Phase II study of neo-adjuvant chemotherapy for locally advanced gastric cancer

Alex Yang-Chi Chang,1 Kian Fong Foo,2 Wen-Hsin Koo,2 Simon Ong,2 Jimmy So,3 Daniel Tan,4 Khong Hee Lim5


Abstract

Background: Neoadjuvant chemotherapy improves survival of locally advanced gastric cancer patients. However, benefit is limited and the best regimen remains controversial.

Objectives: Our primary objective of this prospective, multicenter phase 2 study was to evaluate the pathological complete response rate (pCR) with 2 cycles of docetaxel and capecitabine.

Methods: To be eligible, patients had to have histologically documented gastric cancer, a ECOG performance status 0 or 1, T3 or 4 Nany M0 staging after endoscopic ultrasound (EUS), CT scan of thorax and abdomen, and negative laparoscopic examination and peritoneal washing. Eligible patients received two cycles of intravenous docetaxel 60 mg/m2 on day 1 and oral capecitabine 900 mg/m2 two times per day from day 1 to day 14 every 3 weeks. We evaluated the response by CT scan and EUS. The patients underwent curative resection with D2 lymphadenectomy subsequently.

Results: 18 patients were enrolled in the study; 66% were male and the median age was 60 years. 17 patients had T3 disease at diagnosis. There was no pCR noted. 4 patients had a partial response of 22% (95% CI: 7–42%), 8 patients had stable disease and 3 patients had disease progression. The median survival was 17.1 months with 3 long-term survivors after at least 3 years of follow-up. The treatment was well tolerated with neutropenia being the most common toxicity. We observed 22% grade III and 33% grade IV neutropenia, but no neutropenic fever or death was observed from chemotherapy.

Conclusion: Neoadjuvant chemotherapy with docetaxel and capecitabine has limited activity against GC. More effective treatment regimens are needed urgently.

Trial registration number: NCT00414271.

Introduction

Gastric cancer represents a major global health problem, with nearly 1 million newly diagnosed cases and more than 700 000 deaths yearly worldwide.1 In Singapore, gastric cancer is one of the leading causes of death with over 480 new cases of gastric cancer each year. The outcome in patients with gastric cancer is poor. The 5-year survival rate after apparently curative surgical resection remains ∼20% in Singapore and in many Western countries. This dismal outcome is associated with the advanced stage at presentation. In Singapore, the majority of patients with gastric cancer present with late stage of disease.2 Survivability was mainly affected by local recurrence at tumour bed, or lymph node, as well as diffuse peritoneal involvement and distant metastases.
Summary box

How might it impact on clinical practice in the foreseeable future?
We pointed out that:
- Once a patient is diagnosed with gastric cancer, the standard staging procedures such as oesophagogastrroduodenoscopy (OGD), endoscopic ultrasound, computed tomography scan of abdomen and pelvis, laparoscopic examination of the abdominal cavity with peritoneal washing should be used before surgery.
- Neo-adjuvant chemotherapy should be considered for locally advanced gastric cancer as one of the standard therapies.
- More research are urgently needed to look for more effective regimens; either targeted therapy, immunotherapy or their combination.
- We advocate to use the pathological complete remission rate as one of the measurements of efficacy of neo-adjuvant chemotherapy in gastric cancer.

The mainstay of treatment of gastric cancer is surgery. However, despite apparent curative resection, relapse is common especially when the tumour is in the advanced stage. Numerous studies have been conducted to evaluate the use of adjuvant therapy. Recently, a multicentre, randomised, controlled trial from the USA did support the use of adjuvant chemoradiotherapy after surgery for gastric cancer, but over 50% of patients developed relapse despite chemo-irradiation in that trial. Adjuvant chemoradiotherapy did not become standard therapy in our region initially, as surgical resection for gastric cancer differs significantly between the East and the West. There was a controversy whether patients would benefit from adjuvant treatment after D1 or D2 resection until the most recent trials demonstrated the survival benefit of S-1 and combination of oxaliplatin and capecitabine in D2 resected patients with gastric cancer.

Neo-adjuvant chemotherapy for gastric cancer was first studied for the locally advanced unresectable disease. Some investigators then employed the concept of neo-adjuvant approach for resectable gastric cancers generally with encouraging results. Neo-adjuvant therapy has several potential benefits:
1. Chemotherapy may downstage cancer to enhance resectability.
2. Patients receive immediate chemotherapy without delay from the major surgery; thus, they may reduce micrometastases.
3. Allows investigators to assess the long-term results in patients who had obtained a complete response with neo-adjuvant chemotherapy at the time of surgery.
4. Those patients with rapidly progressive tumours can be identified. Hence, we could spare them from unnecessary exploratory laparotomy.

At the beginning of our study in 2005, neo-adjuvant chemotherapy for gastric cancer was viewed as experimental. It has become the standard treatment since the MAGIC trial with epirubicin, cisplatin and 5-FU (ECF), and the FFCD study with cisplatin and 5-FU (FP) reported superior survival benefit when compared to surgery alone. However, the best regimen remains to be established.

Various neo-adjuvant chemotherapy regimens have been reported in phase II or III trials. In general, the R0 resection rate was 70–80%, pathological complete response (pCR) was 0–11.7% and median survival was 15–30 months in resectable patients with gastric cancer receiving neo-adjuvant chemotherapy. Clearly, more effective treatment is urgently needed.

Docetaxel is a taxane derivative, which inhibits the depolymerisation of microtubule and arrests the cells in mitosis. As a single agent docetaxel yielded 17.5–24% objective response rate. When it is added to CF regimen, DCF (docetaxel, cisplatin, 5-FU) has been reported to be superior to CF at the expense of more severe toxicity. DCF and its modified regimens have become a common treatment of choice in the USA. In a recent report of a pharmacokinetic study of docetaxel in Singaporeans, 60 mg/m² every 3 weeks rather than ≥75 mg/m² was suggested as a single agent in patients with cancer due to decreased clearance of docetaxel.

Capecitabine is an oral fluoropyrimidine and an active drug for treating gastric cancer with a response rate of 20%. Capecitabine is metabolically activated by thymidylate phosphorylase preferentially in the tumour cells and has been shown to be synergistic with docetaxel which upregulates the level of thymidylate phosphorylase in cancer cells. The combination of these two agents has been used commonly for breast cancer. The initial result of a phase II study of docetaxel and capecitabine for metastatic gastric cancers showed an overall response rate of 60%. The current dose regimen in the treatment of breast cancer has used capecitabine at 950 mg/m² instead of 1250 mg/m². This dose regimen of capecitabine is associated with reduced side effects (such as hand-foot syndrome, mucositis and diarrhoea) with the same efficacy. Therefore, we adopt this dose regimen to combine with docetaxel at 60 mg/m² as a reasonable and safe treatment. Another advantage of this combination is the convenience to the patient, as capecitabine is an oral agent without a need to use a central venous catheter for continuous intravenous infusion of 5-FU. The Randomized ECF for Advanced and Locally Advanced Esophagogastric Cancer 2 (REAL-2) trial by Cunningham et al showed that there was no significant difference in terms of progression-free survival (PFS) and response rate in 5-FU versus capecitabine group, as well as cisplatin versus oxaliplatin group. Docetaxel and capecitabine can be delivered as an outpatient regimen during the entire treatment. Therefore, because docetaxel and capecitabine have been shown to have significant single-agent antitumour activity against advanced gastric cancer, synergistic interaction between each other and very promising partial response (PR) rate
METHODS

This trial was a single-arm, prospective, multicentre, phase II study performed through the Singapore Gastric Cancer Cooperative Group. Patients were accrued from September 2005 to May 2008. We wanted to report the frequency of long-term survival; therefore, there is a delay in reporting. The protocol was formally approved by the Institutional Review Board of all the participating hospitals and all patients provided informed consent.

Eligibility criteria

Patients must have endoscopic ultrasound (EUS) staged T3-4 NanyM0 gastric (GC) or gastroesophageal carcinoma (GEC) adenocarcinoma in order to be eligible. They must also have negative metastases in the abdomen cavity by laparoscopic examination and peritoneal washing. They could have either initially operable or locally advanced/inoperable disease. GEC tumours had to be Siewert type III lesions. The patients were required to have a Karnofsky performance status ≥70% and adequate haematological, renal, hepatic and pulmonary function. Exclusion criteria included metastatic disease (such as positive peritoneal lavage at staging laparoscopy), prior chemotherapy or radiation therapy, and severe comorbid medical conditions.

Neo-adjuvant chemotherapy

Treatment consisted of two cycles of induction chemotherapy. The patients received docetaxel 60 mg/m² in 150–250 mL normal saline given intravenously over 1 hour on day 1, while capecitabine was administered at 950 mg/m² two times per day on days 1–14. The cycle was repeated every 21 days. Supportive medications included dexamethasone 8 mg two times per day orally for 3 days, starting 1 day prior to docetaxel administration. Antiemetics were administered at the investigator’s discretion. Prophylactic growth factor support was not permitted.

A 25% dose reduction for second cycle was done for grade IV neutropenia lasting ≥7 days, neutropenic fever or grade IV thrombocytopenia from the first treatment. A delay of ≤21 days was permitted prior to the second chemotherapy cycle. Dose delays and reductions were also permitted for non-haematological grade III/IV toxicities.

Surgery

The patients underwent surgery 3–6 weeks following the last chemotherapy. The extent of gastric resection was dependent on the location of the primary tumour: subtotal gastrectomies were permissible for distal tumours, provided a proximal margin of ≥5 cm could be achieved. Total gastrectomies were indicated for more proximal tumours. The method of reconstruction was at the surgeon’s discretion. After a total gastrectomy, a Roux-en-Y esophagojejunostomy was the method of choice. After a subtotal gastrectomy, the gastrojejunostomy could be either a Billroth II type or a Roux-en-Y type.

A D2 dissection of lymph nodes was mandated, that is, all perigastric nodes except the right and left cardial nodes were resected for distal cancers. The decision to perform a more extensive D2 nodal resection was at the surgeon’s discretion.

Adjuvant therapy

The patients with pathological lymph node involvement following surgery were offered adjuvant chemoradiation, based on the Intergroup 0116 study. The exact treatment schema or the use of capecitabine versus infusional 5-FU was not specified.

Pre-treatment evaluation and evaluation on study

Prior to treatment, the patients underwent laboratory evaluation, CT of the abdomen/pelvis, chest X-ray (or CT chest for GEC tumours), esophagastroduodenoscopy (EGD) with EUS and staging laparoscopy with peritoneal lavage. Upon completing neo-adjuvant chemotherapy, a repeat CT and EUS were performed prior to surgery. When analysing the response in the primary tumour, the results of EUS superseded those of CT in the event of a discrepancy. Postoperatively, the patients were evaluated every 3 months for the first 2 years, then every 6 months for the next 3 years, then annually. Imaging and testing were carried out as clinically indicated. All toxicities were graded using National Cancer Institute Common Terminology Criteria for Adverse Events, V3.0.

Statistics

The primary objective of this study was to estimate the pCR rate to neo-adjuvant chemotherapy by using radiological methods, such as CT scan and EUS. A minimum sample size of 30 patients would permit the pCR rate to be characterised within ±15%. Secondary end points included PFS and overall survival (OS), which were estimated using the Kaplan-Meier method. The pCR was defined as the absence of cancer cells in the resected surgical specimen, including lymph nodes. The OS was defined as the period from the initiation of neo-adjuvant chemotherapy to any cause of death, and the PFS was...
defined as the period from the initiation of neo-adjuvant chemotherapy to the occurrence of an event, recurrence or death, whichever came first.

Analyses were performed on an intention-to-treat basis.

**RESULTS**

**Demographics**

Eighteen patients were enrolled between May 2005 and May 2008 before the trial was closed by the Research Committee of the Sydney Kimmel Comprehensive Cancer Center of Johns Hopkins University because of slow accrual. Demographics are shown in Table 1. The median age of patients was 60 years and most patients (66%) were men. Slightly more than half (56%) of the tumours were in the proximal and mid-stomach.

**Chemotherapy delivery and toxicity**

Of the 18 patients, 17 (94%) completed all chemotherapy. One patient developed a myocardial infarction (MI) after the first cycle of chemotherapy and was taken off the protocol. Twenty-two per cent of patients required a dose reduction of capecitabine during the treatment, while 22% of patients had a dose reduction of docetaxel.

Grade III/IV toxicities and significant grade I/II toxicities observed are listed in Table 2. In general, toxicities were consistent with those of the chemotherapy agents. Grade III/IV neutropenia occurred in 10 of the 18 patients (55%), but no patient developed neutropenic fever. Grade III nausea and diarrhoea occurred in one (6%) and two (11%) patients, respectively. No treatment-related death was observed. No mucositis, hand and foot syndrome or transaminitis was reported.

**Response to therapy by CT scan and EUS**

Of the 17 patients who completed neo-adjuvant chemotherapy, all underwent repeat CT and EUS but 2 patients’ tumours were not measurable by both methods. There were no pCR (0%, 95% CI 0% to 18%). Four of these patients (22%, 95% CI 7% to 42%) were noted to have a PR in the primary tumour, eight patients had stable disease and three patients (16.7%) had progressive disease, as shown in Table 3. Three of the four patients who had PR with the neo-adjuvant chemotherapy had a downstaging of their gastric cancer after their surgeries.

**Surgery and adjuvant therapy**

One of the 17 patients (6%) who completed neo-adjuvant chemotherapy developed progressive disease and did not undergo surgery. Another patient was found to have metastatic disease during surgery and underwent a palliative surgical bypass; the patient who developed MI also did not go for surgery. So, 15 patients (83%) underwent an R0 resection.

Following surgery, eight patients received adjuvant therapy—four patients were treated with radiotherapy with concurrent fluorouracil (infusional, 5-FU or capecitabine), three patients received fluoropyrimidine alone and one patient was treated with the regimen epirubicin, oxaliplatin and capecitabine (EOX).

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**Table 1** Patient demographics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Patients (n=18)</th>
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<tbody>
<tr>
<td>Age, years</td>
<td>No.</td>
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<tr>
<td>Median</td>
<td>60</td>
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<tr>
<td>Range</td>
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<td>Female</td>
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<td>ECOG performance status</td>
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</tr>
<tr>
<td>1</td>
<td>10</td>
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<tr>
<td>Location</td>
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</tr>
<tr>
<td>Proximal stomach</td>
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</tr>
<tr>
<td>Middle stomach</td>
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<td>Distal stomach</td>
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<tr>
<td>Staging</td>
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<tr>
<td>T3N1</td>
<td>10</td>
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<tr>
<td>T4N0</td>
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</table>

**Table 2** Chemotherapy toxicities

<table>
<thead>
<tr>
<th>Toxicity</th>
<th>Grade* (% of patients)</th>
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<tbody>
<tr>
<td></td>
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<tr>
<td>Anemia</td>
<td>2 (11)</td>
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<tr>
<td>Constipation</td>
<td>4 (22)</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>3 (17)</td>
</tr>
<tr>
<td>MI</td>
<td>–</td>
</tr>
<tr>
<td>Nausea</td>
<td>2 (11)</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>–</td>
</tr>
<tr>
<td>Alopecia</td>
<td>2 (11)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>2 (11)</td>
</tr>
<tr>
<td>Myalgia</td>
<td>3 (17)</td>
</tr>
<tr>
<td>Insomnia</td>
<td>2 (11)</td>
</tr>
<tr>
<td>Hyperglycaemia</td>
<td>–</td>
</tr>
</tbody>
</table>

*National Cancer Institute Common Terminology Criteria for Adverse Events, V.3.0.
MI, myocardial infarction.

**Table 3** Response after neo-adjuvant therapy

<table>
<thead>
<tr>
<th>Radiological response</th>
<th>Number of patients (percentage)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR</td>
<td>0 (0)</td>
</tr>
<tr>
<td>PR</td>
<td>4 (22)</td>
</tr>
<tr>
<td>SD</td>
<td>8 (47)</td>
</tr>
<tr>
<td>PD</td>
<td>3 (16.7)</td>
</tr>
<tr>
<td>unmeasurable</td>
<td>2 (11.7)</td>
</tr>
</tbody>
</table>

CR, complete response; PD, progression of disease; PR, partial response; SD, stable disease.
Follow-up and survival

One patient was lost to follow-up after progression from neo-adjuvant chemotherapy. The rest has been followed up until October 2014. Eleven patients developed recurrent or metastatic disease during follow-up and died of their disease, and three patients were still alive without any evidence of recurrent gastric cancer. The median PFS of the 18 patients was 7 months. The median survival calculated by the Kaplan-Meier method was 17.1 months (7.4 to >84.7 months).

Initially, we also planned to study the thymidylate synthetase expression, methylation of RUNX-3 gene and comprehensive genomic hybridisation before and after chemotherapy to look for biomarkers of response and prognostic indication. However, due to the lack of pCR and the small number of patients enrolled, we stopped the correlative studies.

DISCUSSION

We employed two cycles of neo-adjuvant docetaxel and capecitabine in 18 patients with T3 or T4 gastric adenocarcinoma. Although our trial was the first to employ docetaxel and capecitabine as the neo-adjuvant therapy for GC with innovative translational research plans, we closed our study prematurely due to poor accrual. We observed 83% R0 resection rate, no pCRs and four patients (22%, 95% CI 7% to 42%) with PRs. Three patients had progression of disease after neo-adjuvant chemotherapy and the overall median survival was 17.1 months. There were three long-term survivors. Overall, our results are in line with the literature reports and did not appear to be promising. We did not perform any planned correlative laboratory study due to inadequate clinical results.

The strength of our study is in its prospective nature with complete TNM staging of all patients with strict criteria of conducting the trial. Before entry, patients must have CT scan of the abdomen and pelvis (for N and M staging), upper endoscopy with EUS (for TNM staging) and laparoscopic examination of peritoneal cavity and peritoneal washing (for M staging).

These three procedures are still the standard practice. Laparoscopy is performed to evaluate peritoneal spread when considering whether to give chemotherapy or to do resection first and is indicated for clinical stage $T_1b$ or higher. It is not universally accepted among patients and gastric surgeons, which is one of the causes of poor accrual in our trial. EUS performed prior to any treatment is important in the initial clinical staging of gastric cancer. Patients, who refused EUS, while the initial diagnosis was made by endoscopy, had to be excluded from our study. This also contributes to slow accrual. Currently, the common practice in Singapore for patients with operable gastric cancer is surgery first, as preferred by surgeons and patients, and then followed up by adjuvant chemotherapy. The standard surgical procedure is a subtotal or total gastrectomy with D2 resection. Adjuvant chemotherapy can be either S1 or oxaliplatin/5-FU/leucovorin. In 2004 or 2005, adjuvant chemotherapy or neo-adjuvant chemotherapy was not uniformly accepted. This might have contributed to slow accrual of our trial. During the course of our study, we learnt the importance of multidisciplinary collaboration and difficulties in conducting clinical trials of gastric cancer. EUS done after chemotherapy or radiation has a reduced ability to accurately determine the post-treatment stage of disease. We understood the limitation of CT scan and EUS as tools for evaluating the response of neo-adjuvant docetaxel and capecitabine in our trial. Therefore, we used pCR as the primary objective of our trial.

The low PR rate (22%) in our trial might have been accounted by the lower and more tolerable dose of capecitabine 950 mg/m$^2$ and docetaxel 60 mg/m$^2$. A study by Park et al showed that 42 patients with advanced gastric cancer who received 21-day cycles of oral capecitabine (1250 mg/m$^2$) and docetaxel (75 mg/m$^2$) on day 1 had an overall response rate of 60%. The median PFS was 5.2 months and median OS was 10.5 months. Relatively high rate of toxicity was reported, such as grade III hand-foot syndrome (50%), neutropenia (15%) and leucopenia (12%). Hence, Park et al recommended that the dose of capecitabine and docetaxel need to be reduced to 1000 and 60 mg/m$^2$, respectively.

Thuss-Patience et al investigated the dose-dependent efficacy of docetaxel and capecitabine in two patient cohorts with metastatic or recurrent gastric cancer. The first cohort received docetaxel 75 mg/m$^2$ on day 1 plus capecitabine 1000 mg/m$^2$ two times per day on days 1–14 every 3 weeks. The second cohort received docetaxel 60 mg/m$^2$ on day 1 and capecitabine 800 mg/m$^2$ two times per day on days 1–14 every 3 weeks. The first cohort of patients had a higher response rate (50% vs 23.5%), longer median time to tumour progression (5.6 vs 3.7 months) and survival (10.1 vs 7.2 months). They also noticed more dose reductions were required in the first cohort of patients mainly due to more grade III/IV toxicities. Grade III/IV neutropenia occurred (20% and 7.8%) in first and second cohort of patients, respectively. There was a trend in higher response rates with higher doses of docetaxel and capecitabine in other phase II trials. However, our regimen of docetaxel 60 mg/m$^2$ on day 1 and capecitabine 950 mg/m$^2$ days 1–14 every 3 weeks produced grade III/IV neutropenia of 55%, suggesting that this would be near the maximal tolerated doses without G-CSF support. When added to cisplatin and 5-FU (CF), docetaxel improved the response rate and survival when compared with CF alone at the expense of more toxicity in patients with metastatic or recurrent gastric cancer. Thuss-Patience et al showed that docetaxel and infusional 5-FU had similar efficacy to the standard ECF. Capecitabine has been shown to have at least equivalent efficacy to infusional 5-FU when given as part...
of a combination regimen in patients with advanced gastric cancer. Several phase II trials have reported promising results with the combination of docetaxel and capecitabine in patients with metastatic gastric cancer. Therefore, it seemed logical to choose docetaxel and capecitabine in the neo-adjuvant setting. Very few studies on the efficacy of docetaxel or other taxane as neo-adjutivant therapy in gastric cancer have been reported. The results of Korean NCT1 0151748 study of docetaxel, oxaliplatin and tegafur as neo-adjutivant chemotherapy is still pending. A German study by Glatz et al. demonstrated the survival advantage of using neo-adjuvant and adjuvant chemotherapy, as compared to using neo-adjuvant chemotherapy alone. The chemotherapeutic regimens used were FLOT (docetaxel, folinic acid, fluorouracil and oxaliplatin), ECF (epirubicin, cisplatin and folinic acid) and EOX (epirubicin, oxaliplatin and capecitabine).

Local pharmacogenetics study by Goh et al. also showed that certain polymorphism in the CYP3A4 gene, the enzyme responsible for the metabolism of docetaxel, was associated with variability in terms of docetaxel clearance from patients’ bodies. This study signified that we still have to come up with a better chemotherapeutic regimen that is tailored for the local patient population.

We cannot comment on the HER-2 status on our patients as none had been tested for it, and HER-2 was not a standard test then. HER-2 overexpression indicates poor clinical response and outcome without HER-2 directed therapy.

There are a number of limitations in our trial, which include a small number of patients with wide CIs, premature closure of the trial and delays in reporting as well as lower dose of docetaxel based on the pharmacokinetic and pharmacodynamic study on Singaporeans. We cannot be sure whether higher dose of docetaxel with GCSF (granulocyte-colony-stimulating factor) would give better results.

In conclusion, neo-adjuvant chemotherapy with docetaxel and capecitabine at doses used in our study had limited efficacy against locally advanced gastric cancer. More effective and standardised regimens are needed to improve the treatment outcome.

Contributors ACY-C organised the Singapore Gastric Cancer Cooperative Group to run this study, prepared the study protocol and obtained the grant from Singapore Cancer Syndicate. He also prepared the manuscript. FKF, KWH, SJ, DS, DT, LHK are members of the Singapore Gastric Cancer Cooperative Group. They contributed to the research idea, actively participated in the research study and enrolled patients in the trial.

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Competing interests None declared.

Patient consent Obtained.

Ethics approval National Healthcare Group Review Board (Domain specific review board).

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