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Clinical report

Phase II study of the combination cisplatin, etoposide, 5-fluorouracil and folinic acid in patients with advanced squamous cell carcinoma of the esophagus

MB Polee,[1] TC Kok,[1] PD Siersema,[2] HW Tilanus,[3] TAW Splinter,[1] G Stoter[1] and A Van der Gaast[1]

Departments of [1]Medical Oncology, [2]Gastroenterology and [3]Surgery, University Hospital Rotterdam-Dijkzigt, 3015 GD Rotterdam, The Netherlands.

The objective of this study was to determine the toxicity and the efficacy of the combination of cisplatin, etoposide, 5-fluorouracil (5-FU) and folinic acid in the treatment of patients with advanced squamous cell carcinoma of the esophagus. Patients received cisplatin 80 mg/m^2 i.v. on day 1, etoposide 125 mg/m^2 i.v. on day 1 and etoposide 200 mg/m^2 p.o. on days 3 and 5, 5-FU 375 mg/m^2/day continuously i.v. combined with folinic acid 30 mg p.o. 6 times per day on days 1–4. Courses were repeated every 4 weeks until progression or up to a maximum of 6 courses. Patients were evaluated for response after every two courses. Sixty-nine patients received a total of 291 courses (median 4, range 1–6). The hematological toxicity consisted of leukocytopenia grade 3 or 4 in 17 and 16% of patients, respectively. Leukocytopenic fever was seen in 19% of patients. Thrombocytopenia grade 3 or 4 was seen in 13 and 7% of patients, respectively. Non-hematological toxicity consisted of nausea/vomiting grade 3 in 32%, diarrhea grade 3 in 6% and mucositis grade 3 or 4 in 23% of patients. The overall response rate was 34% (complete response 4%, partial response 30%) and the median time to progression was 7 months in 13 patients who received no additional treatment. The median survival for all patients was 9.5 months with a 1-year survival rate of 36%. Ten patients with initially locally unresectable disease (*N*=2) or celiac or supraclavicular lymph node metastases (*N*=8) who received additional treatment (esophageal resection in seven patients and radiotherapy in three patients) after they had responded to chemotherapy had a 3-year survival of 50%. We conclude that the combination cisplatin and etoposide combined with 5-FU and folinic acid is a safe and active regimen for patients with advanced squamous cell carcinoma of the esophagus. Mucositis is the most prevalent toxicity. [© 2001 Lippincott Williams & Wilkins.]

Correspondence to MB Polee, Department of Medical Oncology, University Hospital Rotterdam-Dijkzigt, Dr Molewaterplein 40, 3015 GD Rotterdam, The Netherlands.
Tel: (+31) 10 4634897; Fax: (+31) 10 4634627;
E-mail: polee@oncd.azr.nl

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Introduction

The prognosis for patients with carcinoma of the esophagus or gastro-esophageal junction is still poor. More than 50% of symptomatic patients have already locally advanced non-resectable tumors, overt metastatic disease or at least T3N0 or T3N1 tumors. The 5-year survival rate of patients who are thought to have resectable disease is in the range of 10–20%.[1,2] The pattern of relapse in resected patients is both locoregional as well as the development of distant metastases.

Cisplatin-based combination chemotherapy is moderately effective in the treatment of metastatic esophageal cancer. In combination with 5-fluorouracil (5-FU), response rates of 19–55%[3–5] are obtained and by some authors this combination is considered to be standard therapy.[6]

Folinic acid is a biochemical modulator of 5-FU and is known to enhance 5-FU activity in the treatment of colorectal and gastric cancer.[7,8] We previously treated 29 patients with adenocarcinoma of the esophagus with 5-FU (500 mg/m^2/day for 5 days continuous infusion) and folinic acid (loading dose 4×90 mg followed by 6×60 mg for 5 days orally). This treatment was tolerated well with an overall response rate of 19%.[9] In patients with squamous cell carcinoma of the esophagus a response rate of 17% was achieved with a comparable regimen.[10] We have also investigated cisplatin in combination with etoposide in a phase II study in patients with advanced squamous cell

carcinoma of the esophagus.[11] The overall response rate in 65 evaluable patients was 48%. Toxicity was manageable and consisted mainly of myelosuppression.

Based on the favorable toxicity profile of the cisplatin/etoposide combination we decided to add 5-FU and folinic acid to this regimen. A combination of cisplatin, etoposide and 5-FU seemed attractive since all three drugs are active as single agents against esophageal cancer, and their toxicity profiles are only partially overlapping. Furthermore, these agents may have synergistic interactions.[12,13] We here report the toxicity and efficacy of this combination in the treatment of patients with advanced squamous cell carcinoma of the esophagus.

Patients and methods

All patients who entered the study had inoperable or metastatic, histologically proven squamous cell carcinoma of the esophagus. Further eligibility criteria were: age $\leqslant 75$ years, performance status WHO 0–2, a life expectancy of >3 months, a reasonable food passage, bidimensionally measurable disease (or evaluable disease if the primary tumor was the only indicator lesion), white blood cell (WBC) count $>3.0\times10^9$/l, platelets $>100\times10^9$/l, creatinine clearance >60 ml/min. Prior chemotherapy was not allowed. Patients with overt brain metastases or an irradiated primary tumor as the sole indicator lesion were excluded. All patients gave informed consent.

The i.v. treatment consisted of pre-hydration with 1500 ml saline/glucose (0.45/2.5%) and 4 g of magnesium sulfate over 14 h, followed by etoposide 125 mg/m^2, dissolved in 500 ml 0.9% saline given over 2 h (day 1). Cisplatin (80 mg/m^2) dissolved in 1000 ml 0.9% saline was then administered over 4 h, followed by 5-FU (375 mg/m^2/day) dissolved in 1000 ml 0.9% saline per day for 4 days. To prevent chemotherapy-induced phlebitis, 5000 E heparin was added to 5-FU infusion each day.

Oral treatment consisted of etoposide 200 mg/m^2/day on days 3 and 5, divided in three doses on each day (at 10 a.m., 2 p.m. and 6 p.m.). In case of stenosis with dysphagia the content of the capsules was dissolved in lemonade. Folinic acid 30 mg was administered 6 times per day from day 1 (at the start of 5-FU infusion) until day 5 (at the end of 5-FU infusion).

In case the WBC nadir remained $>2.0\times10^9$/l and/or the platelet nadir $>100\times10^9$/l the oral doses of etoposide were increased until a nadir (WBC $1.0–2.0\times10^9$/l and/or platelets $25–100\times10^9$/l) was reached in the subsequent courses. This was done in order to counterbalance possible differences in bioavailibility of oral etoposide. In case of WBC nadir $<1.0\times10^9$/l and/or platelet nadir $<25–100\times10^9$/l a 25% dose reduction of oral etoposide was carried out in the next and subsequent courses. Courses were postponed 1 week if WBC $<3.0\times10^9$/l and/or platelets $<100\times10^9$/l on day 1 of the next course. If after 2 weeks of delay WBC and/or platelets had not recovered, patients went off treatment. In case of severe mucositis (WHO grade $\geqslant 3$) the dose of 5-FU was reduced by 25%. In case of severe neurotoxicity (WHO grade $\geqslant 3$) or renal insufficiency (WHO grade $\geqslant 2$) treatment was stopped permanently. Routine anti-emetic support consisted of 10 mg dexamethasone before and after administration of cisplatin, in combination with ondansetrone 8 mg twice daily. Courses were repeated every 4 weeks until progression, or up to a maximum of 6 courses.

Response evaluation was done according to standard WHO criteria.[14] Time to progression and survival were calculated from the first day of treatment. Patients were evaluated for response after two courses of chemotherapy or earlier if treatment was stopped due to severe toxicity. Response evaluation was performed after every second course. If progression of disease was evident after one course, the patients were classified as having early progressive disease. Toxicity was graded according to standard WHO criteria.[13]

Results

Sixty-nine patients entered the study. Patient characteristics are listed in Table 1. All patients were evaluable for toxicity; one patient was not evaluable for response because he refused further treatment after one course of treatment.

A total of 291 courses were given (median 4, range 1–6). Four patients discontinued treatment because of toxicity; three because of an episode of neutropenic fever and one because of neurotoxicity grade 3 after the fifth course. Fifteen cycles (7%) had to be postponed; four cycles because of leukocytopenia, 11 because of non-resolved non-hematological toxicity. The oral dose of etoposide had to be reduced in 20 patients; in five patients because of a WBC nadir $<1.0\times10^9$/l, in 14 patients because of a platelet nadir $<25\times10^9$/l, and in one patient because of both leukocytopenia and thrombocytopenia. The dose of 5-FU was reduced in 23 patients because of mucositis.

The hematological toxicity consisted of leukocytopenia WHO grade 3 in 17% and grade 4 in 16% of

Table 1. Patient characteristics

Characteristic	No. of patients
Male	53
Female	16
Age (years)	
median	55
range	28–71
WHO performance status (*n*=65)	
0	15
1	35
2	15
Weight loss (%)	
median	9
range	0–35
Extent of disease	
locally advanced	13
metastatic disease	56
lymph nodes	
supraclavicular	28
mediastinal	8
celiac	22
lung	13
liver	13
other	6
Prior treatment	
radiotherapy	4
surgical resection	7
endoprothesis	4

patients. Fourteen episodes of leukocytopenic fever occurred in 13 patients. Ten patients developed leukocytopenic fever after the first course, the other four episodes were seen after the second and fourth course of chemotherapy. All patients with leukocytopenic fever had also grade 3 or 4 mucositis except for one patient who had a pneumonia. All patients were admitted and recovered after treatment with antibiotics. There were no toxic deaths. Seven patients developed infections without leukocytopenia. Two of these patients were admitted: one patient with mediastinitis after dilatation of his esophageal tumor and one patient with pneumonia. Both patients recovered. Thrombocytopenia grade 3 and 4 was seen in 13 and 7% of patients, respectively. Four patients received platelet transfusions. Blood transfusions were administered to 18 patients.

The most important non-hematological toxicities are listed in Table 2. Grade 3 nausea and vomiting occurred in 32% of the patients. Most patients experienced this toxicity during the last 2 days of each cycle. Four patients had grade 3 diarrhea, all four after the first course of treatment. Grade 3 mucositis was seen in 22% of the patients and one patient had to be admitted because of a grade 4 mucositis. Despite dose reductions of 5-FU/folinic acid and prophylactic measurements, grade 2 or 3 mucositis re-occurred in 12 patients after the second course and in eight patients in the next courses. Neuropathy grade 1 or 2 was seen in 20 patients and one patient developed a grade 3 neuropathy. Three patients experienced grade 2 hearing toxicity; two of these patients had tinnitus. Nephrotoxocity grade 1 was observed in one patient. Alopecia was common. Three patients experienced retrosternal pain while they were at home. Two of these three patients had a previous history of cardiac disease. The third patient had an endoprothesis in the esophagus. No EKG abnormalities or enzymatic changes were observed.

Table 2. Non-hematological toxicity, worst grade per patient

Toxicity	Maximum WHO grade in % of all patients				
	0	1	2	3	4
Nausea/vomiting	23	16	29	32	0
Diarrhea	67	19	9	6	0
Mucositis	28	20	29	22	1

The overall response rate in the 68 evaluable patients was 34% [95% confidence interval (CI) 22–46%], including three complete responses (CR, 4%) and 20 partial responses (PR, 30%). Twenty-six patients had stable disease (SD, 38%) and 19 patients progressive disease (PD, 28%). The duration of CR was 8 months in a patient with lung and lymph node metastases who received no further treatment. One patient with an initially irresectable tumor and one patient with supraclavicular lymph node metastasis who had a clinical complete response after chemotherapy were referred for surgery; no viable tumor was found after surgical resection of the esophagus, and both patients are still disease free after 53 and 76 months. The median response duration of the 18 patients with PRs was 9 months (range 3–16 months). Ten patients who had a PR or CR after chemotherapy and either locally advanced disease or lymph node metastasis confined to the supraclavicular or celiac region received additional treatment. Three patients were treated with radiotherapy at a dose of 50–54 Gy on the esophagus and supraclavicular or celiac regions. Seven patients underwent a radical transhiatal esophageal resection. The median time to progression in patients who received additional treatment was 15 months (range 8–76 months).

All patients, with the exception of the two patients who had pT0 resections after chemotherapy, have died. The median survival time for all patients was 9.5 months (range 2–76+ months) and the 1-year survival rate was 36%. The median survival for responding

patients was 17 months (range 7–76+ months), compared to a median survival of 6 months (range 2–18 months) in non-responding patients. The median survival of the 10 patients who received additional treatment (surgery or radiotherapy) was 36 months (range 11–76+ months).

Discussion

Patients with esophageal cancer frequently present with, or develop, metastatic disease later in the course of their disease. Intubation, external beam radiotherapy, endo-esophageal intraluminal brachytherapy and endoscopic laser therapy or combinations of these modalities are most frequently used for symptomatic palliation.[15–17] Despite effective palliation of dysphagia, quality of life rapidly deteriorates as a result of pain, fatigue, appetite loss and constipation,[18,19] and median survival after palliative treatment is 3–6 months.

In the current study we investigated the efficacy and toxicity of the combination 5-FU and folinic acid added to a chemotherapy schedule of cisplatin and etoposide previously used by us. The observed hematological toxicity consisted of leukocytopenia grade 3 or 4 in 33% and thrombocytopenia grade 4 in 7% of patients. Febrile leukocytopenia occurred in 19% of patients and all but one patient had also a concurrent mucositis. Compared to our previous study with cisplatin and etoposide,[11] the rate of myelosuppression was not increased; however, the incidence of leukocytopenic fever increased most probably as a result of the concurrent mucositis caused by the addition of 5-FU and folinic acid.

In this study, we observed an overall response rate of 34% in 68 evaluable patients, a median survival of 9.5 months and a 1-year survival rate of 36%. In our study with cisplatin and etoposide, the overall response rate was 48% and the median survival 8.5 months, and 26% of patients survived for more than 1 year.

The combination of cisplatin, etoposide, 5-FU and folinic acid has also been studied by Stahl *et al*. as part of a multimodality treatment program which also comprised chemoradiotherapy and/or surgery.[20,21] In two phase II studies, these investigators treated 110 patients, mostly with locally advanced esophageal cancer, with three or four cycles of cisplatin 30 mg/m^2, etoposide 100 mg/m^2, 5-FU 500 mg/m^2 and folinic acid 300 mg/m^2 each administered on days 1, 2 and 3. Grade 3 or 4 leukocytopenia and thrombocytopenia was observed in, respectively, 52 and 51%, and leukocytopenic fever in 29% of patients. Surprisingly, mucositis and diarrhea grade 3 or 4 was reported in less than 10% of the patients. The overall response rate in both studies was almost 50%. Preoperative treatment with cisplatin 20 mg/m^2 days 1–5, 5-FU 900 mg/m^2 days 1–5, and etoposide 90 mg/m^2 days 1, 3 and 5 without folinic acid in patients with resectable adenocarcinoma of the esophagus resulted in a response rate of 49%.[22] Because of the combined modality approach the median survivals of these latter studies cannot be compared with the median survival obtained in our study.

Eight patients with celiac or supraclavicular lymph node metastases and two patients with locally unresectable disease were additionally treated with radiotherapy or surgery and had a 3-year survival rate of 50%. It seems that patients with M1a disease who respond to chemotherapy and additionally are treated with radiotherapy or surgery may achieve a prolonged survival. Concurrent chemotherapy and radiotherapy in patients with T4 or M1a disease resulted in a 3-year survival of 23% in one study but at the cost of significant toxicity.[23]

Future improvement in the systemic treatment of esophageal cancer may come from the incorporation of new drugs such as the taxanes and irinotecan. In a number of studies it has been demonstrated that these agents can be combined with cisplatin with relatively mild toxicity and that high response rates up to 50% may be achieved.[24–26] Mucositis is usually a less prominent side effect of these new drug combinations compared to 5-FU-based combinations.

In conclusion, the combination of cisplatin, etoposide, 5-FU and folinic acid is a safe and active regimen in the treatment of advanced squamous cell carcinoma of the esophagus. Mucositis is the most prevalent toxicity of this regimen. A select group of patients with M1a disease who responded to treatment and additionally were treated with radiotherapy or surgery had a 3-year survival of 50%.

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