Further evaluation of this regimen is warranted in the management of patients with operable gastric and gastroesophageal junction cancer as neoadjuvant.

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