European experience of docetaxel and cisplatin in advanced gastric cancer

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Abstract

The combination of docetaxel with cisplatin in gastric cancer is a promising development. In a phase II study, 85–100 mg/m² docetaxel plus 75 mg/m² cisplatin was established as an active regimen in advanced gastric cancer (with an overall response rate of 56%) with a manageable safety profile. Up to 300 mg/m² 5-fluorouracil (5-FU) given by continuous infusion for 2 of 3 weeks can be added to this regimen without an increase in appreciable toxicity. The efficacy of docetaxel-based regimens remains to be established by a randomized phase III study. However, the results of such trials are eagerly awaited, as are data from studies of docetaxel-based combinations in the adjuvant and neoadjuvant settings.

Key words Metastatic gastric cancer · Docetaxel

Introduction

In Europe, several avenues are being explored in the treatment of advanced gastric cancer. There is interest in the intensive use of chemotherapy (with weekly regimens supported by growth factors), in the use of 5-fluorouracil (5-FU) as protracted continuous infusion or at high dose, and in oral fluoropyrimidines such as UFT, capecitabine, and S-1. However, the advent of newer drugs for this indication, notably docetaxel and irinotecan, has attracted considerable attention.

Preclinically, the combination of cisplatin and docetaxel has produced varying results, with either no therapeutic synergism observed in certain cell lines, or with additive or supra-additive effects observed in other cell lines [1–3]. Furthermore, the preclinical studies and

clinical studies in non-small cell lung cancer (NSCLC), in particular the phase III trials utilizing docetaxel in platinum-resistant or refractory disease, have suggested that there is a lack of cross-resistance between docetaxel and cisplatin [4–6]. This combination is also interesting, as the mechanism of action is different for the two agents and they have limited overlapping toxicities [7]. In phase I trials in various tumor types, the combination of docetaxel and cisplatin has been found to be active and feasible [8–15]. In a development program in gastric cancer, which began in 1996, docetaxel was combined initially with cisplatin in a phase II trial [16]. Following encouraging results, docetaxel was combined with both cisplatin and continuous 5-FU infusion in a phase I/II trial. This led to a three-arm randomized phase II study which compared docetaxel plus cisplatin against docetaxel plus cisplatin and 5-FU (TCF) and against epirubicin plus cisplatin plus 5-FU (ECF). Over the same period, a study of TCF in the neoadjuvant setting was initiated. This paper summarizes the results of these trials, which were conducted by the European Institute of Oncology and the Swiss group for Clinical Cancer Research (SAKK).

Docetaxel plus cisplatin: a phase II study

In the original phase II trial, the first 5 patients received 100 mg/m² docetaxel over 1–2 h on day 1, plus 75 mg/m² cisplatin over 4 h. However, this combination proved too toxic, and the following 43 patients were treated with 85 mg/m² docetaxel and 75 mg/m² cisplatin [16]. Treatment was administered every 3 weeks for up to eight cycles. Analysis was conducted on all 48 patients.

The mean age was 55 years (range, 27 to 75 years); 75% were men, 48% of performance status (PS) 0 and 52% of PS 1. Appetite was good in 27%, fair in 56%, and poor in 15%. The mean weight loss over the previ-

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Table 1. Efficacy results in the phase II trial of docetaxel plus cisplatin in the treatment of gastric cancer [16]

Response (<i>n</i> = 48)	Number of patients	Percentage of patients
Complete response	2	4
Partial response	25	52
Stable disease (for ≤ 3 cycles)	12	25
Progressive disease	6	13
Early death	2 ^a	4
Non-measurable disease	1	2

^a One early death, one suicide**Table 2.** Hematological adverse events in the phase II trial of docetaxel plus cisplatin in the treatment of gastric cancer [16]

Toxicity grade	Percentage of cycles (<i>n</i> = 229)		Percentage of patients (<i>n</i> = 47)	
	3	4	2	4
Leucopenia	21%	4%	40%	11%
Granulocytopenia	25%	31%	24%	57%
Thrombocytopenia	0%	1%	0%	4%
Anemia	—	—	21%	11%

Nine episodes of non-fatal febrile neutropenia occurred in eight patients

ous 3 months was 4.5 kg. Of the patients included, 48% had had primary resection and 6% had adjuvant or neoadjuvant chemotherapy.

By intent-to-treat analysis, the overall response rate (RR) of 56% was very encouraging: two patients had a complete response (CR rate, 4%) and 25 a partial response (PR, 52%) (Table 1). The median time to progression (TTP) was 6.6 months and median overall survival (OS), 9 months. There was one early death and one case of suicide.

Toxicity was primarily hematological, with grade 4 leucopenia in 11%, and grade 4 granulocytopenia in 57% of patients (Table 2). Nine episodes of febrile neutropenia occurred in eight patients, but none was fatal. No grade 4 non-hematological toxicity was seen, and the incidence of grade 3 toxicity was relatively low: 2% of patients experienced grade 3 fatigue, diarrhea, and mucositis; the incidence of grade 3 nausea/vomiting was 1%, and that of neuropathy, fluid retention, and anaphylaxis was less than 1% for each (Table 3).

Docetaxel plus cisplatin and 5-FU

In considering a third agent with which docetaxel and cisplatin might be combined, attention focused on drugs with low hematotoxicity, such as 5-FU administered by continuous infusion. The choice of this third agent

Table 3. Non-hematological adverse events in the phase II trial of docetaxel plus cisplatin in the treatment of gastric cancer (*n* = 229 cycles) [16]

Toxicity grade	1	2	3
Nausea/vomiting	29%	12%	1%
Fatigue	40%	21%	2%
Diarrhea	5%	5%	2%
Mucositis	13%	4%	2%
Neuropathy	14%	8%	0.4%
Fluid retention	9%	4%	0%
Anaphylactoid reaction	2%	0%	0.4%

was also influenced by indications of activity: in the European reference regimen of ECF, both epirubicin and cisplatin are administered at relatively low doses (50 mg/m² and 60 mg/m², respectively), suggesting that much of the effectiveness of ECF is contributed by the continuous infusion of 200 mg/m² 5-FU.

The original intention in the phase I/II study of TCF was to have five dose levels, increasing the dose of cisplatin administered from 60 mg/m² to 75 mg/m², the dose of docetaxel from 70 mg/m² to 85 mg/m², and the dose of 5-FU (given as continuous infusion for 2 of 3 weeks) from 200 mg/m² to 250 mg/m². Because no dose-limiting toxicities were experienced, the escalation of 5-FU continued to a maximum of 350 mg/m², accompanied by 75 mg/m² cisplatin and 85 mg/m² docetaxel.

The mean age of the 53 patients treated in the study was 57 years (range, 36 to 70 years); 69% were men, 50% of PS 0, 44% of PS 1, and 6% of PS 2. The median weight loss over the previous 3 months was 2 kg. Of the patients included, 52% had had primary resection, and 6% had adjuvant or neoadjuvant chemotherapy. Importantly, bidimensionally measurable disease was present in 81%.

There were suggestions early in the escalation program of dose-limiting febrile neutropenia, diarrhea, nausea, and mucositis in certain patients. However, further experience showed that this response was not typical. Among the 52 patients treated, the overall rate of

grade 4 leucopenia was 8% and that of grade 4 granulocytopenia, 54%. The non-hematological grade 4 toxicities at 1% frequency, were nausea/vomiting, fatigue, mucositis, and diarrhea. These findings led to the recommendation of a combination regimen consisting of 85 mg/m² docetaxel, 75 mg/m² cisplatin, and 300 mg/m² 5-FU.

Full report of this trial is presently in preparation.

Discussion

The data noted above are promising. However, randomized studies are needed to determine any improvement in outcome. To this end, the European Institute of Oncology and the SAKK have organized a randomized phase II study (which may develop into a phase III trial) in which patients with metastatic gastric cancer are randomized to TC, TCF, or ECF.

A relatively high incidence of febrile neutropenia at the start of the study led to a reduction in the docetaxel dose from 85 mg/m² to 75 mg/m², since when no adverse events have been reported.

The addition of docetaxel to chemotherapy is also being investigated in locally advanced resectable disease. In a randomized phase III study, patients with T2N+M0 or T3–4 any N M0 cancer are being randomized to either: surgery followed (whenever possible) by four cycles of adjuvant TCF, or to four cycles of TCF before surgery. This study will demonstrate the feasibility and efficacy of a docetaxel-based approach to neoadjuvant and adjuvant treatment.

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