Phase II trial of docetaxel and oxaliplatin in patients with advanced gastric cancer and/or adenocarcinoma of the gastroesophageal junction

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Background: Platinum-based chemotherapy is the standard treatment for advanced gastric cancer (GC). This trial explored the efficacy and tolerability of combined docetaxel (Taxotere) + oxaliplatin (DOCOX) in GC patients.

Patients and methods: Patients with untreated stage IV GC or adenocarcinoma of the gastroesophageal junction (AGEJ) received docetaxel 60 mg/m^2 followed by oxaliplatin 130 mg/m^2 on day 1 of each 21-day cycle until progression or unacceptable toxicity. The primary end points were response rate (RR), toxicity, progression-free survival (PFS), and overall survival (OS).

Results: Baseline characteristics (N = 71): median age 59 years, 72% male, 51% esophagogastric junction cancer, and Eastern Cooperative Oncology Group performance status of zero, one, two were 42%, 51%, 7%, respectively. The median number of cycles was 6 (range, 1–19). Grades 3–4 toxic effects: neutropenia (70%); vomiting (17%); nausea (16%); dehydration, fatigue, or diarrhea (13%, each); and thrombocytopenia or febrile neutropenia (7%, each). Sixty-six patients completed ≥ 2 cycles. The RR was 36% with 25 partial response (PR) and no complete responses (CRs); stable disease (SD) was 49%. Clinical benefit rate (CBR = CR + PR + SD ≥ 6 months) was 40%; median PFS was 4.3 months, and OS was 8.5 months.

Conclusions: DOCOX produced manageable toxicity in patients with advanced GC and AGEJ. The confirmed RR of 36%, CBR of 40%, and median survival of 8.5 months are encouraging and comparable to standard front-line regimens.

Key words: docetaxel, gastropesophageal junction, gastric, oxaliplatin, phase II

Introduction

Gastric cancer (GC) is a significant worldwide health issue, second only to lung cancer as the leading cause of cancer deaths worldwide [1]. Despite recent advances in the treatment of many solid tumors, patients with advanced GC have a relatively poor prognosis with a 5-year survival of ~14% [2]. Modern multiagent chemotherapy regimens, generally incorporating cisplatin and 5-fluorouracil (5-FU), offer a survival advantage over best supportive care alone [3]. However, these regimens result in significant toxicity (emesis, renal toxicity, and a higher risk of toxic death). Moreover, inconveniences for patients include extensive time spent at the chemo clinic for i.v. hydration required for cisplatin and the requirements of a protracted infusion of 5-FU.

Newer generation platinum compounds (e.g. oxaliplatin) are associated with less toxicity and improved convenience. Oxaliplatin, when combined with bolus and infused 5-FU (FOLFOX) has demonstrated significant activity in patients with advanced GC. Previous phase II studies had response rate (RR) ranging 38%–55% with overall survival (OS) (range, 7.1–11.4 months) [4–10]. Oxaliplatin has been utilized in the recently reported Randomised Ecf for Advanced and Locally advanced oesophago-gastric cancer trial [11].

Docetaxel has significant activity against advanced GC. In the recent TAX 325 phase III trial, the addition of docetaxel to cisplatin and 5-FU (DCF) significantly improved time to progression (5.6 versus 3.7 months, \( P < 0.001 \)) when compared with cisplatin and 5-FU alone [12]. OS was also improved, with a 1-year survival of 40% for the DCF arm versus 32% for the cisplatin and 5-FU (CF) arm (\( P = 0.02 \)).

Several potential advantages support the rationale for testing the combination docetaxel + oxaliplatin (DOCOX) for the treatment of advanced GC. Both agents have significant activity in this disease. Oxaliplatin has similar efficacy to cisplatin with less hematological toxicity. Moreover, oxaliplatin is less emetogenic potential and eliminate the need for i.v. hydration, which translates to patient convenience. Lastly, the regimen can be administered as a single infusion room visit.

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without the need for ambulatory infusion devices. This multicenter phase II trial was thus undertaken to define the efficacy and toxicity of the combination of docetaxel and oxaliplatin in patients with advanced GC and adenocarcinoma of the gastroesophageal junction.

patients and methods

study design
This trial was designed as a multicenter, single-arm phase II study. All patients received the same treatment, docetaxel (Taxotere; sanofi-aventis, New York, NY, USA) 60 mg/m² as an i.v. infusion >1 h, followed by oxaliplatin 130 mg/m² i.v. >2 h. Both drugs were administered on day 1 of each 21-day cycle. Treatment continued until disease progression or intolerable toxicity. Patients who achieved a complete response (CR) could receive an additional two cycles of treatment.

The protocol was approved by a central Institutional Review Board with jurisdiction over specific sites that registered patients on study, and all patients were required to sign an informed consent form before being enrolled into the study.

patients
Eligible patients had histologically confirmed, measurable stage IV adenocarcinoma of the stomach or esophagogastric junction; an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of zero to two; adequate renal, liver, and bone marrow function; and if present, peripheral neuropathy was lesser than or equal to grade 1. No prior chemotherapy was allowed for advanced stage disease; however, prior 5-FU ± biological modulators such as leucovorin or interferon given as a radiation sensitizer was permitted as long as the patient had fully recovered before randomization.

Patients were excluded from study participation if they had any other malignancy in the past 5 years with the exception of squamous or basal cell carcinoma of the skin, carcinoma in situ of the cervix, or superficial transitional cell carcinoma of the bladder; had a history of either uncompensated congestive heart failure or myocardial ischemia in the prior 6 months; were currently on immunotherapy or had received an investigational therapy within the past 30 days; or were pregnant or breast-feeding.

treatment
Patients were premedicated for docetaxel with dexamethasone, and premedication for oxaliplatin, including magnesium sulfate and calcium gluconate infusions, was at the treating physicians’ discretion. Patients received docetaxel 60 mg/m² as an i. v. infusion >1 h, followed by oxaliplatin 130 mg/m² i.v. >2 h. Both drugs were administered on day 1 of each 21-day cycle. Treatment continued until disease progression or intolerable toxicity. Patients who achieved a CR could receive an additional two cycles of treatment at the investigator’s discretion. Doses were recalculated before each cycle and adjusted as needed.

assessments
At baseline, the following were completed: inclusion and exclusion validation, informed consent completions, pregnancy test (if indicated), and medical history. Additionally, a complete physical exam, assessment of ECOG PS, complete blood count with differential and platelet count, disease assessment, and laboratory tests (total bilirubin, serum creatinine, aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase, serum calcium) were done. Toxicity was assessed at each patient visit and for 30 days after the last dose. Assessment of disease status (computed tomography, ultrasonad, routine X-rays, bone scans, etc) was done every 6 weeks. Recommended follow-up was at 3 month intervals to collect survival data as well as additional therapy.

criteria for assessing response
Responses were evaluated in this study using standard international criteria, Response Evaluation Criteria in Solid Tumors [13]. To be assigned a status of partial response or CR, changes in tumor measurements were confirmed by repeat assessments carried out no less than 4 weeks after the criteria for response were first met. Responses were assessed by each treating physician and were not assessed centrally.

criteria for assessing toxicity
Toxicities and adverse events were graded and reported using the Common Terminology Criteria for Adverse Events Version 3.0 [14]. Relationships to drug were assigned by the treating physician.

statistical analysis
The main goal of this study was to estimate the antitumor activity of the combination of DOCOX in first-line metastatic GC patients. The primary end point was objective RR. The secondary end points were progression-free survival (PFS), duration of response, toxicity, and OS at 1 and 2 years. This was an open-label, phase II nonrandomized study. PFS and survival were estimated using the method of Kaplan–Meier [15]. Statistica’99 Edition (Statsoft, Inc. Tulsa, OK, USA) was used to carry out the analysis. PFS was calculated from the first day of treatment to the first sign of progressive disease or death. Survival was calculated from the first day of treatment to the last date of follow-up for living subjects or until the date of death. Subjects lost to follow-up were censored at the last available date. Intent-to-treat patients included all eligible patients who enrolled in the study, assessable patients included all patients who received ≥2 cycles of treatment with ≥1 follow-up tumor assessment, and the safety population included all patients who received ≥1 dose of the study drug.

A two-stage method of Simon’s Optimum Design [16] was used to estimate sample size with \( p_0 = 0.24 \) (null hypothesis) and \( p_1 = 0.40 \) (alternative hypothesis) with a significant level of 0.05 and a power of 80%. The result specifies a sample size of 63 patients distributed in two stages. The sample size of the first stage was 20 patients.

results

patient characteristics
Seventy-one (71) patients were registered at 48 sites through the US Oncology Network of community-based cancer clinics; 70 patients received ≥1 dose of study drug. Patients received a median of six cycles (range, 1–19). Patient characteristics are summarized in Table 1.

treatment efficacy
The overall response rate (ORR) produced by DOCOX was 36% [95% confidence interval (CI) 24.8% to 48.0%]. Responses and reasons for discontinuation are summarized in Table 2. For patients who progressed, the median PFS was 4.3 months (range, <1–26.3; 95% CI 3.4–5.3) and, for all patients, the median OS was 8.5 months (range, <1–26.4; 95% CI 6.6–11.2). The median time to response was 1.4 months (range, 1.1–4.4), and the median duration of response was 5.6 months (range, 2.7–23.8; 95% CI 4.1–8.6). Median survival at 1 and 2 years was 32.8% and 9.4%, respectively.

drug delivery
The mean relative dose intensity of oxaliplatin was 96.3% (range, 74.5%–100%) and for docetaxel it was 94.7% (range,
72.1%–100%). The median cumulative dose of oxaliplatin was 1312 mg; for docetaxel it was 585 mg. Over half of the patients (60%) had doses delayed or reduced, primarily due to neutropenia, thrombocytopenia, vomiting, neuropathy, or fatigue.

toxicity

Overall grades 3–4 treatment-related toxic effects are summarized in Table 3. Grades 3–4 neutropenia occurred in 70% of patients, however only five patients (7%) developed febrile neutropenia. Neuropathy was limited to grade 3 neuropathy (n = 2); peripheral sensory neuropathy (n = 1); and neuropathic pain, peripheral sensory neuropathy, and peripheral motor neuropathy (n = 1).

Sixteen patients experienced 31 serious adverse events, primarily febrile neutropenia, vomiting, nausea, dehydration, altered mental status, and sepsis. Fifty-five patients died on study. Deaths were attributed to progressive disease (n = 48); renal failure (n = 2); and pneumonia, sepsis, shortness of breath, and emphysema (n = 1 each); one death was due to unknown causes. None of the deaths were treatment related.

discussion

Recently, docetaxel has been approved for patients with advanced GC. This approval was largely based on the results of the large international TAX 325 study [12]. In this trial, the addition of docetaxel to the index regimen of cisplatin and 5-FU resulted in improved RRs, improved PFS, and improved OS. Specifically, the ORR in the DCF arm was 37% compared with 27% in the CF arm. The confirmed RR of 36% seen in this study of DOCOX in an analogous...
population of patients is very similar to that reported in the DCF arm of the TAX 325 trial. The median OS in patients randomized to DCF in the TAX 325 trial was 9.2 months (95% CI 8.4–10.6), which is comparable to the 8.3 month median OS seen in our trial (95% CI 6.5–11.2), as is apparent by overlapping CIs. In this multicenter phase II trial, the combination of DOCOX produced a confirmed ORR of 36% with a median survival of 8.3 months. Moreover, the toxicity associated with the DOCOX regimen was mild to moderate and more manageable in this study.

Although the DCF regimen was found to be superior to the index regimen of CF in the TAX 325 trial, there are obvious difficulties with this regimen. The regimen is markedly myelosuppressive with an 84% incidence of grades 3–4 neutropenia and 29% incidence of febrile neutropenia. In contrast, the DOCOX regimen produced a febrile neutropenia rate of only 7% in this trial, although 70% of the patients in this study did experience grades 3–4 neutropenia. In addition, the use of cisplatin necessitates aggressive hydration and infusion time, issues that are bypassed by an oxaliplatin-containing regimen. Several recent studies have demonstrated that oxaliplatin has at least equivalent activity to cisplatin in this disease [11, 17]. Lastly, the use of infusional 5-FU requires the placement of an indwelling venous access device and the use of a portable infusion pump. Because the DOCOX regimen is delivered >3 h on day 1 of a 21-day cycle, these requirements are also simplified.

Another large trial that was recently reported evaluating new regimens in advanced GC is the REAL 2 trial [11]. The index regimen employed in the REAL 2 trial was the combination of epirubicin, cisplatin, and protracted venous infusional 5-FU. This was compared with three experimental arms in a 2 × 2 factorial design wherein oxaliplatin was compared with cisplatin and capcitabine was compared with protracted infusional 5-FU. In summary, all of the treatment arms were found to be statistically equivalent, although the combination of epirubicin, oxaliplatin, and capcitabine produced the best outcomes with a median survival time of 11.2 months. The REAL 2 study, however, included a number of patients with locally advanced disease—patients who are known to have a more favorable prognosis than those with widely metastatic disease. The current study of DOCOX as well as the TAX 325 trial required all patients to have stage IV disease. This may partly account for the improved survival seen in the best arm of the REAL 2 trial as compared with the results seen in the TAX 325 trial or the current study of DOCOX.

One common feature of the DCF arm of the TAX 325 trial and the four arms of the REAL 2 trial is the three-drug nature of the regimens. This is in contrast to the current DOCOX regimen which contains only a platinum agent and taxane. Since the development of this regimen and the accrual of the current study, a meta-analysis has indicated an advantage to three-drug regimens over two-drug regimens in the management of advanced GC. In this meta-analysis, the three-drug regimens were associated with improvements in outcomes with regards to RRs as well as survival times. It is unclear what advantage would be seen with the addition of a fluoropyrimidine to the DOCOX regimen, however, this question will be addressed in the ongoing GATE trial. In this large international, randomized, phase II trial, patients will be randomly assigned to DOCOX alone or DOCOX plus 5-FU or capcitabine. This study will also address the relative dose intensity of docetaxel. It will attempt to increase the dose intensity of docetaxel by 25%.

The benefits of systemic cytotoxic therapy in advanced GC seem to be reaching a plateau. Despite the use of more intensive regimens, which may be associated with heightened toxicity, the RRs and survival seen in patients with this disease has not substantially increased in recent years. The introduction of novel molecularly targeted agents in the management of patients with other advanced solid tumors has improved outcomes in colorectal, non-small-cell lung, breast, and head and neck cancers in recent years. The combination of docetaxel and oxaliplatin seems a reasonable foundation onto which new targeted agents can be added. Although it may be slightly less efficacious than DCF, DOCOX has a better toxicity profile, which might make it a good alternative for patients who are not candidates for DCF. Currently, this regimen is being evaluated in combination with bevacizumab and plans are under way to combine the DOCOX regimen with an epidermal growth factor receptor antagonist. It is hoped that these combinations will improve outcomes and limit the additional toxic effects of therapy.

funding
Sanofi-aventis, New York, NY, USA.

acknowledgements
We thank the patients who shared their experiences with US Oncology physicians (see Appendix 1), the site coordinators in the field, project manager S. Bell, and data reviewer T. Locke.
who assured the accuracy and integrity of the data. Richards has served in an advisory capacity, within the past 2 years for both Eli Lilly and Company and sanofi-aventis. McCollum has, in the past 2 years, received honoraria from Pfizer and Genentech.

Appendix 1

The following medical oncologists from the USON network institutions also participated in this study: A. Cohn, Rocky Mountain Cancer Centers, Denver, CO; K. J. Mcintosh, Texas Oncology, P.A., Dallas, TX; P. R. Conkling, Virginia Oncology Associates, Norfolk, VA; J. D Hunter, Cancer Center of the Carolina, Greenville, SC; J. Sandbach, Texas Oncology Cancer Center, Austin, TX; M. Neubauer, Kansas City Cancer Centers, Overland Park, KS; P. J. Flynn, Minnesota Hematology Oncology, Minneapolis, MN; J. E. Cantrell, Birmingham Hematology and Oncology, Birmingham, AL; J. L. Blum, Charles A. Sammons Cancer Center, Dallas, TX; J. A. Lopez, San Antonio Tumor and Blood Clinic, Fredericksburg, TX; V. A. Canfield, Cancer Care Associates, Oklahoma City, OK; A. M. Keller, Cancer Care Associates, Tulsa, OK; A. Solky, Interlakes Oncology, Hematology, Rochester, NY; A. Mellott, Hematology and Oncology Associates of Illinois, Chicago, IL; B. D. Brooks, Texas Cancer Center—Medical City Radiation, Dallas, TX; B. S. Berman, Cancer Centers of Florida, Orlando, FL; D. A. Smith; Northwest Cancer Specialists, Vancouver, WA; D. Barrera, Texas Cancer Center; Fort Worth, TX; D. Dong, Puget Sound Cancer Centers, Seattle, WA; E. Lee, Maryland Oncology; P.A., Columbia, MD; E. C. King, Comprehensive Cancer Centers of Nevada; Las Vegas, NV; G. Wright, Florida Cancer Institute, Hudson, FL; G. Buchanan, Williamette Valley Cancer Center, Eugene, OR; H. Allen, Comprehensive Cancer Centers of Nevada; Las Vegas, NV; J. (Jay) L. Lohrey, Cancer Care Associates, Tulsa, OK; J. Rubins, Interlakes Oncology, Hematology, Rochester, NY; L. E. Garbo, New York Oncology Hematology, Albany, NY; M. Olsen, Cancer Care Associates, Tulsa, OK; M. A. Savin, Texas Cancer Center—Medical City Radiation, Dallas, TX; M. Park, Texas Oncology, P.A.—Lake Vista Cancer Center, Lewisville, TX; P. D. Richards, Oncology and Hematology Associates of Southwest Virginia, Roanoke, VA; R. E. Barrington, San Antonio Tumor and Blood Clinic, Kerrville, TX; R. Anderson, Texas Oncology and Cancer Research Center, Waco, TX; R. M. Rifkin, Rocky Mountain Cancer Centers, Denver, CO; R. N. Raju, Dayton Oncology and Hematology, Kettering, OH; S. Awasthi, Texas Cancer Center, Arlington, TX; S. Lakanpal, Birmingham Hematology and Oncology, Birmingham, AL; P. P. Kubica, New Mexico Cancer Care Associates, Santa Fe, NM, USA.

references