Weekly Taxotere and cisplatin with continuous-infusion 5-fluorouracil for the treatment of advanced gastric and esophageal cancer: a prospective, observational, single-institution experience

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Abstract The combination of Taxotere (docetaxel), cisplatin, and prolonged-infusion 5-fluorouracil (5-FU) has emerged as an active treatment for advanced gastric cancer. However, the regimen proposed by van Cutsem et al. (J Clin Oncol 24:4991–7, 2006) is associated with significant toxicity and therefore alternative schedules are needed. In the present study, patients with advanced gastric or esophageal cancer received Taxotere 35 mg/m² and cisplatin 25 mg/m² on day 1, followed by 5-FU 180 mg/m²/day as a 7-day prolonged infusion. Drugs were given weekly for 3 consecutive weeks followed by 1 week's rest. Cycles were repeated every 4 weeks. Overall, a total of 110 cycles were administered to 27 patients (median age 63 years, range 40–78 years). The median number of cycles per patient was 4 (range 2–6). Nine partial responses were obtained, resulting in an overall response rate of 33% [95% confidence interval (CI) 16–51], a median time to progression of 6.4 months (95% CI 5.4–7.4), and a median overall survival of 10.7 months (95% CI 6.6–14.8). Toxicity was mild; grade III–IV neutropenia was the most frequently observed side effect, in 9 administered cycles (8%); neutropenia was complicated by fever in 2 cycles. Other grade III–IV toxicities observed in >5% of patients were anemia and mucositis.

Keywords Advanced gastric and esophageal cancer · Taxotere · Cisplatin · 5-fluorouracil

Introduction

For patients with advanced gastric cancer, systemic chemotherapy represents the main treatment option because it improves survival as compared with best supportive care [1–4]. A meta-analysis of randomized phase II and III clinical trials evaluating different chemotherapy regimens for the front-line treatment of advanced gastric cancer concluded that the best survival results were achieved with three-drug regimens containing 5-fluorouracil (5-FU), an anthracycline, and cisplatin [5]. However, optimal first-line combination chemotherapy is still controversial and, based on the results of randomized phase III trials, different options are possible. In particular, the demonstrated activity of Taxotere (docetaxel, Aventis Pharma S.A., Antony Cedex, France) both as a single agent [6–8] and in combination [9, 10] prompted the conduct of a randomized comparison between a three-drug regimen (Taxotere, cisplatin, and 5-FU) and the two-drug combination of cisplatin and 5-FU, which led to the conclusion that the inclusion of Taxotere was associated with better time to progression (TTP) and overall survival (OS) (the V325 study [11]). However, the significant grade III–IV toxicity associated with this regimen stimulated the evaluation of schedules of administration in which Taxotere (and cisplatin) were given weekly, with the aim of maintaining the strength while attenuating the side effects. We report here our experience with a weekly schedule of Taxotere, cisplatin, and continuous-infusion 5-FU.

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Patients and methods

Patients

Entry criteria included the following: a pathologically confirmed diagnosis of metastatic gastric or esophageal cancer for first-line chemotherapy and an Eastern Cooperative Oncology Group (ECOG) performance status of ≤ 2 ; and measurable lesion(s) as per modified Response Evaluation Criteria in Solid Tumors (RECIST). Clinical staging was based upon a complete history, physical examination, a routine biochemical profile, a complete blood cell count, carcinoembryonic antigen (CEA) determinations, and the results of a computed tomography (CT) scan performed before the beginning of treatment and then regularly every 2 months.

Treatment schedule

The treatment schedule was: Taxotere 35 mg/m² diluted in 250 ml normal saline and infused in 60 min on day 1; cisplatin 25 mg/m² in 250 ml NaCl 3% and infused in 30 min on day 1; and 5-FU 180 mg/m²/day as a 7-day prolonged infusion starting on day 1. For hydration, on day 1 all patients received 1,000 ml of normal saline with 20 mEq KCl and 500 ml of 5% dextrose solution with 2 g magnesium sulfate. Antiemetics used included dexamethasone, metoclopramide, and an HT3 antagonist. Drugs were given weekly for 3 consecutive weeks (one cycle) followed by 1 week's rest. No reduction of drug doses was planned; cycles were delayed if there was myelosuppression (neutrophil count $<1,000$ cells/ μ l and/or platelet count $<100,000$ cells/ μ l) or non-hematological toxicity $>$ grade II.

The received dose intensity (DI) was calculated using the method of Hryniuk and Bush [12] and was expressed as mg/m²/week.

Study objectives and statistical considerations

This was a prospective, observational study. The primary objective was the response rate (RECIST criteria). The threshold for activity was set at the 0.30 cut-off value. Secondary objectives were safety [National Cancer Institute Common Toxicity Criteria (NCI-CTC), version 3.0], OS and TTP (time from first day of the cycle to progression). OS and PFS were calculated using the Kaplan-Meier method.

Results

From April 14, 2004, to December 31, 2009, 27 patients gave their consent to participate in this study, conducted at

the Department of Oncology, Mater Salutis Hospital, Legnago, Italy (Table 1).

Extent of exposure, dose intensity, and cycle delays

Overall, a total of 110 cycles were administered to the 27 patients. The median number of cycles per patient was 4 (range 2–6). Median cumulative doses (ranges) of Taxotere, cisplatin, and 5-FU were 634.7 mg (240–1,260 mg), 452.5 mg (180–900 mg), and 19,684 mg (8,500–42,500 mg), respectively. The number of cycles, cumulative doses, and dose intensities of Taxotere, cisplatin, and 5-FU are listed in Table 2. A cycle delay of >3 days was observed in 22/110 cycles (20%); the median delay was 7 days (range 4–28). The main causes of delay were myelosuppression (neutrophils $<1,000$ μ l or platelets $<100,000$ μ l) in 9 cycles (8%), mucositis, fatigue, and unrelated to the patient's medical condition (e.g., patient's personal reasons, excluding toxicity) (Table 2).

Toxicity

All patients were assessable for toxicity. Table 3 outlines the grade III–IV toxicities observed during treatment. Grade III–IV neutropenia was the most frequently observed side effect, present in 9 administered cycles (8%); neutropenia was complicated by fever in 2 cycles. Other grade III–IV toxicities observed in $>5\%$ of patients were anemia, mucositis, and diarrhea.

Table 1 Patient characteristics

Number of patients	27
Male:female	19:8
Age (years)	Median 63 (range 40–78)
Performance status (ECOG)	
0	16
1	7
2	4
Primary tumor site	
Stomach	22
Esophagus	5
Histology	
Adenocarcinoma, intestinal type	18
Adenocarcinoma, diffuse	5
Squamous cell carcinoma	4
Stage	
Locally advanced	3
Metastatic	24
Number of metastatic sites	
1	4
>1	23

ECOG Eastern Cooperative Oncology Group

Table 2 Number of cycles and dose intensity (DI)

Total number of cycles	110
Median number of cycles/patient	4 (range 2–6)
Number of delayed cycles (>3 days)	26 (24%)
Length of delay (median, days)	7 (range 4–28)
Causes of delay	
Myelosuppression	9 (8%)
Mucositis	5 (4.5%)
Fatigue	3 (2.7%)
Fever	2 (1.8%)
Anorexia	1 (1%)
Other (not medical)	5 (4.5%)
Cumulative dose, median (range)	
Cisplatin	452.5 mg (180–900)
Taxotere	633.7 mg (240–1,260)
5-FU	19,684 mg (8,500–42,500)
Received DI, median	
Cisplatin	15.3 (80%) ^a
Taxotere	20.8 (79%) ^a
5-FU	759.5 (80%) ^a

5-FU 5-fluorouracil

^a Percentage of the planned DI of cisplatin (18.75 mg/m²/week), Taxotere (26.25 mg/m²/week), and 5-FU (945 mg/m²/week)

Table 3 Main grade III–IV toxicities per patient and per cycle (%)

Toxicity	Per patient, <i>n</i> (%)	Per cycle, <i>n</i> (%)
Myelosuppression		
Neutropenia	4 (14.8)	9 (8)
Febrile neutropenia	2 (7)	2 (1.8)
Anemia	2 (7.4)	2 (1.8)
Mucositis	2 (7.4)	3 (2.7)
Diarrhea	1 (3.7)	1 (1)
Fatigue	1 (3.7)	1 (1)
Skin (nail changes)	1 (3.7)	1 (1)
Allergic reactions	1 (3.7)	1 (1)
Alopecia	1 (3.7)	1 (1)

Efficacy

Response to treatment could be evaluated in the whole group of 27 patients. Sixteen patients (59%; 95% CI 41–78%) showed disease stabilization as their best response to treatment, 9 patients (33%; 95% CI 16–51%) had a partial response, and 2 patients (7%; 95% CI 0–17%) showed progressive disease as their best response. One patient was rendered disease-free following the surgical removal of lymph nodes in the lower mediastinum. Upon progression, ten patients received further lines of chemotherapy. As second-line therapy, six patients were treated

Fig. 1 Overall survival (OS) and time to progression (TTP) curves

according to the simplified FOLFOX regimen (folinic acid, 5-FU bolus, and prolonged infusion of oxaliplatin), while the remaining four patients received capecitabine combined either with irinotecan ($n = 2$) or with oxaliplatin ($n = 1$) or cisplatin ($n = 1$). The median number of cycles given to each patient was 6 (range 4–12). Four patients received further lines of chemotherapy.

The Kaplan–Meier curves for TTP and OS during the protocol are shown in Fig. 1. Median TTP was 6.4 months and median OS 10.7 months. At the time of this analysis 4 patients are still alive (3 with disease, 1 with no evident disease).

Discussion

In patients with advanced gastric cancer the role of chemotherapy is clearly palliative and it is therefore important to reduce the toxicity of treatment while maintaining the efficacy [13]. The high incidence of grade III–IV toxicity reported in the V325 study was confirmed in a 3-arm randomized phase II trial [14] in which Taxotere (85 mg/m²), cisplatin (75 mg/m²), and continuous-infusion 5-FU (300 mg/m²/day, days 1–14) (TCF) were compared with the combination of Taxotere (85 mg/m²) and cisplatin (75 mg/m²) (TC) and with the combination of epirubicin (50 mg/m²), cisplatin (60 mg/m²), and continuous-infusion 5-FU (200 mg/m²/day, days 1–21) (ECF), with cycles given every 3 weeks in each arm. In the TCF arm, febrile neutropenia and severe diarrhea were experienced by 41 and 15% of patients, respectively ($n = 41$), higher than the frequencies observed in TC patients (21 and 3%, $n = 38$) and in ECF patients (18 and 6%, $n = 40$).

The toxicity of a 3-drug regimen including Taxotere given weekly for 3 consecutive weeks might be reduced by substituting capecitabine for continuous-infusion 5-FU and oxaliplatin for cisplatin, as shown in a small phase I study

[15], in which the recommended doses (RDs) were: capecitabine 1,000 mg/m² bid, days 1–14, Taxotere 60 mg/m², and oxaliplatin 100 mg/m², each administered on day 1. However, the overall toxicity was by no means negligible, because, of the 12 patients treated at the RDs, 25% suffered neutropenia complicated by fever and 17% experienced diarrhea.

In the present study, grade III–IV toxicities observed in >5% of patients were neutropenia, anemia, and mucositis; febrile neutropenia was observed in only two patients (7%). As a result of the good tolerability, the received DI for the three drugs was around 80% of the planned DI. Toxicity data are in keeping with the data reported by Pasini et al. [16], in which the same regimen as that used in the present study was used as the induction component of a multi-modality treatment for operable cancers of the esophagus and the gastroesophageal junction. Several attempts have been made to improve the tolerability of three-drug regimens including Taxotere administered at lower doses and repeated more frequently. Reduced doses of Taxotere (40 mg/m²) and cisplatin (40 mg/m²) given biweekly in combination with the weekly administration of 5-FU (2,000 mg/m² as a 24-h infusion) and leucovorin (200 mg/m²) were investigated in 60 patients with metastatic ($n = 36$) or locally advanced ($n = 24$) cancer of the stomach or the gastroesophageal junction [17]. In that study, febrile neutropenia was observed in only 5% of patients, while grade III–IV diarrhea and lethargy were reported in 20% and 18% of patients, respectively. The particularly favorable outcome of patients, with an OS of 17.9 months, was probably due to the high percentage of locally advanced cases. In the ATTAX trial, a randomized phase II study [18], 106 patients with gastric or esophageal cancer received either weekly Taxotere (30 mg/m², days 1 and 8) combined with cisplatin (60 mg/m², day 1) and continuous infusion 5-FU (200 mg/m²/day, days 1–21) (wTCF) or weekly Taxotere according to the same dose and schedule as above, combined with capecitabine (800 mg/m² bid, days 1–14) (wTX); in both arms cycles were repeated every 3 weeks. Weekly TCF was associated with a higher overall response rate (ORR) (49 vs. 26%), and a longer OS (12.8 vs. 10.1 months); toxicity was mild: febrile neutropenia in 4% of patients, and stomatitis, diarrhea, and fatigue in 22, 10, and 10% of patients, respectively. The favorable toxicity profile of reduced doses of Taxotere (50 mg/m², day 1) given biweekly with leucovorin (200 mg/m², day 1) and 24-h continuous-infusion 5-FU (2,600 mg/m²) was confirmed in a study (FLOT) in which oxaliplatin (85 mg/m², day 1) was given as a substitute for cisplatin [19], following the results of a phase III trial [20] showing that the biweekly administration of oxaliplatin 85 mg/m², leucovorin 200 mg/m², and 5-FU 2,600 mg/m² via 24-h infusion (FLO) was associated with

reduced toxicity and perhaps improved activity compared to a regimen including cisplatin 50 mg/m² (every 2 weeks), leucovorin 200 mg/m², and 5-FU 2,000 mg/m² via 24-h infusion (weekly) (FLP). The FLOT trial was conducted in 59 patients with locally advanced ($n = 4$) or metastatic ($n = 55$) adenocarcinoma of the stomach or the gastroesophageal junction. With an ORR observed in 57.7% of patients and a median OS of 11.1 months, febrile neutropenia, grade III–IV diarrhea, and fatigue were present in 1.9, 14.8, and 11.1% of patients, respectively.

In conclusion, the weekly administration of Taxotere and cisplatin with continuous-infusion 5-FU is associated with a toxicity profile that compares favorably with other published three-drug regimens including Taxotere, cisplatin (or oxaliplatin), and a fluoropyrimidine. According to the metanalysis carried out by Wagner et al. [5], a triplet should be preferred as first-line regimen for patients with advanced gastric cancer. However, at present it is not clear which, among the three-drug regimens including Taxotere or epirubicin, is the best to propose in this setting. Furthermore, we believe that further efforts should be addressed toward developing new drugs/combinations rather than performing comparisons of existing regimens.

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