Oxaliplatin and capecitabine in patients with metastatic adenocarcinoma of the esophagus, gastroesophageal junction and gastric cardia: a phase II study from the North Central Cancer Treatment Group


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Purpose: The synergic combination of oxaliplatin and capecitabine has demonstrated activity against various gastrointestinal cancers, including colon cancer. We therefore undertook this phase II study to test this first-line combination in patients with metastatic adenocarcinoma of the esophagus, gastroesophageal junction and gastric cardia.

Patients and methods: Forty-three patients with histologic or cytologic confirmation of the above malignancy were recruited. The cohort had Eastern Cooperative Oncology Group performance statuses of 0, 1 and 2 in 47%, 51%, and 2%, respectively. Median age was 61 years (range 32–80). All had adequate organ function. Initially, patients were prescribed 130 mg/m² intravenously on day 1 and capecitabine 1000 mg/m² orally twice a day, on days 1–14 of a 21-day cycle. Four treatment-related deaths in the first 24 patients led to a reduction in capecitabine to 850 mg/m² orally twice a day, days 1–14, for the remainder of the cohort.

Results: The tumor response rate was 35% [95% confidence intervals (CI) 23% to 50%]. All responses were partial; seven of 24 occurred before the capecitabine dose reduction, and eight of 19 after. Median time to tumor progression was 4 months (95% CI 3.1–4.6), and median survival 6.4 months (95% CI 4.6–10). To date, there have been 36 deaths. Four were treatment-related (one infection, two myocardial infarctions, one respiratory failure), and all occurred before the capecitabine dose reduction. Notable grade 4 events from the entire cohort included diarrhea (two patients), vomiting (three), dyspnea (one), thrombosis (two) and anorexia (two). Grade 3 events included nausea (12 patients), diarrhea (12), fatigue (10), abdominal pain (seven), vomiting (six), dyspnea (six), hypokalemia (six), dehydration (five), hypokalemia (five) and infection (four).

Conclusions: Oxaliplatin and capecitabine in combination demonstrates activity in metastatic adenocarcinoma of the esophagus, gastroesophageal junction and gastric cardia. The lower dose (capecitabine 850 mg/m² orally twice a day, days 1–14, and oxaliplatin 130 mg/m² intravenously on day 1) yielded an acceptable toxicity profile and merits further study.

Key words: chemotherapy, esophageal cancer, metastatic, oral therapy, response rate

introduction

The drug combination of oxaliplatin and capecitabine appears to provide synergic antitumor effects in gastrointestinal malignancies, and hence further testing of this combination should be undertaken in cancer clinical trials. Utilizing a human colon cancer xenograft model, Cassidy et al. [1] found that the combination of oxaliplatin and capecitabine inhibited tumor growth to a much greater degree than either one of these agents when given individually at a maximally tolerated dose. Moreover, the adverse event profiles of each of these agents do not overlap, thus suggesting that utilizing these agents as a doublet regimen is reasonable.

The combination of oxaliplatin and capecitabine has yielded favorable tumor response rates in patients with gastrointestinal malignancies. Auspicious reports of single-agent activity and of second-line activity with oxaliplatin/fluoropyrimidine-based combinations are rapidly emerging. In addition, several studies have tested this regimen in patients with metastatic colorectal cancer. Response rates have been as high as 54% [2–4]. Such...
response rates suggest that this drug combination is worthy of further testing in patients with gastrointestinal malignancies [5–8].

Finally, two pieces of information point to the feasibility of conducting a phase II trial of oxaliplatin and capcitabine in patients with adenocarcinoma of the esophagus, gastroesophageal junction and gastric cardia. First, Díaz-Rubio et al. [9] reported on a phase I trial that tested this combination. This 23-patient trial found that capcitabine 1000 mg/m² given twice daily on days 1–14 plus oxaliplatin 130 mg/m² on day 1, both of which were given on a 21-day cycle, were well tolerated. This study helped to provide the groundwork for the present trial. Secondly, the North Central Cancer Treatment Group (NCCTG) has explored the prevalence and severity of dysphagia in an earlier trial conducted in patients with metastatic esophageal cancer [10]. At first glance, the use of oral chemotherapy in patients with esophageal cancer might seem counterintuitive in light of the possibility that dysphagia might preclude capcitabine administration. However, a previous NCCTG study showed that while dysphagia is prevalent, most patients who remain eligible for chemotherapy do not suffer from severe dysphagia to the point that it interferes with their ability to take pills [10].

The present study was therefore undertaken to test the combination of oxaliplatin and capcitabine as first-line therapy in patients with metastatic adenocarcinoma of the esophagus, gastroesophageal junction and gastric cardia. A variety of clinically relevant end points, such as response rate, survival, time-to-tumor progression, adverse events and quality of life, are reported.

patients and methods

overview

This phase II trial was conducted within the NCCTG, and the Institutional Review Boards at each specific study site within this cooperative group approved the study protocol before patient enrollment. All patients provided signed informed consent prior to trial participation.

eligibility

Eligibility criteria consisted of the following: (i) histologic or cytologic confirmation of adenocarcinoma of the esophagus, gastroesophageal junction or gastric cardia; (ii) Eastern Cooperative Oncology Group performance status of 2 or better; (iii) age 18 years or older; (iv) measurable disease; (v) physician-estimated life expectancy of 12 weeks or longer; (vi) able to swallow pills; (vii) able to complete questionnaires relevant to quality of life; and (viii) willingness to participate in a translational component that entailed submission of a urine sample.

In addition, all patients must have had the following laboratory parameters 14 days prior to registration: (i) absolute neutrophil counts ≥1.5 × 10⁹/μL; (ii) platelet count ≥100 × 10⁹/μL; (iii) serum creatinine ≤1.5 mg/dL and a calculated creatinine clearance of ≥60 mL/min; (iv) total bilirubin within the normal range at that institution; (v) aspartate aminotransferase ≤2 times the upper limit of normal; (vi) the alkaline phosphatase ≤2 times the upper limit of normal.

Finally, patients were not eligible if they had any one of the following: (i) prior treatment for metastatic cancer, although prior adjuvant or neo-adjuvant treatment was permissible; (ii) prior radiation to over 25% of the marrow cavity or any radiation within 4 weeks prior to registration; (iii) exploratory laparotomy within 3 weeks; (iv) availability of potentially curative treatment, an eligibility criterion that the investigators interpreted as excluding patients with locally advanced disease; (v) uncontrolled infection or chronic debilitating illness; (vi) peripheral neuropathy of grade 2 or worse; (vii) pregnant, nursing, or of child-bearing potential and unwilling to employ adequate contraception; (viii) known central nervous system metastases; (ix) prior malignancy, except for adequately treated basal cell/squamous cell carcinomas or other cancer for which the patient has been disease free for 5 years or longer.

treatment

Patients were originally treated with oxaliplatin 130 mg/m² intravenously on day 1 and capcitabine 1000 mg/m²/dose orally twice a day on days 1–14, both of which were given as part of a 21-day cycle. However, because of three initial and one subsequent treatment-related deaths in the first 24 patients (discussed below), the starting dose at study entry was changed to the following: oxaliplatin 130 mg/m² intravenously on day 1 and capcitabine 850 mg/m²/dose orally twice a day on days 1–14, both of which were still prescribed on a 21-day cycle.

Subsequent reductions of the starting dose were in part based on toxicity at the time of re-treatment. Neutropenia and fevers or transient renal insufficiency in the preceding cycle prompted a 20% reduction in both agents for the next cycle. Capcitabine alone was reduced by 20% or 30% for grade 2 or 3 hand–foot syndrome, respectively, as occurred in the preceding cycle. It was reduced in the next cycle by 20% or 30% for grade 2 mucositis or for grade 3 or 4 mucositis, respectively. Oxaliplatin was to be held in the event of cough or another indicator of interstitial lung disease or in the event of suspicion for hemolytic uremic syndrome. Confirmation of either of these diagnoses was to result in complete discontinuation of this agent. Grade 2 peripheral neuropathy prompted a 25% dose reduction of oxaliplatin, but more severe neuropathy resulted in its discontinuation. For interval diarrhea of grade 2 or 3, capcitabine was to be reduced by 20%, and for diarrhea of grade 4, it was to be reduced by 30%. Oxaliplatin was to be reduced by 25% for grade 4 diarrhea. Other clinical parameters, including depressed blood counts, persistent diarrhea, hyperbilirubinemia or, as mentioned above, persistent renal insufficiency, called for holding chemotherapy until complete or partial resolution.

Holding treatment for more than 3 weeks precluded patients’ continued treatment. The protocol also stated that capcitabine should be held mid-cycle in the event of any grade 4 event and should not be reintiated that cycle. In the event of grade 3 neutropenic fever and grade 2 mucositis, diarrhea or hand–foot syndrome, capcitabine was again to be held mid-cycle. However, decisions as to when and how to resume capcitabine before the beginning of the next cycle were left to the discretion of the treating oncologist. For most other grade 3 events that occurred mid-cycle, it was strongly advised that the treating oncologist hold treatment, but the final decision on this matter was left to the discretion of the treating oncologist.

pretreatment and follow-up evaluations

All patients were to undergo a history and physical examination within 14 days of trial registration. Laboratory testing was to be performed within this time frame as well, and included a hemogram, serum alkaline phosphatase, aspartate aminotransferase (AST), total bilirubin and creatinine. A chest radiograph had to have been performed between 14 and 28 days of registration, depending on whether it was to be used for tumor assessment. All radiographs that were to be used for tumor assessment had to have been performed within 14 days of trial registration. All patients were to have completed quality of life questionnaires that consisted of the FACT-E [11]. These questionnaires were to be completed by the patient with every other chemotherapy cycle. Finally, all patients had to have
provided a urine sample for a translational component to be reported as a separate manuscript.

All patients were monitored throughout the study with weekly hemograms. Monitoring of other blood tests such as chemistry profiles were left to the discretion of the treating oncologist. The National Cancer Institute Common Toxicity Criteria, version 2.0, were used for the assessment of adverse events. On the first day of each 21-day chemotherapy cycle, a history and physical examination, hemogram, and other blood tests, including the serum total bilirubin, AST, alkaline phosphatase and creatinine, were checked.

Tumor evaluations, which assessed response to therapy, were performed immediately before every scheduled odd treatment cycle. The RECIST criteria were used for this purpose (http://www.nci.nih.gov/bip/RECIST.htm), and as per these criteria, a 30% decrease in the sum of the largest dimension of target lesions from baseline was indicative of a possible response to treatment. Confirmatory scans at least 4 weeks apart were required before a patient was determined to have had an actual response to treatment. Chemotherapy was continued after each tumor evaluation if there appeared to be disease stability or a complete or partial response to treatment. Patients with evidence of cancer progression were not treated further with chemotherapy as prescribed in this study protocol.

### statistical analyses

The primary objective of this trial was to report the proportion of patients with a response to this chemotherapy regimen. All patients who met the eligibility criteria, signed a consent form and began treatment were included in the tumor response analyses.

A two-stage phase II Fleming design was used to test whether there was sufficient evidence to determine whether the confirmed response rate was at least 35%, a rate the study team viewed as clinically promising, versus at most 15%, a rate the study team viewed as not clinically promising. With 40 patients, this trial carried 87% power to detect a response rate of 35% with a 0.06 level of significance.

An interim analysis was to be performed after the first 10 evaluable patients were enrolled. If at least seven of these were to have a tumor response, this information alone would have constituted evidence of promising activity of the study regimen. If one or fewer of these 10 patients had a response, this information would have suggested the regimen is not promising activity of the study regimen. If two to six of these initial 10 patients were to have manifested a tumor response, study enrollment would then proceed to full accrual of 40 patients. If at least seven of 40 patients manifested a tumor response, this information would be interpreted to suggest evidence of promising activity and in turn might merit further study.

A confidence interval for the percentage of patients with a tumor response was calculated using the method of Duffy and Santner [12].

Secondary end points include descriptive summaries of adverse events, time to tumor progression, overall survival and quality of life. Adverse events are presented in part in tabular form. Time to progression was defined as the time from study registration to tumor growth (defined as a ≥20% increase in size of summed largest dimensions of the target lesions). Patients who died without tumor assessment were viewed as having tumor progression at death unless there was sufficient documentation to prove otherwise. Overall survival was defined as the time from study registration to death from any cause. Time-to-event distributions were estimated with the Kaplan-Meier method [13]. Quality of life data are also presented descriptively.

### results

#### demographics

Forty-three eligible patients were enrolled from December 2002 to April 2004. Two patients never received any study medication, and three other patients were later found not to meet the original eligibility criteria; hence, these five patients are excluded from the analyses and in most of the descriptions that follow except in the reporting of adverse events. Unless specified, study results focus primarily on the 43 patients mentioned above.

Patient characteristics are listed in Table 1. The median age of the cohort was 62 years (range 32–80). Eleven per cent were women. Eastern Cooperative Oncology Group performance statuses of 0, 1 and 2 were observed in 47%, 51% and 2% of the cohort, respectively.

#### drug administration

Patients completed a median of four cycles of chemotherapy (range one to 12). No patients are still receiving chemotherapy at the time of this report. There was some overlap in reasons for stopping chemotherapy, but the initial reasons cited in the study records included cancer progression (n=28), intolerable adverse events or unwillingness to proceed further (n=16), or death (n=2).

Although periodic dose reductions were necessary, patients consistently received the entire anticipated dose (99–100%) of oxaliplatin for each of the first six cycles of chemotherapy. Similarly, patients received between 92% and 100% or more of their prescribed capcitabine dose for each or the first six cycles of chemotherapy. This slight reduction in prescribed dose presumably reflects a need to cut back on dosing mid-cycle because of adverse events.

#### response data

Of the 43 patients evaluable for tumor response, there were a total of 15 tumor responses, yielding a tumor response rate of 35% [95% confidence interval (CI) 23% to 50%]. All were partial. Of note, seven of 24 patients sustained a partial response before the protocol was amended to include a dose reduction of capcitabine, and eight of 19 manifested a partial response after the protocol was amended. The median duration of chemotherapy cycle was 56 days (range 40–74). Patients were able to proceed to full accrual of 40 patients. There was some overlap in reasons for stopping chemotherapy, but the initial reasons cited in the study records included cancer progression (n=28), intolerable adverse events or unwillingness to proceed further (n=16), or death (n=2).

![Table 1. Baseline characteristics](table1.png)
of response was 3.9 months (range 2.3–11.1) for 13 of the 15 patients who ultimately manifested tumor progression.

Patients were followed until death. As of the time of this report, there have been 36 deaths. For the surviving patients, median follow-up has been 12.4 months (range 8.8–25.9). The median time-to-tumor progression was 4 months (95% CI 3.1–4.6) and median survival 6.4 months (95% CI 4.6–10). (See Figures 1 and 2 for Kaplan–Meier time-to-tumor progression and overall survival curves.)

adverse events

Adverse event data include all 46 patients who received chemotherapy. Only grade 3 or worse events are reported, and all adverse events are included together regardless of whether they are directly attributable to chemotherapy. Adverse events are also reported together regardless of whether they occurred before or after the protocol was amended to include a dose reduction of capecitabine.

Four patients had grade 5, treatment-related events. These deaths consisted of a severe infection manifesting as an empyema, two myocardial infarctions, including one that occurred in the setting of a gastrointestinal bleed, and one episode of respiratory failure of unclear etiology. All four of these events occurred in patients who had started receiving chemotherapy on the protocol prior to an amendment to cut the capecitabine dosing. Frequent grade 4 events, defined as having occurred more than twice within the cohort, included only vomiting. Frequent grade 3 events, defined as having occurred more than five times within the cohort, included the following: nausea, vomiting, abdominal pain, fatigue, diarrhea, hypokalemia and shortness of breath. See Table 2 for listings of severe adverse events.

quality of life

Summed and averaged FACT-E scores demonstrated an almost consistent decline from baseline with repeated measurement. This trend was observed in global quality of life, the social/family well-being subscales, the physical well-being subscales and the functional well-being subscale. Of note, the emotional well-being subscale seemed to improve. Differences in scores from baseline were 12.1, 11 and 18.1 among the 30 remaining patients at cycle 2, the 21 remaining patients at cycle 4 and the nine remaining patients at cycle 6, respectively. Evidence of improvement hinged on favorable responses to questions such as 'I feel sad’, ‘I feel nervous’, ‘I worry about dying’ and ‘I worry my condition will get worse’.

discussion

This phase II study tested the combination of oxaliplatin and capecitabine as first-line therapy in patients with metastatic adenocarcinoma of the esophagus, gastroesophageal junction and gastric cardia. Four treatment-related deaths after roughly half the cohort had been enrolled prompted a dose reduction of capecitabine to 850 mg/m2 days 1–14 of a 21-day cycle. The overall tumor response rate observed in this study was

Table 2. Non-hematological adverse events of maximum severity, including four grade 5 events (n = 46)

<table>
<thead>
<tr>
<th>Event</th>
<th>Grade 3</th>
<th>Grade 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea</td>
<td>12 (26)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>7 (15)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>10 (22)</td>
<td>1 (2)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>12 (26)</td>
<td>2 (4)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>6 (13)</td>
<td>3 (7)</td>
</tr>
<tr>
<td>Anorexia</td>
<td>3 (7)</td>
<td>2 (4)</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>6 (13)</td>
<td>1 (2)</td>
</tr>
<tr>
<td>Dehydration</td>
<td>5 (11)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Infectiona</td>
<td>4 (9)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Hypokalemia</td>
<td>6 (13)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>AST abnormality</td>
<td>0 (0)</td>
<td>1 (2)</td>
</tr>
<tr>
<td>Myocardial ischemia/infarctionb</td>
<td>1 (2)</td>
<td>1 (2)</td>
</tr>
<tr>
<td>Melena</td>
<td>1 (2)</td>
<td>1 (2)</td>
</tr>
<tr>
<td>Pulmonaryy</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Thrombosis</td>
<td>1 (2)</td>
<td>2 (4)</td>
</tr>
<tr>
<td>Hematentasis</td>
<td>1 (2)</td>
<td>1 (2)</td>
</tr>
<tr>
<td>Hypoxia</td>
<td>0 (0)</td>
<td>1 (2)</td>
</tr>
<tr>
<td>Acidosis</td>
<td>30 (65)</td>
<td>1 (2)</td>
</tr>
<tr>
<td>ALT abnormality</td>
<td>0 (0)</td>
<td>1 (2)</td>
</tr>
<tr>
<td>Microangiopathic anemia</td>
<td>0 (0)</td>
<td>1 (2)</td>
</tr>
</tbody>
</table>

*aOne such grade 5 adverse event occurred.

*bTwo such grade 5 events occurred.

*cOne such grade 5 event occurred.

AST, aspartate aminotransferase; ALT, alanine aminotransferase.
35% (95% CI 23% to 50%), and seven of 24 responses occurred before the capcitabine dose reduction, and eight of 19 after. This study suggests that the lower dose of capcitabine is safe, that it carries activity in the first-line setting in patients with adenocarcinoma of the esophagus, gastroesophageal junction and gastric cardia.

An important aspect of this study focuses on the appropriate dosing of this drug combination. The need to cut back on the dosing of capcitabine might be explained from two different perspectives. First, patients with metastatic esophageal cancer may be more vulnerable to adverse events from the higher dose. It is true that the preliminary data from Makatsoris et al. [4] suggested that the original doses of capcitabine and oxaliplatin used in this trial were reasonable, and since the completion of our study, other data from patients with colorectal cancer have suggested that this dosing is relatively safe. Although our study included patients with a reasonable performance status and no prior therapy for metastatic disease—entry criteria that would suggest this cohort would tolerate chemotherapy quite well—it is important to point out that few published studies have examined this regimen in patients with metastatic esophageal cancer. We contend that although a higher dose of capcitabine may be safe for patients with other malignancies, it is prudent to opt for a lower dose of capcitabine at least initially in patients with metastatic esophageal cancer. Secondly, differences in tolerance of dosing appear to differ in North American versus European studies, with the latter being able to prescribe higher doses of chemotherapy. It is unclear whether these differing adverse event rates reflect differences in how patients or health-care providers report adverse events or whether they reflect perhaps differences in the genetic make-up between the two continents and differences in patients’ ability to clear drugs.

As a minor point, the quality of life data presented here are intriguing. Curiously, patients reported an improvement in emotional well being consistently throughout the trial, even when other aspects of quality of life were declining. Often, high drop-out rates result in more favorable scores among the remaining survivors. However, such favorable scores were observed exclusively within the emotional well being subscale. Patients consistently denied such statements as ‘I feel sad’, ‘I feel nervous’, ‘I worry about dying’ and ‘I worry my condition will get worse’. These findings suggest that the very act of receiving chemotherapy enhances the emotional well being of cancer patients, perhaps at the same time that it detracts from other aspects of quality of life. Future studies may focus on this phenomenon of improved emotional well being with the chemotherapy in an effort to better understand the reasons behind it.

Finally, do the results of this study merit testing this regimen in a phase III setting? It is unlikely that this regimen could stand alone as a first-line, highly effective therapy for patients with metastatic adenocarcinoma of the esophagus, gastroesophageal junction and gastric cardia. Some might argue that the median survival of 6.4 months (95% CI 4.6–10) observed in this trial is inferior to that observed with other regimens. However, the fact that this regimen, after a dose alteration, was fairly well tolerated and the fact that it appears amenable to the addition of one of many rapidly emerging biologic agents suggest that further testing of a modified version of this regimen could easily be justified. In effect, utilizing this combination of oxaliplatin and capcitabine as a so-called ‘backbone’ regimen, adding a newer biologic agent, and testing this three-drug regimen against any one of several other commonly used regimens appears to be a reasonable trajectory of future development.

In summary, the combination of oxaliplatin and capcitabine is active in metastatic adenocarcinoma of the esophagus, gastroesophageal junction and gastric cardia. The lower dosing, which includes capcitabine 850 mg/m² orally twice a day, days 1–14, in conjunction with oxaliplatin 130 mg/m² intravenously on day 1, both of which are given together as part of a 21-day cycle, yields an acceptable toxicity profile and merits further study.

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References


