



# Adjuvant chemoradiation for gastric cancer with infusional 5-fluorouracil and cisplatin: a phase I study

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## ABSTRACT

### Objective

This phase I study aimed to determine the maximal tolerated dose of cisplatin administered every 2 weeks with infusional 5-fluorouracil (5FU) and concurrent radiation therapy (RT) in patients after complete resection of gastric adenocarcinoma.

### Methods

Patients with resected stage IB to IV (M0) gastric adenocarcinoma were treated with 12 weeks of infusional 5FU (200 mg/m<sup>2</sup> daily) and with RT (45 Gy in 25 fractions starting on day 16). Cisplatin was administered in escalating doses (0, 20, 30, and 40 mg/m<sup>2</sup>) in weeks 1, 3, 5, and 7. In the final cohort, patients received an additional dose of cisplatin (40 mg/m<sup>2</sup>) in week 9.

### Results

Among the 34 patients [median age: 56 years (range: 31–77 years)] who were assessable for toxicity, 5 experienced dose-limiting toxicities: 1 sepsis (cohort 1), 1 fatigue (cohort 2), 3 upper gastrointestinal toxicity (1 in cohort 2, 2 in cohort 5). Cohort 5 exceeded the maximal tolerated dose. Median follow-up was 2.5 years (range: 0.3–5 years). The 3-year overall and relapse-free survival rates were 86% and 71% respectively; median survival was not reached.

### Conclusions

Cisplatin was well tolerated in combination with infusional 5FU and RT, showing promising activity in the

adjuvant treatment of gastric cancer. Infusional 5FU 200 mg/m<sup>2</sup> daily for 12 weeks with cisplatin 40 mg/m<sup>2</sup> in weeks 1, 3, 5, and 7 and with concurrent RT 45 Gy in 25 fractions, starting at day 16, is being explored in a phase II study at our institution.

## KEY WORDS

Adjuvant therapy, chemoradiation, gastric cancer, phase I study, cisplatin, 5-fluorouracil

## 1. INTRODUCTION

Since the publication of the Intergroup INT-0116 trial, a randomized controlled study that at 3 years showed a 9% absolute survival benefit for concurrent 5-fluorouracil (5FU) and radiation after gastrectomy as compared with surgery alone, adjuvant treatment has become the standard of care in North America<sup>1,2</sup>. Unfortunately, acute toxicity rates were high, with the incidence of grades 3, 4, and 5 toxicity being 41%, 32%, and 1% respectively.

A recent review of 82 patients with Union Internationale Contre le Cancer (UICC) stage IB to IV (M0) gastric adenocarcinoma treated at our institution showed a 3-year overall survival (OS) of 69% (95% confidence interval: 55% to 82%)<sup>3</sup>. Despite the use of three-dimensional conformal radiation techniques, toxicity remained comparable to that seen in the Intergroup study. The need to improve the outlook for patients with gastric cancer, while reducing the toxicity of treatment, is urgent.

A meta-analysis of patients with advanced colorectal cancer showed that, compared with bolus 5FU, continuous-infusion 5FU improves tumour response and survival outcomes and reduces hematologic toxicity<sup>4</sup>. Cisplatin is known to have activity in metastatic

and locally unresectable gastric cancer, with higher response rates of up to 46% in the cisplatin-containing regimen as compared with 21% in the non-cisplatin-containing regimen; a benefit in survival outcomes is also seen<sup>5,6</sup>. In the treatment of cervical cancer, weekly cisplatin has long been used concurrently with radiotherapy, with acceptable toxicity<sup>7,8</sup>.

The aim of the present phase I study was to define the maximal tolerated dose (MTD) of cisplatin given every 2 weeks with infusional 5FU and concurrent radiation therapy (RT). In the treatment arm of the INT-0116 study, 41% of patients experienced grades 3, 4, and 5 toxicity. The present study aimed to find a dose of cisplatin that would produce rates of acute grades 3–5 toxicity of 40% or less.

## 2. PATIENTS AND METHODS

Approval to conduct the study was granted by the institutional research ethics board at the Princess Margaret Hospital, University Health Network. The study was monitored by the Princess Margaret Hospital data safety monitoring board.

### 2.1 Eligibility Criteria

Patients with UICC stages IB to IV (M0) histologically confirmed gastric or gastroesophageal junction adenocarcinoma who had undergone a resection with curative intent and with negative microscopic margins (R0) were eligible for the study (Table I)<sup>9</sup>. Additional eligibility criteria included being at fewer than 90 days post surgery, having an Eastern Cooperative Group performance status of 2 or less, and having a nutritional intake of at least 1500 calories daily. Patients were excluded if the tumour had more than 2 cm of esophageal extension. No upper age limit was initially specified, but after encountering significant toxicities in the first 3 treated patients over the age of 70 years (2 in cohort 2 and 1 in cohort 3), the protocol was amended to exclude patients older than 70.

### 2.2 Patient Evaluation

Pretreatment assessment included a history and examination, hematology and chemistry profiles, a nutrition assessment, and a postoperative computed tomography (CT) scan of chest, abdomen, and pelvis within the 4 weeks before the start of treatment. Initially, a renal functional scan was acquired only at the discretion of the treating clinician, but this scan is now standard at our institution.

### 2.3 Radiation Therapy

Participants were treated according to institutional protocol with three-dimensional conformal planning and delivery<sup>3,10</sup>. The clinical target volume was defined using the criteria from the INT-0116 study<sup>11</sup>. Initially,

TABLE I Baseline patient characteristics

| Variable                  | Value     |
|---------------------------|-----------|
| Patients (n)              | 34        |
| Age (years)               |           |
| Mean                      | 55.8      |
| Range                     | 30.8–77.2 |
| Sex [n (%)]               |           |
| Female                    | 16 (47)   |
| Male                      | 18 (53)   |
| T stage (n)               |           |
| T1                        | 4         |
| T2                        | 15        |
| T3                        | 14        |
| T4                        | 1         |
| N stage (n)               |           |
| N0                        | 8         |
| N1                        | 18        |
| N2                        | 5         |
| N3                        | 3         |
| Overall stage (n)         |           |
| IB                        | 9         |
| II                        | 10        |
| IIIA                      | 8         |
| IIIB                      | 3         |
| IV (M0)                   | 4         |
| Surgery [gastrectomy (n)] |           |
| Partial                   | 28        |
| Total                     | 5         |
| Subtotal                  | 1         |
| Lymph node dissection (n) |           |
| D0                        | 2         |
| D1                        | 19        |
| D2                        | 12        |
| Unknown                   | 1         |

conventional simulation was used to assess breathing motion; later, four-dimensional CT scans were used to individualize the margin for the planning target volume. Radiation dose was 45 Gy in 25 fractions, typically given using 5–7 fields (coplanar conformal technique), starting on day 16 of chemotherapy.

### 2.4 Chemotherapy

Continuous infusional 5FU 200 mg/m<sup>2</sup> daily was administered for 12 weeks through a peripherally inserted central catheter (PICC). Escalating doses of cisplatin were administered in weeks 1, 3, 5, and 7 using the schema shown in Table II. In cohort 5, an additional dose of cisplatin was given in week 9. A standard antiemetic regimen was prescribed: ondansetron 8 mg orally 1 hour before and 3 hours after RT,

with prochlorperazine as required. Ranitidine was recommended for partial gastrectomy patients.

## 2.5 Toxicity

Acute toxicity was assessed according to the *Common Toxicity Criteria* version 2.0 (CTC v2.0), and late toxicity was assessed using the Radiation Therapy Oncology Group (RTOG) late toxicity score<sup>12,13</sup>. “Dose-limiting toxicity” (DLT) was defined as a grade 3 or greater acute toxicity related to the study therapy and requiring treatment or hospitalization. Uncomplicated hematologic or biochemical changes requiring no treatment were not considered to be DLTs.

A baseline toxicity assessment was obtained before the commencement of chemotherapy. Acute toxicity was assessed weekly during concurrent RT, within the final week of chemotherapy (week 12), and at 4 weeks post chemotherapy. All toxicities occurring 90 days or more after treatment completion were considered late toxicities. Late toxicity was documented at all subsequent follow-up visits.

## 2.6 Dose Modification

For uncomplicated grade 3 neutropenia, cisplatin was withheld until neutropenia below grade 2 was reached. For grade 4 neutropenia, or neutropenia complicated by fever or infection, cisplatin and 5FU were withheld until recovery to neutropenia below grade 2 was reached. The chemotherapeutics were then restarted at 75% dose. For platelet levels of  $100 \times 10^9/L$  or less, cisplatin was held until recovery to  $100 \times 10^9/L$  or more. For grade 2 changes in creatinine, cisplatin was held until recovery to below grade 1; the cisplatin was restarted at 75% dose and stopped completely for grade 3 or 4 changes. For grade 2 neurologic changes, the cisplatin dose was reduced to 75%; cisplatin was stopped completely for grade 3 or 4 toxicity. The 5FU was restarted upon recovery to below grade 2. For all other grade 3 or 4 toxicities (except alopecia), all chemotherapy was stopped until recovery to below grade 2. Chemotherapeutics

were restarted at the investigators' discretion and at no more than 75% of the previous dose.

## 2.7 Follow-Up

Patients underwent a complete blood count and clinical assessment 4 weeks after completion of treatment, and then every 3 months for the first 2 years of follow-up. Imaging (abdominal CT) was performed 4–12 weeks after completion of chemotherapy, and then annually.

Disease relapse was reported according to the site of first relapse (local, regional, or distant) documented by one or more of operative findings, biopsy report, or radiologic evidence. Regional relapse was defined as relapse in the regional nodal areas included in the radiation target volume. Distant recurrence included peritoneal relapse and distant metastases.

## 2.8 Study Design

Consecutive patients were entered into each dose level (Table II) in a standard 3+3 design. The MTD was defined as the highest dose level at which 6 patients were treated and no more than 1 experienced a DLT. If 1 patient within the first 3 accrued to each cohort experienced a DLT, another 3 were treated at the same dose level. If 2 or more patients experienced a DLT in any cohort, that dose level was considered to have exceeded the MTD. If, at the previous dose level, only 3 patients were treated, then 3 additional patients were treated with that dose.

Based on the INT-0116 results, we decided that, to be clinically acceptable, the MTD dose level would produce toxicity rate at grades 3 and 4 of no more than 40%. The probability of having 1 or fewer DLTs in 6 patients, when the proportion of toxicity is 40% or more, is 23% or less.

## 2.9 Statistical Considerations

The primary endpoint was toxicity; all patients were evaluated for safety analysis. The null hypothesis was

TABLE II Acute and dose-limiting toxicities<sup>a</sup> in each cohort

| Cohort | Cisplatin                    |                | Pts<br>(n) | Patients experiencing toxicity (n) |                                |                         | Non-hematologic<br>grade 3 toxicity<br>by type                    |
|--------|------------------------------|----------------|------------|------------------------------------|--------------------------------|-------------------------|-------------------------------------------------------------------|
|        | Dose<br>(mg/m <sup>2</sup> ) | Doses<br>given |            | All<br>grades<br>1–2               | Non-<br>hematologic<br>grade 3 | Hematologic<br>grade ≥3 |                                                                   |
| 1      | 0                            | 0              | 6          | 6                                  | <b>2 (1)</b>                   | 0                       | <b>Sepsis</b> , hyponatremia not requiring treatment, hypokalemia |
| 2      | 20                           | 4              | 10         | 9                                  | <b>1</b>                       | 0                       | <b>Fatigue</b>                                                    |
| 3      | 30                           | 4              | 7          | 7                                  | <b>1</b>                       | 3                       | <b>Vomiting with dehydration</b> , stomatitis, hypokalemia        |
| 4      | 40                           | 4              | 6          | 6                                  | 2                              | 0                       | Hyponatremia not requiring treatment                              |
| 5      | 40                           | 5              | 5          | 5                                  | <b>2</b>                       | 3                       | <b>Anorexia, dehydration, weight loss</b>                         |

<sup>a</sup> Dose-limiting toxicities are shown in boldface type.

that the toxicity rate is 40% or more; the alternative was that the toxicity rate is 25% or less. The probability of correctly deciding that the treatment was not excessively toxic (“power”) was 0.74 ( $\beta = 0.26$ ), and the probability of deciding incorrectly that the treatment was too toxic ( $\alpha$ ) was 0.11.

Secondary endpoints were survival outcomes. Time to relapse was calculated as the difference between the date of diagnosis and the date of the first event observed (or the date of the last follow-up when an event was not observed). For survival, the time was calculated as the difference between the date of diagnosis and the date of death or the date of last follow-up. Patients for whom death was not observed were censored. The OS and relapse-free survival (RFS) were estimated using the Kaplan–Meier method.

### 3. RESULTS

Between September 2002 and March 2007, the study enrolled 34 patients. Table I shows patient and tumour characteristics. Patients underwent surgery in more than 16 centres.

#### 3.1 Compliance with Treatment

Eleven patients (32%) were unable to complete the prescribed 5FU: 1 of 6 patients in cohort 1, 3 of 10 in cohort 2, 3 of 7 in cohort 3, 1 of 6 in cohort 4, and 3 of 5 in cohort 5. Treatment was stopped for toxicity ( $n = 9$ ), poor coping and language difficulties ( $n = 1$ ), and a combination of toxicity and nonmedical reasons ( $n = 1$ ). Among the non-completers, the mean duration of 5FU was 7 weeks (range: 0.5–11 weeks). Of these 11 patients, 4 (11%) also did not complete cisplatin: in cohort 2, 1 of 10 patients received only 1 of 4 planned doses, and in cohort 5, 1 of the 5 patients received 3 of 5 planned doses and 2 received 4 of 5 planned doses.

#### 3.2 Radiation Therapy

Of the 11 patients who did not complete chemotherapy, 3 also did not complete RT on study. Of those 3 patients, 1 patient in cohort 1 experienced a DLT (sepsis related to a PICC line infection) that required hospitalization. Although this participant came off study, she received standard chemoradiation at a later date. A participant in cohort 2 stopped all treatment after 1 week because of coping and language difficulties. A participant in cohort 3 received only 36 Gy of the 45-Gy treatment because of upper gastrointestinal toxicity. All other study patients completed the full RT dose without significant delays.

#### 3.3 Toxicity

##### 3.3.1 Acute Toxicity

Five patients experienced DLT. In cohort 5, 2 patients experienced DLTS (see Table II), and cohort 4

(4 cycles of cisplatin 40 mg/m<sup>2</sup>) was defined as the MTD. No grade 5 events occurred. Only 1 patient, in cohort 5, experienced grade 4 toxicity: uncomplicated neutropenia in week 12 of treatment. Table II shows the overall acute toxicity and DLTS occurring in each cohort. Tables III, IV, and V show, by grade and dose level, the individual RTOG and CTC v2.0 acute toxicities that occurred.

Only 3 patients over the age of 70 were entered into the study before a protocol amendment. Two experienced a grade 3 DLT and failed to complete all protocol therapy (cohorts 2 and 3); the third patient completed the protocol but experienced multiple grade 2 upper gastrointestinal toxicities and required intravenous hydration during treatment.

##### 3.3.2 Late Toxicity

One patient who underwent total gastrectomy and remained relapse-free at the latest follow-up experienced late grade 3 weight loss and became feeding-tube dependent at 6 months, continuing in that status at the latest follow-up (2 years).

Pre-radiation renal function scans were obtained in 17 patients. In 10 patients, scans were obtained post radiation (between 4 months and 31 months). One patient (67 years old at diagnosis) with no other medical problems had an abnormal differential with reduced right side function (42% vs. 51% pre-treatment) at his scan 17 months after radiation treatment, with a reduction in glomerular filtration rate of 12 mL/min. Radiation doses to both of his kidneys fell within the dose constraints.

#### 3.4 RFS and OS

Median follow-up for living patients was 2.7 years (range: 0.3–5 years). One patient was lost to follow up. Relapse occurred in 9 patients (26%—2 from

TABLE III Patients with acute toxicity by Radiation Therapy Oncology Group category, maximal grade, and dose level

| Toxicity |       | Patients (n) experiencing toxicity at each dose level |             |            |            |            |
|----------|-------|-------------------------------------------------------|-------------|------------|------------|------------|
| Category | Grade | 1<br>(N=6)                                            | 2<br>(N=10) | 3<br>(N=7) | 4<br>(N=6) | 5<br>(N=5) |
| Skin     | 1     | 5                                                     | 2           | 1          | 2          | 0          |
|          | 2     | 0                                                     | 2           | 0          | 1          | 1          |
|          | 3     | 0                                                     | 0           | 1          | 0          | 0          |
| GI       | Lower | 1                                                     | 2           | 4          | 1          | 2          |
|          |       | 2                                                     | 0           | 2          | 1          | 1          |
|          |       | 3                                                     | 0           | 0          | 0          | 0          |
|          | Upper | 1                                                     | 1           | 0          | 3          | 1          |
|          |       | 2                                                     | 2           | 7          | 2          | 4          |
|          |       | 3                                                     | 0           | 0          | 0          | 0          |

GI = gastrointestinal.

TABLE IV Patients with non-hematologic acute toxicity<sup>a</sup>, by maximum grade and dose level

| Toxicity                | Grade | Patients (n) experiencing toxicity at each dose level |             |            |            |            |
|-------------------------|-------|-------------------------------------------------------|-------------|------------|------------|------------|
|                         |       | 1<br>(N=6)                                            | 2<br>(N=10) | 3<br>(N=7) | 4<br>(N=6) | 5<br>(N=5) |
| Lethargy                | 1     | 2                                                     | 1           | 0          | 2          | 0          |
|                         | 2     | 4                                                     | 7           | 7          | 4          | 5          |
|                         | 3     | 0                                                     | 1           | 0          | 0          | 0          |
| Anorexia                | 1     | 2                                                     | 1           | 1          | 2          | 0          |
|                         | 2     | 4                                                     | 8           | 6          | 2          | 4          |
|                         | 3     | 0                                                     | 0           | 0          | 0          | 1          |
| Weight loss             | 1     | 2                                                     | 4           | 3          | 3          | 0          |
|                         | 2     | 2                                                     | 2           | 4          | 2          | 4          |
|                         | 3     | 0                                                     | 0           | 0          | 0          | 1          |
| Dehydration             | 1     | 0                                                     | 0           | 0          | 0          | 3          |
|                         | 2     | 1                                                     | 2           | 3          | 1          | 0          |
|                         | 3     | 0                                                     | 0           | 1          | 0          | 1          |
| Diarrhea                | 1     | 0                                                     | 1           | 0          | 1          | 2          |
|                         | 2     | 0                                                     | 1           | 2          | 0          | 0          |
|                         | 3     | 0                                                     | 0           | 0          | 0          | 0          |
| Dysphagia               | 1     | 1                                                     | 0           | 0          | 1          | 0          |
|                         | 2     | 0                                                     | 0           | 0          | 0          | 1          |
|                         | 3     | 0                                                     | 0           | 0          | 0          | 0          |
| Dyspepsia/<br>heartburn | 1     | 3                                                     | 2           | 3          | 3          | 2          |
|                         | 2     | 0                                                     | 0           | 2          | 2          | 2          |
|                         | 3     | 0                                                     | 0           | 0          | 0          | 0          |
| Nausea                  | 1     | 5                                                     | 3           | 2          | 3          | 0          |
|                         | 2     | 0                                                     | 6           | 4          | 2          | 4          |
|                         | 3     | 0                                                     | 0           | 1          | 0          | 0          |
| Vomiting                | 1     | 3                                                     | 2           | 2          | 1          | 1          |
|                         | 2     | 0                                                     | 2           | 2          | 0          | 3          |
|                         | 3     | 0                                                     | 0           | 1          | 0          | 0          |
| Gastritis/reflux        | 1     | 0                                                     | 0           | 2          | 1          | 2          |
|                         | 2     | 1                                                     | 2           | 2          | 0          | 1          |
|                         | 3     | 1                                                     | 0           | 0          | 0          | 0          |
| Abdominal pain          | 1     | 0                                                     | 0           | 0          | 0          | 0          |
|                         | 2     | 0                                                     | 1           | 0          | 0          | 0          |
|                         | 3     | 0                                                     | 0           | 0          | 0          | 0          |
| Stomatitis              | 1     | 0                                                     | 2           | 1          | 0          | 1          |
|                         | 2     | 0                                                     | 1           | 0          | 1          | 0          |
|                         | 3     | 0                                                     | 0           | 0          | 0          | 0          |
| Hand-foot<br>syndrome   | 1     | 1                                                     | 2           | 1          | 1          | 0          |
|                         | 2     | 0                                                     | 2           | 1          | 1          | 1          |
|                         | 3     | 0                                                     | 0           | 0          | 0          | 0          |
| Skin                    | 1     | 0                                                     | 2           | 0          | 2          | 2          |
|                         | 2     | 0                                                     | 1           | 0          | 0          | 0          |
|                         | 3     | 0                                                     | 0           | 0          | 0          | 0          |

<sup>a</sup> According to the *Common Terminology Criteria*, version 2.0<sup>13</sup>.

cohort 1, 3 from cohort 2, 1 from cohort 4, 3 from cohort 5). The sites of first relapse were local only ( $n = 2$ ), regional and distant ( $n = 1$ ), and distant only ( $n = 6$ ). Six patients (18%) died from their disease (2 from

TABLE V Patients with hematologic acute toxicity<sup>a</sup>, by maximum grade and dose level

| Toxicity              | Grade | Patients (n) experiencing toxicity at each dose level |             |            |            |            |
|-----------------------|-------|-------------------------------------------------------|-------------|------------|------------|------------|
|                       |       | 1<br>(N=6)                                            | 2<br>(N=10) | 3<br>(N=7) | 4<br>(N=6) | 5<br>(N=5) |
| Anemia                | 1     | 4                                                     | 4           | 3          | 4          | 3          |
|                       | 2     | 0                                                     | 0           | 1          | 1          | 1          |
|                       | 3     | 0                                                     | 0           | 0          | 0          | 0          |
| Neutropenia           | 1     | 2                                                     | 2           | 2          | 2          | 0          |
|                       | 2     | 0                                                     | 2           | 1          | 1          | 3          |
|                       | 3     | 0                                                     | 0           | 3          | 0          | 0          |
| Thrombo-<br>cytopenia | 1     | 0                                                     | 0           | 0          | 0          | 1          |
|                       | 2     | 1                                                     | 5           | 4          | 5          | 5          |
|                       | 3     | 0                                                     | 1           | 0          | 0          | 1          |
|                       | 1     | 0                                                     | 0           | 0          | 0          | 0          |
|                       | 2     | 0                                                     | 0           | 0          | 0          | 0          |
|                       | 3     | 0                                                     | 0           | 0          | 0          | 0          |

<sup>a</sup> According to the *Common Toxicity Criteria*, version 2.0<sup>13</sup>.

cohort 1, 2 from cohort 2, 2 from cohort 5). Figure 1 shows the Kaplan–Meier estimates for OS and RFS. The rates of OS and RFS at 3 years were 83% and 71% respectively, with median survival not reached.

#### 4. DISCUSSION

Our study shows that infusional 5FU and cisplatin can safely be administered to patients with gastric cancer. The current practice in North America of adjuvant chemoradiation for high-risk gastric adenocarcinoma is based on the INT-0116 study. That randomized controlled trial for completely resected gastric and gastroesophageal adenocarcinoma patients showed a survival benefit for treatment with adjuvant 5FU chemotherapy and radiation treatment over treatment with surgery alone<sup>11</sup>. Although 5FU alone was an appropriate choice at the time the INT-0116 study was designed, that chemotherapy regimen is not now considered to be the most active for gastric adenocarcinoma. Patterns of relapse in the INT-0116 study showed that the regimen used was more effective at reducing locoregional recurrence than extra-abdominal relapse. Efforts to improve adjuvant treatment in this setting have had two competing foci: to reduce acute toxicity and to reduce distant failures by providing more effective systemic therapy.

Acute toxicity in INT-0116 was high, with the incidences of grade 3, 4, and 5 toxicity being 41%, 32%, and 1% respectively. In addition, 36% of patients were unable to complete therapy because of several factors, including toxicity, patient preference, and progression of disease. These levels of acute toxicity (and concomitant compliance) have been similar in other series, including in a review from our institution<sup>3,15,16</sup>. The INT-0116 study showed a 3-year OS of

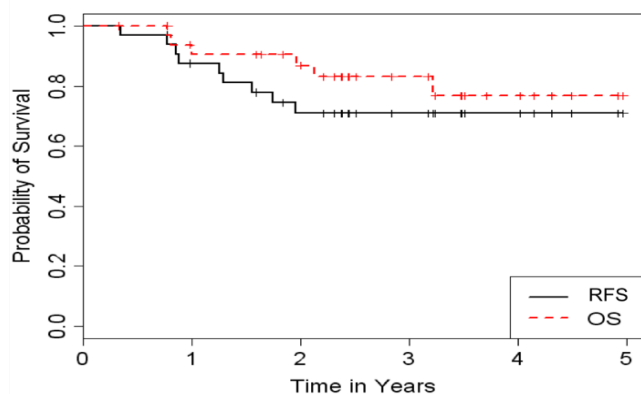


FIGURE 1 Kaplan-Meier curves for overall (os) and relapse-free survival (RFS).

50% with adjuvant chemoradiation, compared with 41% for treatment with surgery alone. Although our study has small numbers and a relatively short follow-up, the 3-year os of 83% is reassuring. However, elderly patients tolerated the cisplatin-containing regimen poorly, and it is our impression that, for the schedule we tested, the MTD for patients over 70 years of age may be cohort 1 (12 weeks of infusional 5FU with radiotherapy).

One strategy to optimize the balance of acute toxicities and survival outcomes in gastric cancer is an assessment of alternative chemoradiation regimens in the adjuvant setting<sup>17–23</sup>. The use of infusional 5FU may itself improve survival and toxicity outcomes. In advanced colorectal cancer, continuous-infusion 5FU, as compared with a bolus 5FU regimen, improved response rates and survival outcomes<sup>4</sup>. Continuous-infusion 5FU was also associated with lower rates of hematologic toxicity, although more hand-foot syndrome occurred. Those findings are supported by our study, in which no grade 4 hematologic toxicity was seen in cohorts 1–4. Additionally, cisplatin has been studied in the metastatic setting in gastric cancer, and response rates have generally been higher with cisplatin-containing regimens<sup>5,6,24</sup>. Cisplatin has also been used as a radiosensitizer in other malignancies, and compared with radiation alone, it was shown to be associated with improved survival outcomes<sup>8,25,26</sup>.

Other centers have demonstrated the feasibility and tolerability of incorporating pre- or post-radiation cisplatin with concurrent 5FU chemoradiotherapy<sup>27,28</sup>. Lee *et al.*<sup>28</sup> conducted a pilot study of adjuvant chemoradiation in 31 patients after complete resection of stage III and IV (M0) gastric adenocarcinoma<sup>28</sup>. The chemotherapy regimen was infusional 5FU and cisplatin administered pre- and post-RT, with concurrent capecitabine during RT. The toxicity profile was similar to that seen in the INT-0116 study, and 3-year OS was 83%. Kollmannsberger *et al.*<sup>27</sup> reported a phase II study of 45 patients, stages IB to IV (M0), treated with adjuvant infusional 5FU and cisplatin,

with infusional 5FU alone during radiation<sup>27</sup>. That regimen was well tolerated, with less toxicity than in the INT-0116 study and with a 2-year OS of 79%. A current Intergroup phase III trial is randomizing patients to chemotherapy with epirubicin, cisplatin, and 5FU, or to the 5FU-leucovorin regimen used in INT-0116, and to pre- and post-RT with infusional 5FU during radiation<sup>14</sup>.

In addition to the present study, we are aware of only one other that used cisplatin concurrently with radiation in the adjuvant setting, exploiting the radiosensitizing properties of cisplatin as well as its potentially improved systemic activity<sup>29</sup>. Jansen *et al.* reported on a phase I/II dose-finding study in 32 patients using capecitabine twice daily for 2 weeks, followed by RT with concurrent capecitabine twice daily and daily cisplatin. The MTD was cisplatin 5 mg/m<sup>2</sup> 5 days each week and capecitabine 650 mg/m<sup>2</sup> twice daily. About 28% of patients developed grade 3 or 4 toxicity, with no grade 5 events. The 2-year OS was about 50%. Although 97% of patients completed treatment, this adjuvant regimen was significantly shorter than the one used in INT-0116 and other adjuvant studies. Compared with the INT-0116 study regimen, our regimen is also shorter and easier for patients, demonstrating good tolerability without compromising survival outcomes.

## 5. CONCLUSIONS

The present study shows that radiation combined with infusion 5FU and concurrent cisplatin every 2 weeks in the adjuvant setting is feasible and well tolerated, with favourable survival outcomes. The MTD was cisplatin 40 mg/m<sup>2</sup> given every 2 weeks at weeks 1, 3, 5, and 7; 5FU 200 mg/m<sup>2</sup> daily by continuous infusion for 12 weeks; and radiation therapy 45 Gy in 25 fractions for 5 weeks starting at day 16 of the chemotherapy treatment course. This regimen is currently being explored in a phase II study at our institution.

## 6. ACKNOWLEDGMENTS

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## 7. CONFLICT OF INTEREST DISCLOSURES

All the authors declare that there are no financial conflicts of interest.

## 8. REFERENCES

1. Earle CC, Maroun J, Zuraw L, and members of the Gastrointestinal Cancer Disease Site Group Cancer Care Ontario Practice Guidelines Initiative. Neoadjuvant or Adjuvant

- Therapy for Resectable Gastric Cancer. Practice guideline report #2-14. Toronto, ON: Cancer Care Ontario, Program in Evidence-Based Care; 2003. [Available online at: [www.cancercare.on.ca/common/pages/UserFile.aspx?fileId=13970](http://www.cancercare.on.ca/common/pages/UserFile.aspx?fileId=13970); cited June 8, 2010]
2. Macdonald JS, Smalley S, Benedetti J, *et al*. Postoperative combined radiation and chemotherapy improves disease-free survival (DFS) and overall survival (OS) in resected adenocarcinoma of the stomach and gastroesophageal junction: update of the results of Intergroup Study INT-0116 (swog 9008) [abstract 6]. *Proc Am Soc Clin Oncol Gastrointest Cancers Symp* 2004;:. [Available online at: [www.asco.org/ASCOv2/Meetings/Abstracts?&vmview=abst\\_detail\\_view&confID=27&abstractID=538](http://www.asco.org/ASCOv2/Meetings/Abstracts?&vmview=abst_detail_view&confID=27&abstractID=538); cited June 8, 2010]
  3. Kassam Z, Lockwood G, O'Brien C, *et al*. Conformal radiotherapy in the adjuvant treatment of gastric cancer: review of 82 cases. *Int J Radiat Oncol Biol Phys* 2006;65:713–19.
  4. Meta-analysis Group in Cancer. Efficacy of intravenous continuous infusion of fluorouracil compared with bolus administration in advanced colorectal cancer. *J Clin Oncol* 1998;16:301–8.
  5. 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.
  6. 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;15:261–7.
  7. Whitney CW, Sause W, Bundy BN, *et al*. Randomized comparison of fluorouracil plus cisplatin versus hydroxyurea as an adjunct to radiation therapy in stage IIB–IVA carcinoma of the cervix with negative para-aortic lymph nodes: a Gynecologic Oncology Group and Southwest Oncology Group study. *J Clin Oncol* 1999;17:1339–48.
  8. Rose PG, Bundy BN, Watkins EB, *et al*. Concurrent cisplatin-based radiotherapy and chemotherapy for locally advanced cervical cancer. *N Engl J Med* 1999;340:1144–53.
  9. International Union Against Cancer. *TNM Classification of Malignant Tumors*. 6th ed. New York: Wiley Liss; 2002.
  10. Ringash J, Perkins G, Brierley J, *et al*. IMRT for adjuvant radiation in gastric cancer: a preferred plan? *Int J Radiat Oncol Biol Phys* 2005;63:732–8.
  11. Macdonald JS, Smalley SR, Benedetti J, *et al*. Chemoradiotherapy after surgery compared with surgery alone for adenocarcinoma of the stomach or gastroesophageal junction. *N Engl J Med* 2001;345:725–30.
  12. Radiation Therapy Oncology Group (RTOG). RTOG/EORTC Late Radiation Morbidity Scoring Schema [Web page]. Philadelphia: RTOG; n.d. [Available at: [www.rtog.org/members/toxicity/late.html](http://www.rtog.org/members/toxicity/late.html); cited June 20, 2010]
  13. United States, National Institutes of Health, National Cancer Institute, Cancer Therapy Evaluation Program (CTEP). *Common Toxicity Criteria (CTC)*. Version 2. Bethesda, MD: CTEP; 1999. [Available online at: [ctep.cancer.gov/protocolDevelopment/electronic\\_applications/docs/ctcv20\\_4-30-992.pdf](http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/ctcv20_4-30-992.pdf); cited June 8, 2010]
  14. United States, National Institutes of Health, National Cancer Institute (NCI). Clinical Trials (PDQ). Phase III Randomized Study of Adjuvant Chemoradiation After Resection in Patients with Gastric or Gastroesophageal Adenocarcinoma [Web page]. Bethesda, MD: NCI; 2002. [Available online at: [www.cancer.gov/clinicaltrials/CALGB-80101](http://www.cancer.gov/clinicaltrials/CALGB-80101); cited June 8, 2010]
  15. Hughes BG, Yip D, Chao M, *et al*. Audit of postoperative chemoradiotherapy as adjuvant therapy for resected gastroesophageal adenocarcinoma: an Australian multicentre experience. *ANZ J Surg* 2004;74:951–6.
  16. Park SH, Kim DY, Heo JS, *et al*. Postoperative chemoradiotherapy for gastric cancer. *Ann Oncol* 2003;14:1373–7.
  17. Schwartz GK, Winter K, Minsky B, *et al*. A randomized phase II trial comparing two paclitaxel (P)–cisplatin (C) containing chemoradiation (CRT) regimens as adjuvant therapy in resected gastric cancer (RTOG Intergroup #0114) [abstract 4020]. *Proc Am Soc Clin Oncol* 2005;23:312s. [Available online at: [www.asco.org/ASCOv2/Meetings/Abstracts?&vmview=abst\\_detail\\_view&confID=34&abstractID=30590](http://www.asco.org/ASCOv2/Meetings/Abstracts?&vmview=abst_detail_view&confID=34&abstractID=30590); cited June 8, 2010]
  18. Escudero MP, Alonso V, Valencia J, *et al*. Adjuvant postoperative chemoradiotherapy in gastric carcinoma [abstract 4168]. *Proc Am Soc Clin Oncol* 2004;22:.. [Available online at: [www.asco.org/ASCOv2/Meetings/Abstracts?&vmview=abst\\_detail\\_view&confID=26&abstractID=1634](http://www.asco.org/ASCOv2/Meetings/Abstracts?&vmview=abst_detail_view&confID=26&abstractID=1634); cited June 8, 2010]
  19. Sharma VB, Koong AC, Cho C, *et al*. Adjuvant chemoradiotherapy for T3, T4, or node positive gastric cancer: a phase II trial [abstract 4139]. *Proc Am Soc Clin Oncol* 2004;22:.. [Available online at: [www.asco.org/ASCOv2/Meetings/Abstracts?&vmview=abst\\_detail\\_view&confID=26&abstractID=643](http://www.asco.org/ASCOv2/Meetings/Abstracts?&vmview=abst_detail_view&confID=26&abstractID=643); cited June 8, 2010]
  20. Bokemeyer C. Adjuvant radiochemotherapy (RTX/CTX) using 5-FU/folinic acid (FA) /cisplatin (DDP) ± paclitaxel (P) and radiation in patients (pts) with completely (R0) resected high-risk gastric cancer (UICC stages II–IV (M0)): an extended phase II study of the AIO/ARO/ACO [abstract 4036]. *Proc Am Soc Clin Oncol* 2004;22:.. [Available online at: [www.asco.org/ASCOv2/Meetings/Abstracts?&vmview=abst\\_detail\\_view&confID=26&abstractID=2875](http://www.asco.org/ASCOv2/Meetings/Abstracts?&vmview=abst_detail_view&confID=26&abstractID=2875); cited June 8, 2010]
  21. Leong T, Michael M, Foo K, *et al*. Adjuvant and neoadjuvant therapy for gastric cancer using epirubicin/cisplatin/5-fluorouracil (ECF) and alternative regimens before and after chemoradiation. *Br J Cancer* 2003;89:1433–8.
  22. Arcangeli G, Saracino B, Angelini F, Marchetti P, Tirindelli Danesi D. Postoperative adjuvant chemoradiation in completely resected locally advanced gastric cancer. *Int J Radiat Oncol Biol Phys* 2002;54:1069–75.
  23. Buckley C, Ringash J, Brierley J, *et al*. Prospective phase I study of post-operative adjuvant radiochemotherapy for gastric cancer with infusional 5-fluorouracil and cisplatin: 2005 update [abstract 48]. *Proc Am Soc Clin Oncol Gastrointest Cancers Symp* 2005;:. [Available online at: [www.asco.org/ASCOv2/Meetings/Abstracts?&vmview=abst\\_detail\\_view&confID=36&abstractID=10286](http://www.asco.org/ASCOv2/Meetings/Abstracts?&vmview=abst_detail_view&confID=36&abstractID=10286); cited June 8, 2010]
  24. Wagner AD, Grothe W, Behl S, *et al*. Chemotherapy for advanced gastric cancer. *Cochrane Database Syst Rev* 2005;CD004064.
  25. Al-Sarraf M, Martz K, Herskovic A, *et al*. Progress report of combined chemoradiotherapy versus radiotherapy alone in patients with esophageal cancer: an Intergroup study. *J Clin Oncol* 1997;15:277–84.
  26. Al-Sarraf M, Pajak TF, Byhardt RW, Beitler JJ, Salter MM, Cooper JS. Postoperative radiotherapy with concurrent cisplatin

appears to improve locoregional control of advanced, resectable head and neck cancers: RTOG 88-24. *Int J Radiat Oncol Biol Phys* 1997;37:777–82.

27. Kollmannsberger C, Budach W, Stahl M, *et al.* Adjuvant chemoradiation using 5-fluorouracil/folinic acid/cisplatin with or without paclitaxel and radiation in patients with completely resected high-risk gastric cancer: two cooperative phase II studies of the AIO/ARO/ACO. *Ann Oncol* 2005;16:1326–33.
28. Lee HS, Choi Y, Hur WJ, *et al.* Pilot study of postoperative adjuvant chemoradiation for advanced gastric cancer: adjuvant 5-FU/cisplatin and chemoradiation with capecitabine. *World J Gastroenterol* 2006;12:603–7.
29. Jansen EP, Boot H, Dubbelman R, Bartelink H, Cats A, Verheij M. Postoperative chemoradiotherapy in gastric cancer—a phase I/II dose-finding study of radiotherapy with dose escalation of cisplatin and capecitabine chemotherapy. *Br J Cancer* 2007;97:712–16.

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