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Docetaxel in combination for advanced gastric cancer

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Abstract

Docetaxel is considered to be active in untreated and previously treated patients with gastric carcinoma. In a multinational phase II trial (TAX 325), 158 untreated patients with advanced gastric cancer (99% without prior chemotherapy) were randomized to receive, every 3 weeks, either docetaxel 85 mg/m^2 plus cisplatin 75 mg/m^2 (TC) or docetaxel 75 mg/m^2 plus cisplatin 75 mg/m^2, plus a 5-day continuous infusion of 750 mg/m^2 5-fluorouracil (FU; TCF). By intent-to-treat analysis, patients receiving TCF had a significantly higher response rate and longer time to progression. Overall survival in the two arms was not significantly different. Toxicity (particularly gastrointestinal toxicity) was greater with the TCF combination than in the TC arm, and there was a greater need for dose reduction. However, adverse events in both arms were manageable and there were no deaths associated with either regimen. Following these findings, a phase III trial comparing a control arm of cisplatin plus 5-FU against an experimental arm consisting of the TAX 325 phase II docetaxel/cisplatin/5-FU regimen is now in progress.

Introduction

While chemotherapy for advanced gastric cancer has been established as superior to best supportive care, no particular single-agent or combination regimen has become accepted as the standard of treatment [1]. Among the single agents that have proven activity in the first-line setting are 5-fluorouracil (5-FU), cisplatin, etoposide, irinotecan, paclitaxel, S-1, and UFT, for which response rates (RRs) ranging from 15% to 44% have been reported [2–7]. 5-FU/leucovorin, cisplatin, paclitaxel, and irinotecan have also been used as second-line single agents, with RRs of 17% to 26% [8–18]. In addition to the drugs mentioned, docetaxel has appreciable activity in advanced gastric cancer. In three studies of monotherapy in previously untreated patients, docetaxel at a dose of 100 mg/m^2 achieved RRs of 17% to 24% [17–19]. In the second-line setting, Vanhoefer et al. [20] achieved an RR of 20% using 100 mg/m^2 docetaxel, and Taguchi et al. [21] an RR of 22% with 60 mg/m^2 docetaxel.

Cisplatin is perhaps the most widely used drug in advanced gastric cancer, and two trials have investigated its combination with docetaxel. Roth et al. [22] treated 48 patients with doses of docetaxel ranging from 85 mg/m^2 to 100 mg/m^2 administered every 3 weeks together with cisplatin 75 mg/m^2. Among 45 evaluable patients, the RR was 56% and median survival, 9 months. Similarly encouraging results were obtained by Ridwelski et al. [23]. In 39 evaluable patients treated with an every-3-week regimen of docetaxel 75 mg/m^2 plus cisplatin 75 mg/m^2, the RR was 37% and median survival, 10.4 months.

Given this background, a multinational randomized phase II study (TAX 325) was undertaken to compare the combination of docetaxel with cisplatin against a three-drug arm in which 5-FU was added to docetaxel and cisplatin [24].

TAX 325: docetaxel plus cisplatin vs docetaxel plus cisplatin plus 5-FU

Study design

TAX 325 involved centers in the United States, Europe, Russia, South America, and Asia. Patients were randomized to one of two treatment arms: docetaxel 85 mg/m^2 plus cisplatin 75 mg/m^2, with both drugs administered on day 1 every 3 weeks (TC); or docetaxel 75 mg/m^2 plus cisplatin 75 mg/m^2 on day 1 every 3 weeks plus a continuous infusion of 750 mg/m^2 5-FU given over days 1–5 (TCF). It should be noted that the 85 mg/m^2 docetaxel

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given in the TC arm of the study was a relatively high dose [24].

It was originally intended that the study should accrue around 36 patients in each arm. However, patients continued to be entered into the trial during the period when the initial patients were being assessed. The result was that a total of 158 patients were randomized. With 79 patients entered in each treatment arm, TAX 325 represents one of the largest randomized phase II trials ever undertaken with docetaxel.

The principal efficacy endpoints of the study were response and time to progression. However, data were also collected on overall survival.

Of the 79 patients randomized to TC, 76 were treated, 72 of whom were judged eligible for the study, and 65 (82% of those randomized) were evaluable for response. The corresponding figures for the TCF arm were 79 randomized, 79 treated, 71 eligible, and 64 (81%) evaluable for response. The overall rate of ineligibility among all patients entered was 9.5%.

At the time of this report, 5% of TC patients and 8% of TCF patients were still on study. The principal reason for discontinuation was disease progression (50% of TC and 34% of TCF patients). Adverse events caused withdrawal of 22% and 24% of patients in the two groups.

Patient characteristics

Table 1 shows the characteristics of the patients treated in the trial. The patients entered were reasonably typical of those in gastric cancer trials, with a median age of 57 years and a good performance status (median, 90%). Ninety-nine percent of patients had had no prior experience of chemotherapy.

Globally, distal gastric cancer is the most common form of the disease, and this is reflected in the distribution of anatomic sites in this study. Overall, only 32% of patients had the proximal gastric cancer which is more typical in Western Europe and North America. In 79% of patients overall, two or more organs were involved. Disease was metastatic in 99% of cases and locally recurrent in 1%. Overall, disease was bidimensionally measurable in 79% of patients.

Table 1. Characteristics of patients treated with docetaxel and cisplatin (TC) or docetaxel plus cisplatin and 5-fluorouracil (FU; TCF) [24]

	TC ($n = 76$)	TCF ($n = 79$)
Male	70%	77%
Median age	57 Years	57 Years
Median performance status	90%	90%
Median weight loss	7 kg	7 kg
Median time from:		
Diagnosis to randomization	2.0 Months	1.4 Months
Last surgery to randomization	8.8 Months	8.3 Months

Results

The median duration of treatment was 18 weeks in both arms of the study, with a median of five cycles of TC and six cycles of TCF administered. In the TC arm, the relative dose intensity (RDI) of docetaxel was 0.98, and that of cisplatin, 0.96. Patients in the TCF group also received a high proportion of the intended dose (RDI 0.93 for docetaxel, 0.93 for cisplatin, and 0.95 for 5-FU). In 95% of TC cycles and 86% of TCF cycles no dose reduction was required.

Confining the analysis to patients who received treatment according to the study protocol, the RR in the TC group was 35%, and 56% in the TCF arm. The significantly greater activity of the three-drug regimen was also evident on an intent-to-treat analysis (RR, 28% with TC and 43% with TCF). In addition to a higher RR, patients receiving triple therapy experienced a significantly longer time to progression. Although the median overall survival of TC patients was somewhat longer than that in the TCF arm, this difference was not statistically significant.

Grade 4 fever in the absence of infection was reported by 4% of patients in both arms of the study: there were no grade 3 fevers. The rate of grade 3/4 infection was higher in the TCF than in the TC arm (10% vs 4%). The rates of asthenia were similar in the two arms, while the proportion of patients reporting neurologic events was higher in the two-drug arm, possibly because of the higher dose of docetaxel.

Gastrointestinal toxicities were higher in the TCF arm, and stomatitis (predominantly grade 3) occurred only in the group receiving 5-FU. The incidence of grade 3/4 edema was less than 3% in both arms of the study, as was the incidence of nail changes. Levels of pulmonary toxicity were similarly low (<3%) in the two treatment groups. Alopecia affected 4% of TC and 3% of TCF patients.

The majority of patients had grade 3/4 neutropenia (84% in both arms). The rates of febrile neutropenia were considerably lower and similar across treatments (16% with TC and 19% with TCF). Infection accompanied by grade 3/4 neutropenia was reported in 8% of TC and 10% of TCF patients. There were no deaths associated with hematological toxicities.

Discussion

It is notable that only 1% of patients included in the study had locally recurrent disease in the absence of metastatic spread. Hence, the study did not contain patients potentially treatable by surgical resection,

which may, in certain circumstances, bias trial outcome.

The greater toxicity of the three-drug combination was evident in the fact that 14% of cycles required a dose reduction, while this was true of only 5% of TC cycles. The excess toxicity attributable to the addition of 5-FU was evident, particularly in stomatitis and diarrhea, which may have been confined largely to the early cycles of treatment, i.e., before dose reductions had been effected.

The somewhat greater toxicity of TCF is accompanied by significantly greater activity — evident in a higher RR and time to progression. The phase II study described was envisaged from the outset as part of an integrated phase II/III program. The protocol called for the better of the two phase II regimens to be compared in a phase III trial against a control arm of cisplatin plus 5-FU. Based on the findings reviewed, the independent data monitoring committee concluded that the TCF regimen should proceed to a randomized phase III trial. In this ongoing study, the comparison is therefore between cisplatin plus 5-FU as the control arm and cisplatin plus 5-FU plus docetaxel. The primary endpoint is time to progression, with overall survival as a secondary endpoint.

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