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ORIGINAL PAPER

Phase II studies on docetaxel alone every third week, or weekly in combination with gemcitabine in patients with primary locally advanced, metastatic, or recurrent esophageal cancer

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Abstract
Background The purpose of these studies was to compare efficacy and toxicity of docetaxel alone with the combination of gemcitabine and docetaxel for treatment of metastatic esophageal carcinoma.
Patients and methods These studies enrolled patients with histopathologically verified squamous cell carcinoma or adenocarcinoma of the esophagus or cardia. Between March 1997 and June 1999, 52 patients were enrolled in the initial Phase II study (Study 1). They were scheduled for treatment with docetaxel 100 mg/m^2 every third week as a 1-h infusion. The second Phase II study between September 2000 and March 2003 included 65 patients (Study II). They were given docetaxel 30 mg/m^2, administered as a 30-min i.v. infusion weekly for four times, followed by 2 weeks of rest, and gemcitabine starting with a dose of 750 mg/m^2 (if well-tolerated 1,000 mg/m^2) on days 1 and 15, followed by 3 weeks of rest. A new cycle began on day 36. Patients were premedicated with betamethasone 8 mg p.o. on the evening before, and 8 mg i.v. 30–60 min before the docetaxel infusion. Response was confirmed by computed tomography and assessed at 12 and 24 weeks. Toxicity was assessed according to WHO scales.
Results In study I, 38 out of the 52 enrolled patients were valuable. Two patients experienced complete remission (CR) (5%), 10 patients partial remission (PR) (26%), nine patients stable disease (SD) (24%), and 17 patients showed progressive disease (PD) (45%). Toxicity mainly involved leukopenia, which in some cases required hospitalization and treatment with antibiotics. In Study II, 46 out of the 65 enrolled patients (70%) were assessable. Out of these, three patients (7%) had CR, eight patients (17%) had PR, 10 patients (22%) had SD, and 25 (54%) PD. Overall response was 24% while an additional 22% showed stable disease. Toxicity mainly consisted of leucopenia and pain.
Conclusion Docetaxel as a single agent is active in esophageal cancer, both in treatment naive and in previously treated patients with recurrent disease. The overall response rate was 31%, with a good-safety profile. The addition of gemcitabine is well tolerated, but adds no efficacy. Weekly administration of docetaxel may be less effective. It demonstrates moderate efficacy and the doses used provide an acceptable safety profile.

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Introduction

Esophageal carcinoma is a disease with poor prognosis. While distant metastases do not usually dominate the initial clinical picture in patients with esophageal cancer, autopsies show that widespread distant metastases are almost always present at the time of death [1, 2].

Systemic chemotherapy and/or stent treatment is the mainstay of palliative treatment. Even in patients in whom the disease was thought to be limited to the loco-regional area postmortem, studies reveal disseminated tumor in 51–94% of patients [3–5]. Thus any effort to improve the dismal prognosis of these patients must include a search for effective systemic therapy.

There is an increasing evidence that esophageal cancer may respond well to combination chemotherapy. The most commonly used chemotherapy regimen in both squamous cell and adenocarcinoma of the esophagus is the combination of cisplatin 100 mg/m^2 on day 1, and 5-FU 1,000 mg/m^2 per day by continuous infusion for 96–120 h [6, 7]. In the preoperative setting, response rates as high as 72%, with complete response (CR) as high as 44%, have been reported [8]. For patients with metastatic, recurrent, or locally advanced disease, however, the response rate ranges from 25 to 35% with a low CR rate, short duration of response, and increased toxicity [9]. The toxicity of conventional chemotherapy, combining a continuous infusion of fluorouracil (5-FU) and cisplatin is substantial and includes stomatitis, diarrhea, nausea, fatigue, and myelosuppression. Moreover, the cumulative toxicity of cisplatin substantially limits the number of cycles that can be given. This regimen also has the disadvantage of requiring hospital admission or the use of a more complex and costly route of administration, such as an ambulatory infusion pump. It could therefore be of interest to explore different platinum-free alternatives to these platinum-containing regimens.

Taxanes are a drug class that promote stabilization of microtubules and are potent radiosensitizers. Paclitaxel has been tested in metastatic disease with an overall response of 32% [10, 11]. New drugs are urgently needed to improve treatment results. In an effort to accomplish this, a protocol was established with docetaxel given every third week. In a second study, docetaxel was given on a weekly basis to increase tolerability without compromising effect, and with the addition of gemcitabin. The studies were conducted as multicenter trials in Scandinavia. The purpose was to evaluate the efficacy and safety of docetaxel as a single drug or in combination with gemcitabine in patients with metastatic esophageal carcinoma.

Patients and methods

Study I was conducted between March 1997 and June 1999 and study II between September 2000 and March 2003. They were consecutive Phase II studies performed within the same Scandinavian study group. Patient characteristics are listed in Table 1.

Eligibility

To be eligible for the studies the patients must have histologically confirmed squamous cell carcinoma or adenocarcinoma of the esophagus, that was either metastatic, locally advanced, or recurrent and unsuitable for surgery or radiation therapy. Prior history of chemotherapy administration was permitted. The inclusion criteria were: Measurable disease, age >18, life expectancy of at least 12 weeks; WHO performance status < 2, adequate marrow function (leucocytes 3.0×10^9 and platelet 100×10^9) and adequate liver function. Patients were excluded if they had a history of previous malignancy (other than localized basal or squamous cell carcinoma of the skin, or non-invasive carcinoma of the cervix), brain metastases,

Table 1 Patient characteristics

	Docetaxel *N*	Docetaxel/ Gemcitabin *N*
Entered	52	65
Eligible	38	46
Median Age	62 (42–82)	60 (39–84)
Male/female	46/6	51/14
Adenocarcinoma	13	41
Squamous cell carcinoma	39	21
Undifferentiated cancer		3
Sites of recurrence		
Local	13	5
Lymph nodes	26	36
Liver	20	38
Lung	12	30
Bone	1	2
Other	5	8
Number of organs involved		
1	19	17
2	24	34
>2	9	14

psychosis, or senilities, or life expectancy shorter than 3 months.

Pretreatment evaluation included a chest radiograph and CT scan of the thorax or abdomen. Other investigations such as endoscopies and barium swallow were performed if necessary to evaluate disease.

Bidimensionally measurable disease, or unidimensionally measurable disease assessable by CT scan, chest X-ray, or ultrasound (not within previously irradiated areas) was required. Radiographic investigations were to be done within 28 days before treatment initiation. ECG and baseline tumor measurements were also carried out.

About 14 days prior to the first infusion, history, height measurement, physical examination, performance status, and baseline vital signs were evaluated.

Within 7 days of the first infusion, lab work was assessed including white count, neutrophils, platelets, hemoglobin, alkaline phosphatase, ASAT, ALAT, bilirubin, sodium, potassium, calcium, and albumin. Patients were required to have adequate bone marrow, renal, and hepatic function.

Chemotherapy

Study I: After appropriate steroid prophylaxis (betamethasone 8 mg two times daily, 1 day before treatment, the treatment day, and 1 day after treatment), docetaxel 100 mg/m^2 was administered intravenously in 500 ml normal saline over 60 min. The treatment was repeated every third week until tumor progression.

Study II: Docetaxel 30 mg/m^2 was administered as a 30-min i.v. infusion on a weekly basis on days 1, 8, 15, and 22, followed by 2 weeks of rest with cycle 2 starting on day 36.

In phase I gemcitabine was given at a starting dose of 750 mg/m^2, following docetaxel administration, as a 30-min i.v. infusion on a biweekly basis on days 1 and 15, followed by 3 weeks of rest with cycle 2 starting on day 36. The dose was increased to 1,000 mg/m^2 after all patients at the lower dose were analyzed and found to tolerate the initial dose. Each cycle was 5 weeks long (=35 days).

Premedication with betamethasone or dexamethasone was given at a dose of 8 mg p.o. on the evening before docetaxel infusion and 8 mg i.v. 30–60 min immediately before docetaxel infusion.

Evaluation of toxicity and dose adjustments

Toxicity was graded according to National Cancer Institute Common Toxicity Criteria (CTC). The gemcitabine dose was consolidated at a dose of 1,000 mg/m^2.

An additional chemotherapy cycle was administered if the absolute neutrophil count was $>1.5 \times 10^9$ and platelets $>75 \times 10^9$ and if toxicity had resolved. Otherwise treatment was delayed for 7 or 14 days until hematological and gastrointestinal recovery had occurred.

Statistical considerations

The primary endpoint of the study was to determine the proportion of patients who responded to docetaxel and gemcitabine. The study was designed as a two-stage trial according to Simon [12]. All eligible patients were included in response, toxicity, and survival analyses.

Toxicity evaluation

Hemoglobin, white blood cell, and platelet counts were obtained weekly during treatment cycles. Prior to each treatment, complete blood count and biochemistry were obtained. Patients were questioned specifically about nausea, dysphagia, pain, vomiting, diarrhea, stomatitis, and constipation. Side effects such as alopecia, skin changes, fluid retention, neurological, or heart dysfunction were recorded.

Assessment of response

Response was clinically evaluated every fourth week and radiographically every 12th week. Objective response was defined according to standard criteria. A complete response (CR) was defined as the disappearance of all evidence of disease for at least 4 weeks. A partial response (PR) required a reduction of 50% or more of the sum of the products of the two longest perpendicular diameters of all measurable lesions, maintained for at least 4 weeks with no progression of valuable lesions or new lesions. Stable disease (SD) was defined as less than 50% regression and less than 25% progression of measurable disease for at least 4 weeks with no new lesions. Progressive disease was defined as an increase of greater than 25% in the sum of products of two diameters of one or more measurable tumors or the appearance of new lesions. Overall duration of response was calculated from the start of treatment to disease progression and survival time was calculated from start of treatment to death or last follow-up.

Ethical aspects

Informed consent was obtained prior to therapy from all patients. The study protocols were approved by the ethics committees of participating centers in compliance with the World Medical Association's Declaration of Helsinki 1964 and the Amendment of Tokyo in 1975.

Results

Study I

Between March 1997 and June 1999, 52 patients with a median age of 62 years (range 48–82) were enrolled in this study. A total of 13 patients had adenocarcinoma and 39 had squamous cell carcinoma. The majority of patients were treated for primary disease with chemotherapy (cisplatin and 5-Fluorouracil) and some patients had also received gemcitabine as a second line treatment. Out of the 52 patients enrolled, 38 were valuable (Table 1).

Response to treatment

Two patients experienced complete remission (CR) (5%), 10 patients partial remission (PR) (26%,) 9 patients stable disease (SD) (24%), and 17 patients progressive disease (PD) (45%) (Table 2). Thus the overall response rate was 31%.

Toxicity

Grade 3–4 toxicities were granulocytopenia 14%, infection without grade 3–4 neutropenia 12%, neurotoxicity 8%, anemia 16% and infection with grade 3–4 neutropenia 8%. The major toxicity was thus, hematological and mainly consisted of leucopenia, which in some cases required hospitalization and treatment with antibiotics. Before treatment 10 patients complained of nausea and vomiting grade 1.

Study II

The study included 65 patients with a mean-age of 60 years (range 39–84). A total of 21 patients had squamous cell carcinoma and 41 had adenocarcinoma. Three patients had poorly differentiated cancer. A total of 49 patients were chemotherapy-naive, while 16 had been treated with cisplatin-based chemotherapy for their cancer. About 17 had primary surgery and 13 patients had radiation therapy. Lymph nodes, lung, and liver were the predominant sites of metastatic disease (Table 1).

Response to treatment

Out of the 65 patients included in the study, 46 were assessable, which means they completed three chemotherapy cycles and a subsequent response evaluation. WHO criteria could be applied to evaluate tumor response in these 46 patients. Overall response was 24%. Three patients (7%) had a complete response and eight patients (17%) had a partial response. Disease was stabilized in 10 other patients (22%), while 25 patients (54%) had progressive disease (Table 2).

Those patients who were non-valuable, either demonstrated worsening of their general condition, which made further treatment impossible, or a documented progression of their disease prior to the first evaluation. Treatment-related side effects (neuropathy) caused interruption of treatment in one case.

Toxicity

Major grade 3–4 toxicities are listed in Table 3 and consisted mainly of pain (10%), granulocytopenia (7%) and infection (7%). One patient could have more than one grade 3–4 toxicity.

Reasons for patient discontinuation

In the majority of cases discontinuation was caused by progressive disease. Minor reasons included adverse experiences, death, refusal of further treatment, protocol deviation, and stable disease without further subjective improvement. There were no treatment related deaths.

Table 2 Best response in eligible patients

	Docetaxel *N* (%)	Docetaxel/Gemcitabin *N* (%)
CR	2 (5%)	3 (7%)
PR	10 (26%)	8 (17%)
SD	9 (24%)	10 (22%)
PD	17 (45%)	25(54%)

Table 3 Grade III–IV toxicity

	Docetaxel	Docetaxel/ Gemcitabine
Granulocytopenia	14%	7%
Infection with grade III–IV neutropenia	8%	–
Infection without grade III–IV neutropenia	12%	7%
Anemia	16%	2%
Thrombocytopenia	–	2%
Neurotoxicity	8%	3%
Pain	–	10%
Gastrointestinal problems	–	2%
Fluid retention	–	2%

Discussion

These two studies were performed as consecutive phase II studies conducted within the same Scandinavian study group, the first 1997–1999 and the second 2000–2003. It is interesting to observe the shift of the histological predominance from squamous cell carcinoma to adenocarcinoma in the two consecutive studies. In the latter phase II study, adenocarcinoma accounted for 63%, compared with 25% in the first study, illustrating the problem of comparing different studies even when patients are recruited into consecutive studies with similar inclusion criteria from the same centers. In study II also cardia cancer was included. Comparing results is also problematic.

According to the National Cancer Register, the incidence of adenocarcinoma substantially increased during this period, while the incidence of squamous cell carcinoma decreased. Adenocarcinoma does not demonstrate the same obvious correlation with alcohol or tobacco as squamous cell carcinoma.

Esophageal cancer remains a highly virulent disease with poor prognosis. Only 5–10% of all patients will be alive for 5 years from the date of diagnosis. Approximately 500 new cases are diagnosed in Sweden annually. More than half of them have advanced incurable disease at time of diagnosis, while the remaining 50% have loco-regional disease. In developed countries diagnosis of early disease is uncommon, thus T3 or T4 and *N* positive lesions are observed in 70% of patients. Metastatic carcinoma of the esophagus has a median survival of 6 months, and therefore, most treatment options are palliative. Investigational protocol chemotherapy is the best option for patients with good performance status who desire treatment. If no experimental treatment is available a combination of 5-FU infusion and cisplatin is often used. However, this regimen requires hospitalization and is associated with substantial toxicity.

Taxanes have been tried in other studies. Ajani et al. achieved a 32% response rate in a patient mix of adenocarcinoma and squamous cell carcinoma using the combination of high dose paclitaxel and G-CSF [13]. Muro et al. [14] reported a 20% response rate to single-agent vinorelbine in patients with metastatic squamous cell carcinoma of the esophagus.

Docetaxel as a single agent for treatment of recurrent or metastatic disease is a convenient outpatient regimen with significant activity and ability to produce remissions in some patients with metastatic or recurrent carcinoma of the esophagus.

Treatment with docetaxel/gemcitabine shows only modest activity with a response of 24% (CR, PR) and another 22% with stable disease.

Since esophageal cancer is relatively uncommon, focus on drug development has been less intense than for other tumor types, and differences—if any—in relation to histology have not been fully evaluated. It is assumed that squamous cell carcinoma of the esophagus is a chemotherapy-sensitive esophageal cancer, especially when cisplatin-based combination therapy is used. However, cumulative cisplatin toxicity limits usefulness in the palliative setting.

A number of single agents with documented efficacy are available: cisplatin, 5-FU, mitomycin, methotrexate, paclitaxel, docetaxel, and vindesine. These agents have demonstrated a partial or complete response rate of at least 20% in previously untreated patients with carcinoma of the esophagus [15–22].

Cisplatin is one of the most studied and widely used drugs for patients with carcinoma of the esophagus. It has primarily been studied in squamous cell tumors, though it is also widely used for adenocarcinoma. The age of patients who develop carcinoma of the esophagus (60 years and older) often limits the cumulative cisplatin dose to approximately 500 mg/m^2. A higher cumulative dose can result in debilitating neurotoxicity, ototoxicity, and cardiac toxicity [23]. Therefore, it is of minor importance in the palliative setting where treatment periods may often be prolonged over months and even years.

Further research to discover new active agents against carcinoma of the esophagus is likely to impact patient survival.

In the second Phase II study we hoped that smaller weekly doses would improve dose intensity and response. Even though less Grade 3–4 toxicity was observed, response rates (CR/PR) were lower in this study (24%) compared with (31%) when docetaxel was given as a single dose every third week. Our Phase II chemotherapy trials were an attempt to discover new active chemotherapeutic combinations. We hoped to develop a regimen with a low toxicity profile, but more importantly a high response rate. Our complete response rate in Study II was 7%, which was lower than expected. Nevertheless, the search for less toxic and more active combination chemotherapy regimens in metastatic esophageal cancer seems justified within clinical trials.

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