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Phase II study of neo-adjuvant chemotherapy with paclitaxel and cisplatin given every 2 weeks for patients with a resectable squamous cell carcinoma of the esophagus

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Background: We have previously reported a favourable response rate in patients with advanced esophageal cancer after treatment with a biweekly regimen of paclitaxel and cisplatin. In this study we investigate the feasibility and efficacy of this regimen in a neo-adjuvant setting.

Patients and methods: Patients with resectable squamous cell carcinoma of the esophagus received paclitaxel 180 mg/m^2 and cisplatin 60 mg/m^2 every 2 weeks. Patients received three courses and responding patients received three additional courses; thereafter, patients were referred for surgery. Patient characteristics of 50 eligible patients were as follows: male, 60%; median age, 62 years (range 45–78); median World Health Organization performance status of 1 (range 0–2).

Results: Ninety-four per cent of patients received at least three courses of chemotherapy. Haematological toxicity consisted of National Cancer Institute–Common Toxicity Criteria grade 3 or 4 neutropenia in 71% of patients, with neutropenic fever occurring in only two patients (4%). The overall response rate was 59%. Pathological examination showed tumour-free margins in 38 patients. In seven patients no residual tumour was found. The median overall survival was 20 months and the 1- and 3-year survival rates were 68% and 30%, respectively.

Conclusions: This dose-dense schedule of paclitaxel and cisplatin administered biweekly is well tolerated and the observed overall and complete response rates are promising.

Key words: biweekly, cisplatin, esophageal cancer, neo-adjuvant, paclitaxel

Introduction

Patients who present with esophageal cancer have a poor prognosis. Most patients thought to have resectable disease already have extension into the adventia or through the esophageal wall and/or regional lymph node involvement at the time of diagnosis. The 5-year survival rate of these patients after surgical resection is only 20% [1, 2]. The pattern of failure includes both local recurrence as well as distant metastases.

One way to improve the prognosis of patients with resectable esophageal cancer might be the incorporation of neo-adjuvant chemotherapy. The goals of neo-adjuvant chemotherapy are a reduction of recurrence from occult lymphatic and/or distant metastases with improvement of survival and possible tumour shrinkage with an increased resectability rate.

Most studies of neo-adjuvant chemotherapy have demonstrated that patients achieving an objective response have a significantly better survival compared with non-responding patients [3]. Nevertheless, overall survival remains poor and therefore development of chemotherapy regimens with high response rates and which can be administered to patients with a moderate performance score is a high priority. Paclitaxel has been found to be an active agent in esophageal cancer, either alone or in combination with cisplatin. Ilson et al. [4, 5] investigated conventional 3-week schedules of cisplatin and paclitaxel with or without 5-fluorouracil (5-FU) in patients with advanced oesophageal cancer. The reported response rates were 48% and 44%, respectively. However, in both studies the observed toxicity was substantial, including hospitalisation due to gastrointestinal and haematological toxicity in half of the patients.

In our centre, we have obtained experience with the use of dose-dense chemotherapy regimens with cisplatin and paclitaxel. In a phase I study, we treated patients with advanced esophageal cancer with a biweekly administration of cisplatin 60 mg/m^2 and escalating doses of paclitaxel (3-h infusion) [6]. The recommended dose for paclitaxel was 180 mg/m^2, because at higher doses sensory neuropathy became the dose-limiting toxicity. In a subsequent phase II study we confirmed the feasibility of this regimen, and the observed response rates in these two studies were 52% and 43%, respectively [6, 7]. Both the high response rates

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and the excellent clinical tolerability of this biweekly regimen of cisplatin and paclitaxel urged us to test this regimen in a neo-adjuvant phase II setting in patients with resectable squamous cell carcinoma of the esophagus.

Patients and methods

Patients

Patients with histologically confirmed squamous cell carcinoma of the oesophagus and with no signs of irresectability and no evidence of metastatic disease were eligible for the study. The tumour had to be limited to the oesophagus and regional lymph nodes without involvement of the tracheo-bronchial tree or other structures. Further eligibility requirements were as follows: age ≥18 years; no contraindications for extensive surgery; World Health Organization (WHO) performance status of ≤2; written and voluntary informed consent; and adequate haematological, renal and hepatic functions (granulocytes $\geq 1.5 \times 10^9$/l, platelets $\geq 100 \times 10^9$/l, total bilirubin <1.5 × upper normal limit and creatinine <120 μmol/l). Exclusion criteria were as follows: previous treatment with chemotherapy or radiotherapy; pre-existing neurotoxicity greater than National Cancer Institute–Common Toxicity Criteria (NCI-CTC) grade 1 and inadequate calorie and/or fluid intake. The study was approved by the local ethics committee.

Initial evaluation

Initial evaluation included a complete medical history, physical examination, complete blood cell count and serum biochemistry endoscopy with biopsies, endoscopic ultrasonography, ultrasonography of the supraclavicular region and a computed tomography (CT) scan of the chest and abdomen.

Chemotherapy

Paclitaxel 180 mg/m^2 and cisplatin 60 mg/m^2 were administered by i.v. infusion every 2 weeks. After prehydration with at least 1 l of normal saline, the calculated dose of paclitaxel, diluted in 500 ml of normal saline, was infused over 3 h. Hereafter, the calculated dose of cisplatin was administered over 3 h followed by posthydration with 3 l of normal saline over 24 h. Thirty minutes prior to the paclitaxel infusion, the patients received dexamethasone 10 mg, clemastine 2 mg and ranitidine 50 mg, all given intravenously. Ondansetron 8 mg i.v. was routinely given. Patients were retreated when the granulocytes were $\geq 0.75 \times 10^9$/l and platelets $\geq 75 \times 10^9$/l. When these criteria were not met, treatment was postponed for 1 week.

Tumour response was assessed after the third course of chemotherapy and included a CT scan of chest and abdomen and an endoscopic examination. Non-responding patients were referred for surgery. Patients showing disease regression received three additional courses of chemotherapy. These patients were again evaluated after the sixth course and then referred for surgery.

Toxicity was graded and reported using NCI-CTC criteria (version 2) and response was evaluated using standard WHO criteria [8].

Surgery

For carcinomas proximal to the carina, the esophagus was resected by a right dorso-lateral thoracotomy. For more distal carcinomas the transhiatal approach was preferred. Accessible intra-abdominal, peri-esophageal and subcarinal lymph nodes were sampled. Post-operative radiotherapy or chemotherapy was not given.

The tumour stage after resection was classified according to the TNM classification of the International Union Against Cancer (UICC, fifth edition, 1997). To describe the absence or presence of residual tumour after resection of the primary tumour, the following residual (R) categories were used as appendices: R0 if all the surgical margins were free of tumour; R1 if there was microscopically residual tumour in any of the surgical margins; and R2 if macroscopically residual tumour was detected.

Any type of complication occurring after surgery was considered post-operative morbidity. Treatment-related mortality was defined as any death that occurred before a patient was discharged, or even after discharge when there was any possible correlation with the treatment itself.

Table 1. Patient characteristics (n = 50)

Characteristic	No. of patients	%
Sex		
Male	30	60
Female	20	40
Age (years)		
Median	62	
Range	45–78	
WHO performance status		
0	20	40
1	26	52
2	4	8
Weight loss (%)		
0–5	21	42
5–10	10	20
>10	19	38
TNM classification[a]		
T2N0	1	2
T3N0	10	20
T2N1	6	12
T3N1	21	42
No pass	12	24

[a]Endoscopic ultrasonography.
WHO, World Health Organization.

Statistical considerations

Patient enrolment followed a four-step sequential design. If no response was seen in the first eight patients further accrual had to be halted. Otherwise, an additional 12 patients could be entered. In the third step, 10 more patients were entered if at least four responses were observed in the 20 patients that were treated. Finally, when 30 patients were treated the trial was to be continued with an additional 20 patients if the observed number of responses was at least 50%. Under this design there is only an 18% chance of continuing the trial while the true response percentage is <40%.

Survival time was measured from date of inclusion to death or was censored at the time that the patient was last known to be alive. Median survival times and survival curves were estimated using the method of Kaplan and Meier.

Results

From October 1997 to February 2000, 51 patients entered the study. One patient was ineligible because he had a carcinoma of the gastric cardia. Patient characteristics are listed in Table 1.

Table 2. Worst NCI-CTC grade toxicities ($n = 49$)

	CTC grade (%)				
	0	1	2	3	4
Granulocytopenia	4	10	14	18	53
Thrombocytopenia	96	4			
Nausea	45	37	14	4	
Vomiting	57	31	8	4	
Diarrhoea	90	8	2		
Mucositis	96	4			
Neurotoxicity	49	37	14		
Myalgia	47	35	18		
Fatigue	51	37	12		

NCI-CTC, National Cancer Institute–Common Toxicity Criteria.

Chemotherapy

Of 50 eligible patients, 47 patients (94%) received at least three courses of chemotherapy. One patient refused further treatment after one course of chemotherapy. This patient was considered not evaluable for toxicity and response. In two other patients, treatment was stopped after two courses due to grade 2 sensory neuropathy. Both patients were evaluated and referred for surgery. Thirteen patients with stable disease after three courses were referred for surgery according to the protocol. Treatment was continued in the remaining 34 patients who had at least objective tumour regression at evaluation, although not always qualifying for partial response. Seven of these patients did not receive the planned next three courses due to sensory neuropathy (four patients) and deterioration of general condition mainly due to fatigue and myalgia (three patients).

Sixty-three cycles (26%) were delayed for 1 week in 26 patients. The reason for the delay of treatment was in almost all cases a granulocyte count $<0.75 \times 10^9$/l at the day of retreatment. The planned and achieved dose intensities for cisplatin were 30 mg/m^2/week and 26.6 mg/m^2/week, respectively, and for paclitaxel, 90 mg/m^2/week and 79.8 mg/m^2/week, respectively.

The predominant toxicities are listed in Table 2. Neutropenia grade 3 or 4 was observed in 35 patients (71%), with neutropenic fever occurring in only two patients (4%). Both patients recovered after treatment with broad-spectrum antibiotics. Non-haematological toxicities were usually mild. Sensory neuropathy, the most important non-haematological toxicity, was observed in 25 patients (51%) but never exceeded grade 2. The overall response rate in 49 evaluable patients was 59%; seven patients (14%) had a complete response and 22 patients (45%) had a partial response. Stable disease was observed in 20 patients (41%). No patient had disease progression during treatment.

Surgery

Three patients (6%) were not referred for surgery. These patients had large tumours located above the carina and enlarged mediastinal lymph nodes that remained unchanged during chemotherapy, and were considered not fit enough for thoracotomy due to co-morbidity and a deteriorating general condition. All three patients received radiation therapy up to a total dose of 50 Gy.

Table 3. Pre- and post-treatment stage[a]

Stage	Pre-chemotherapy n (%)[b]	Post-chemotherapy n (%)[c]
T0N0	0	7 (14)
I	0	4 (8)
IIA	11 (22)	19 (38)
IIB	6 (12)	6 (12)
III	21 (42)	6 (12)
IV	0	3 (6)
No pass/unknown	12 (24)	5 (10)

[a]Stage grouping according to the International Union Against Cancer, 5th edition.
[b]Staged by endoscopic ultrasonography.
[c]Staged by pathological examination.

Table 4. Postoperative course and morbidity

Characteristic	No. of patients (%)
Operative mortality	0 (0)
30-day hospital mortality	1 (2)
Median days of hospital stay (range)	15 (8–96)
Postoperative course	
Uneventful	19 (42)
Complications	26 (58)
Respiratory	14 (32)
Sepsis	2 (4)
Anastomotic leakage	7 (13)
Bleeding	1 (2)
Vocal cord paralysis	12 (27)

Forty-seven patients (94%) were referred for surgery. Surgery was performed between 4 and 6 weeks after completion of chemotherapy in all patients. In 45 patients (90%), a resection was carried out. In two patients, who had a locally irresectable tumour or intra-abdominal lymph node metastasis, a resection was not carried out. In 28 patients a transhiatal approach without thoracotomy was performed, while 17 patients underwent a transthoracic esophagectomy.

Of the 45 patients that underwent oesophageal resection, 38 patients (84%) had an R0 resection and seven patients (16%) had an R1 resection. Pathological examination of the resected specimens showed no residual tumour in seven patients. Five of these seven patients had been clinically evaluated as complete responders. A comparison of the pre- and post-treatment staging of all 50 patients is listed in Table 3.

Post-operative complications occurred in 26 of 45 patients (58%) (Table 4). Two patients died in the post-operative period (4%). One patient died of cardiovascular complications directly after surgery and one patient died of respiratory complications 3 months after surgery.

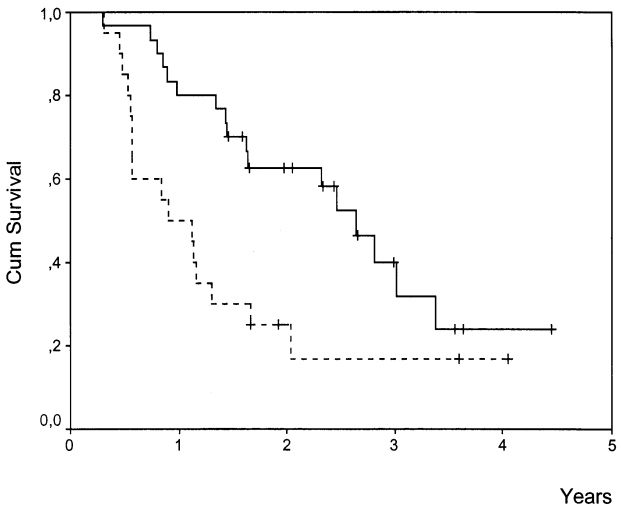

Figure 1. Kaplan–Meier survival curve for responding ($n = 29$; continuous line) and non-responding ($n = 20$; dotted line) patients, $P = 0.008$ (log rank).

Survival and pattern of failure

After a median follow-up period of 41 months (18–54 months), 18 of 50 patients were alive, 17 of them showed no recurrence of disease. The median actuarial survival in all patients was 20 months (3–>50 months), with a 1- and 3-year survival rate of 68% and 32%, respectively. Responders had a significantly better median survival than non-responding patients (32 versus 11 months; $P = 0.009$) (Figure 1). The pattern of disease recurrence in 27 patients was locoregional recurrence in six patients, metastatic disease only in 17 patients and both locoregional and distant disease in four patients.

Discussion

Previous phase II studies with neo-adjuvant chemotherapy have shown encouraging results in patients with squamous cell carcinoma. Response rates of 15–60% with a complete pathological response rate of 4–7% after cisplatin-based combination chemotherapy have been reported [9]. Compared with historical controls the outcome seemed improved after treatment with pre-operative chemotherapy [10].

In two large randomised trials neo-adjuvant chemotherapy followed by surgery was compared with surgery alone [11, 12]. Noteworthy are the conflicting results of the two largest trials. The Medical Research Council (MRC) found a significantly improved survival following neo-adjuvant chemotherapy [11]. In their study, 802 patients with resectable esophageal cancer were randomised to receive pre-operative chemotherapy with two courses of cisplatin and 5-FU followed by surgery or surgery alone. The median survival was 17 months for patients treated with pre-operative chemotherapy versus 13 months after surgery alone [$P = 0.004$; hazard ratio 0.79; 95% confidence interval (CI) 0.67–0.93]. In the Intergroup trial 440 patients were randomised to pre-operative treatment with three courses of cisplatin and 5-FU followed by surgery, or surgery alone [12]. Median survival was comparable in the two groups, 15 months after pre-operative chemotherapy and 16 months after surgery alone ($P = 0.53$; hazard ratio 1.07; 95% CI 0.87–1.32).

The conflicting results of the randomised studies are difficult to explain, particularly because comparable chemotherapy regimens were used. A possible explanation is the type of surgical resection carried out. In the Intergroup study a transthoracic esophagectomy was preferred, while in the MRC study both the transthoracic esophagectomy and the transhiatal esophagectomy were considered appropriate; however, the number of transhiatal resections has not been reported. A transthoracic approach makes a more extended lymph node resection possible and it could be that the benefit of pre-operative chemotherapy in the positive studies was only the result of improved local control in patients treated with less extensive surgery. However, in a recently reported trial comparing transhiatal esophagectomy with transthoracic esophagectomy with extended lymphadenectomy there was only a trend toward improved long-term survival at 5 years with the extended transthoracic approach [13]. A transhiatal esophagectomy was associated with lower morbidity.

In the current study, we treated 50 patients with a resectable squamous cell carcinoma of the esophagus with a biweekly regimen of paclitaxel and cisplatin. This dose-dense treatment was well tolerated and achieved an overall clinical response rate of 59%. Despite the fact that 71% of patients developed grade 3 or 4 neutropenia, we observed only two episodes of neutropenic fever. The majority of patients included in our study had T3 tumours with positive regional lymph node involvement. Forty-five patients (90%) underwent an esophageal resection and the mortality rate was not apparently increased. Pathological examination showed no residual tumour in seven patients (14%) and an R0 resection in 38 patients (76% of all patients and 83% of patients that underwent a resection). The median survival was 20 months and the 1- and 3-year survivals were 68% and 32%, respectively.

Both the overall and complete response rates observed in this study, 59% and 14%, respectively, seem to compare favourably with the response rates observed in other studies with neo-adjuvant chemotherapy. In addition, this dose-dense regimen of cisplatin and paclitaxel was well tolerated and 94% of patients were able to complete the first three courses of chemotherapy. In the Intergroup study, for example, only 71% of patients completed the three pre-operative chemotherapy courses [12].

The design of our study and the chemotherapy regimen differed in several aspects from other studies. This is the first study investigating a neo-adjuvant regimen of dose-dense cisplatin and paclitaxel. Theoretical advantages of a dose-dense schedule could be that more cancer cells are being killed, because there is less time for the tumour to regrow between drug administrations, and that a more continuous exposure to cytotoxic agents may permanently impair growth-promoting intracellular signalling and DNA repair [14]. Furthermore, the study design differed from that of the other trials because we administered three additional courses to responding patients. Although the optimal number of pre-operative chemotherapy courses has not been established, the administration of additional courses to responding patients could have resulted in an increased complete response rate and possible improved survival.

In conclusion, this dose-dense schedule of cisplatin and paclitaxel administered biweekly is well tolerated by patients with resectable squamous cell carcinoma of the esophagus. The overall and complete response rates obtained with this combination are promising. Further evaluation comparing this treatment with other treatment strategies in a randomised trial is warranted.

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