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Original Paper

Randomised Phase II Study of Cisplatin and 5-Fluorouracil (5-FU) Versus Cisplatin Alone in Advanced Squamous Cell Oesophageal Cancer

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Patients with measurable or evaluable locally advanced or metastatic squamous cell carcinoma of the oesophagus were treated with cisplatin (CDDP), 100 mg/m^2, combined with 5-fluorouracil (5-FU) at a dose of 1000 mg/m^2 as a continuous infusion from days 1–5 (Arm A) or with CDDP alone (Arm B). Cycles were repeated every 3 weeks. 92 patients were randomised centrally, 88 were eligible. The response rate was 35% (95% CI (confidence interval), 20–54%) in Arm A and 19% (95% CI, 8–35%) in Arm B. One complete response was observed in each arm. The median duration of survival was 33 weeks and 28 weeks for Arm A and Arm B, respectively. Haematological and non-haematological toxicities were more frequent and more severe in Arm A. The most prominent toxicities were grade 4 aplasia and septicaemia (2), meningeal haemorrhage (1), cerebrovascular accident (3) and ischaemia of the lower limbs (1) all occurring in Arm A. Overall, seven treatment-related deaths (16%) were observed in Arm A, none in Arm B. The severe side-effects induced by the combination suggest that, currently, no standard chemotherapy can be recommended for patients with advanced squamous cell oesophageal cancer. © **1997 Published by Elsevier Science Ltd.**

Key words: cancer, oesophageal, squamous cell carcinoma, 5-FU, cisplatin, chemotherapy, advanced, toxicity

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INTRODUCTION

CHEMOTHERAPY HAS not been extensively investigated in advanced, disseminated squamous cell cancer of the oesophagus. This can be explained by the fact that the main objective in treating advanced oesophageal cancer is to obtain relief of mechanical obstruction and restore the swallowing function. Once this major problem is resolved, the poor general status of disseminated patients makes further treatment rather difficult.

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Chemotherapy has been mainly investigated as a pre-operative modality, often in combination with radiotherapy, in patients with localised disease. Using cisplatin (CDDP) and 5-fluorouracil (5-FU), response rates range from 42 to 72% with 12–44% of complete responses [1]. The role of chemotherapy, at that stage, has been resolved in two studies showing that pre-operative chemotherapy alone is as effective as radiotherapy with an overall response rate of 55% and a complete response rate of 8% [2], and that the combination of chemo–radiotherapy is superior to radiotherapy alone [3].

In advanced disease, CDDP-containing combinations gave an objective response rate of 25–33% but with low complete remission rate, short duration of response and

severe toxicity. Because comparable response rates could be obtained with CDDP alone with much less toxicity, it was suggested that CDDP alone could offer better palliation than in combination with 5-FU [4].

In order to have a better understanding of that question, the Gastro Intestinal Tract Cancer Cooperative Group (GITCCG) of the European Organization of Research and Treatment of Cancer (EORTC) launched a study evaluating the efficacy and toxicity of CDDP alone and of CDDP with 5-FU in patients with advanced oesophageal cancer.

PATIENTS AND METHODS

Patients

Patients had to have measurable or evaluable histologically proven squamous cell carcinoma of the oesophagus. Eligibility criteria included the following: age under 70 years, no prior chemotherapy, performance status <3 (Zubrod–ECOG scale), life expectancy more than 12 weeks, normal liver, renal and haematological functions (BUN <25 mg/dl, creatinine <1.5 mg/dl, bilirubin <1.1 mg/dl, WBC $>4 \times 10^9$/l, haematocrit >30%, platelet count $>100 \times 10^9$/l) and no other major organ dysfunction. Exclusion criteria included: no target lesion outside an irradiated area, brain or leptomeningeal involvement, uncontrolled infection, presence of tracheal involvement. All patients who entered the study gave oral or written informed consent according to the policies followed by the national legislation.

Initial evaluation and follow-up examination

Initial evaluation included history of the disease and physical examination. Biological and radiological evaluations included complete blood cell count, serum electrolytes, chest radiograph, barium oesophagogram, fibre-oesophagoscopy and biopsy, tracheobronchoscopy for cancer of the upper third, liver ultrasound and/or CT (computer tomography) scan of the abdomen and chest (if indicated). Physical examination, chest radiograph, complete blood cell count, serum urea and creatinine were performed before every course.

Tumour measurement

Measurable and evaluable disease were defined as any malignant disease measured in two perpendicular or one diameter, respectively, by ruler, caliper, X-rays, ultrasound or CT scan. CT scan was recommended for the measurement of liver metastases, abdominal masses and the primary tumour, but for the liver, ultrasound was also accepted if the measurement was standardised [5].

Tumour response was defined according to widely accepted standards [6]. For the primary site, the following criteria were used: complete radiological or endoscopic response if no tumour seen on repeated examinations; partial radiological or endoscopic response if more than 50% reduction in tumour bulk but residual disease still evident. A complete response required negative histology, otherwise it was considered as a partial response [7]. Stable disease was defined as no objective change or a decrease of less than 50%, no increase of more than 25% of the two greatest diameters of measurable lesions. Progressive disease was defined as any evidence of progression of more than 25% or appearance of new lesions. All radiological records of responding patients were submitted to an extramural reviewer for the final assessment of antitumour efficacy.

Supportive treatment

All supportive means consistent with optimal patient care were given throughout the study. Local radiation therapy to a field as small as possible was allowed when needed for palliation. Those patients were not considered evaluable for that target site. Parenteral nutrition, gastrostomy or an oesophageal prosthesis could be used.

Chemotherapy

Patients were randomised to CDDP/5-FU (Arm A) or CDDP alone (Arm B). Cycles were repeated every 3 weeks. In Arm A, CDDP was administered at a dose of 100 mg/m^2 in 250 ml of 0.9% sodium chloride given as an i.v. (intravenous) drip over 1 h with pre- and posthydration and mannitol-induced diuresis. Metoclopramide was given as an anti-emetic at the dose of 2 mg/kg every 2 h, 3 times. 5-FU, diluted in 2 l of 5% dextrose, was administered after CDDP at a dose of 1 g/m^2 as a continuous 24 h i.v. infusion from days 1–5. In Arm B, CDDP alone was given as in Arm A.

Dose modifications were made according to the nadir count obtained during the previous cycle. The CDDP dose was reduced by 25% and 5-FU by 50% in case of WBC nadir $<1 \times 10^9$/l and/or platelet nadir $<5 \times 10^9$/l. CDDP was stopped if serum creatinine >3 mg/dl or creatinine clearance < 40 ml/min. CDDP dose was reduced by 50% if serum creatinine was >1.5 mg/dl but <3 mg/dl or creatinine clearance >40 ml/min but <6 ml/min. In case of stomatitis or diarrhoea of grade >2, the 5-FU dose was reduced by 50%. Treatment was delayed until haematological and renal recovery was obtained. If after 3 weeks the patient had not recovered, the patient was withdrawn from the study.

Statistical considerations

Randomisation was centralised at the EORTC Data Centre. During randomisation, patients were stratified by their institution. The randomisation was performed using the minimisation technique [8]. The trial was designed as a phase II trial and the number of required patients was calculated using ECOG's two-stage design with 20 patients in each arm in the first step, then adding 5 patients per response with a maximum total of 40 patients in each arm. This design ensures that if either of the two treatments was active (with response rate >20%), the probability of stopping the trial after the first stage was as low as 0.01, and if either of the two treatments was inactive (response rate <5%), the probability of continuing the second stage of the trial was at most 0.01. Survival curves were estimated using the Kaplan–Meier technique [9]. Response rate was based on eligible patients with a measurable disease.

RESULTS

Between September 1985 and April 1989, 92 patients were randomised at the EORTC Data Centre. Three patients were ineligible. One had hypercalcaemia, 1 had no histology and 1 had an adenocarcinoma. Another patient who did not start the treatment due to a mediastinal fistula was excluded from the study. The total number of patients in the study was, therefore, 88. Three patients aged between 70 and 72 years of age were nevertheless considered eligible. After extramural review of measurability, 10 patients in Arm

Table 1. Patient characteristics

	CDDP/5-FU $n = 44$	CDDP $n = 44$
Median age (range)	58 (36–72)	58 (41–72)
Sex		
male	42	42
female	2	2
WHO performance status		
0	4	6
1	28	24
2	11	14
Unknown	1	0
Weight loss (%)		
None	7	8
≤10	20	20
>10	17	15
Unknown	0	1
Prior surgery	5	8
Prior radiotherapy	4	6
Prior chemotherapy	0	0
Tumour measurability		
Measurable	34	37
Evaluable	7	5
Not measurable	1	0
Unknown	2	2

A and 7 in Arm B had non-measurable tumour. They were maintained in the study for evaluation of toxicity.

There were 84 men and 4 women. The median age was 58 years (range 36–72). Almost all the patients had a performance status ≤2, although 35% had a weight loss of more than 10%. Only 13 patients had previous surgery (11 curative, 2 palliative) and 10 previous radiotherapy, for 6 of the 10 as an adjuvant modality after curative surgery. None had received prior chemotherapy (Table 1).

The median number of cycles was 4 in Arm A (range 1–8) and 3 in Arm B (range 1–11). The median total dose of CDDP was 650 mg (range 130–1260) and 530 mg (range 100–1857) for Arm A and Arm B, respectively. 17 patients (39%) and 8 patients (18%) had at least one delayed course and the delay was considered to be drug-related in 9 and 3 patients in Arm A and Arm B, respectively.

In Arm A, 14% white blood cells and 14% platelets grade 3–4 toxicity was observed. Patients in Arm B did not have any grade 3–4 haematological toxicity. The median nadir of WBC was 3.9×10^9/l (range 0.3–20.0) and that of platelets was 154×10^9/l (range 16–520) in Arm A and 4.4 10^9/l (range 2.3–11.1) and 219×10^9/l (range 66–660), respectively, in Arm B. These nadir values are the lowest at any time point during therapy. Two patients with febrile neutropenia died from septicaemia. All had received 5-FU/CDDP.

Non-haematological toxicities are given in Table 2. Grade 3 nausea/vomiting occurred in 17 patients (12 of Arm A and 5 of Arm B), grade 3 diarrhoea in 1, grade 3 mucositis in 2 and grade 2 renal toxicity in 1, all in Arm A. No patients had grade 4 non-haematological toxicities. Patients treated with the combination had more severe diarrhoea and mucositis than patients receiving CDDP alone. Neurological toxicity did not exceed grade 2 and consisted of hypoacousia (2) and somnolence (1) all occurring in the CDDP alone arm. In Arm A, with the 5-FU/CDDP treatment, we observed 4 cases of vascular toxicity (9%) consisting of 3 cases of major cerebrovascular events and 1 case of acute thrombosis of the lower limbs leading to death.

Table 2. WHO grade 3–4 toxicities

	5-FU/CDDP $n = 44$		CDDP $n = 44$	
	n	%	*n*	%
Haematological				
White blood cells	6	(14)	0	(0)
Platelets	6	(14)	0	(0)
Non-haematological				
Nausea/vomiting	12	(27)	5	(11)
Diarrhoea	1	(2)	0	(0)
Mucositis	2	(4)	0	(0)
Vascular thrombosis	4	(9)	0	(0)

The reasons for treatment discontinuation are listed in Table 3. For most of the patients, treatment discontinuation was related to progression of the disease or treatment toxicity. The major toxicities that led to treatment discontinuation were grade 4 aplasia and septicaemia (2) or meningeal haemorrhage (1), renal insufficiency (2), cerebrovascular accident (3) and ischaemia of the lower limbs (1) in Arm A; ototoxicity (2) and renal insufficiency (1) in Arm B.

The 2 patients with septicaemia and the one with meningeal haemorrhage died. The 3 cases of death with cerebrovascular symptoms during the first treatment cycle in Arm A were all attributed to the treatment: 1 patient fell into deep coma on day 8 without any other clinical symptoms, 2 had cerebrovascular thrombosis and died after 3 and 5 days. The patient who had an acute ischaemia of the lower limbs died after two cycles. Although occurring only in 1 patient, this event was attributed to 5-FU/CDDP.

8 patients in Arm A and 9 in Arm B stopped their treatment for various reasons including surgery (2), intercurrent radiotherapy (6) or choice of another chemotherapy (1), complete remission (2) and arbitrary stop after 6 cycles (4).

Table 3. Reason for treatment discontinuation

	CDDP/5-FU ($n = 44$)		CDDP ($n = 44$)	
	n	%	*n*	%
Death not due to malignant disease nor toxicity*	3	(7)	0	(0)
Death due to vascular events†	4	(9)	0	(0)
Patient refusal	4	(9)	4	(9)
Excessive toxicity‡ of treatment	5	(11)	3	(7)
Progressive disease (including death due to malignant disease)	19	(43)	27	(61)
Major protocol violation	1	(2)	1	(2)
Other§	8	(18)	9	(20)

*Pneumonia 1, septicaemia 1, unspecified infection 1; †Cerebrovascular accident 3, ischaemia of lower limbs 1; ‡Arm A: septicaemia 2, meningeal haemorrhage 1, nephrotoxicity 2; Arm B: hypoacousia 2, nephrotoxicity 1; §Arm A: surgery 2, radiotherapy 6; Arm B: other chemotherapy 1, complete response 2, arbitrary stop 4, undetermined 2.

Table 4. Response to treatment in patients with measurable disease

	CDDP/5-FU (n = 34)		CDDP (n = 37)	
	n	%	n	%
Complete response	1	(3)	1	(3)
Partial response	11	(32)	6	(16)
Stable disease	10	(29)	14	(38)
Disease progression	6	(18)	16	(43)
Early death	5	(15)	0	(0)
Not assessable	1	(3)	0	(0)

In 2 cases the reason for stopping treatment could not be determined.

Among the patients with measurable disease, 19 patients responded to treatment: 12 in Arm A (35%, 95% CI, 20–54%) with 11 partial and 1 complete response and 7 in Arm B (19%, 95% CI, 8–35%) with 6 partial and 1 complete responses (Table 4). 10 patients had stable disease in Arm A and 14 in Arm B. 6 patients progressed while under 5-FU/CDDP and 16 under CDDP alone. The median duration of response was 40 weeks (range 18–182) in Arm A and 26 weeks (15–87) in Arm B (Figure 1). The median time to progression based on all eligible patients was 27 weeks in Arm A and 18 weeks in Arm B (Figure 2).

The median duration of survival was 33 weeks and 28 weeks for Arms A and B, respectively. The 1-year survival was 34% (95% CI, 20–48%) and 27% (95% CI, 14–40%), the 2-year survival was 18% (95% CI, 7–29%) and 9% (95% CI, 1–17%) for Arms A and B, respectively (Figure 3).

DISCUSSION

The role of chemotherapy has been poorly investigated in patients with advanced oesophageal cancer. A recent review of the literature emphasises the poor quality of trials mainly due to the small number of patients included, the mix of treated and untreated patients, the mix of adenocarcinoma and epidermoid cancer, the lack of standardised treatment schedule and response criteria [10]. The high response rate of 42–72% obtained with two cycles of the combination of 5-FU/CDDP and radiation therapy in locally advanced patients [1] probably does not predict what will be obtained using chemotherapy alone in patients with advanced disease. The poor general status of these patients might preclude the administration of any treatment with a high toxic potential, in particular if more chemotherapy cycles are required to obtain a substantial decrease of the tumour bulk. Although combination chemotherapies seem superior to single agents, the gain in response might be counterbalanced by a decreased tolerability and/or an increased toxicity. Therefore, even now, the benefit of chemotherapy in patients with disseminated disease is far from being proven.

This randomised phase II study ensured that the same population was investigated in both treatment arms. It did not allow any statistical comparison to be performed between the two arms, and response, survival and toxicity

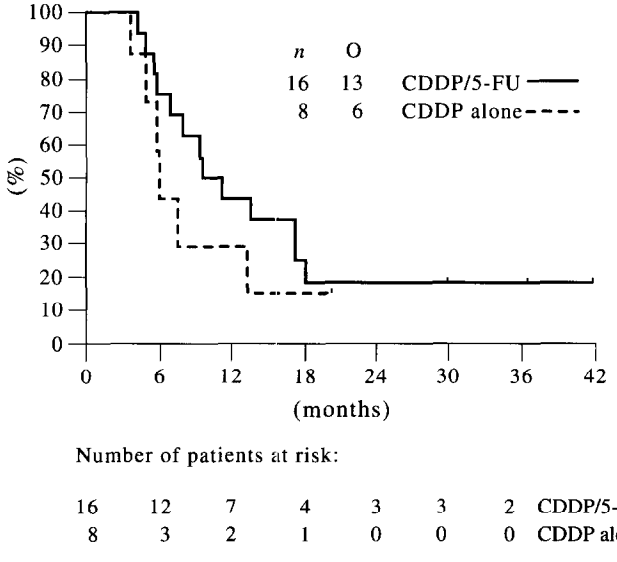

Figure 1. Duration of response.

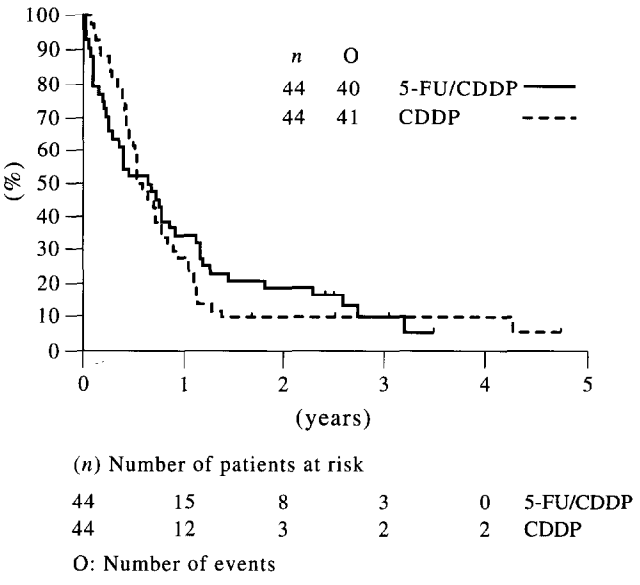

Figure 2. Time to progression.

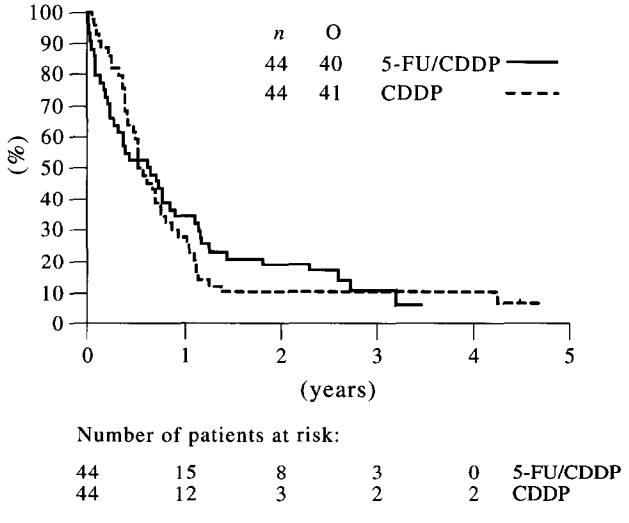

Figure 3. Overall survival.

data were not formally compared with the application of statistical tests.

The combination 5-FU/CDDP had a higher response rate than CDDP alone (35% versus 18%) and fewer patients had progressive disease (6 versus 16). This level of activity is comparable to that of a subgroup of metastatic patients treated with a combination of folinic acid, 5-FU, etoposide and CDDP (FLEP) [11] and is also comparable in terms of response rate to the 25% obtained in 12 patients with epidermoid cancer of the oesophagus treated with paclitaxel alone [12] and the 44% obtained in patients treated with a combination of paclitaxel, CDDP and 5-FU for epidermoid and adenocarcinoma of the oesophagus [13].

However, toxicity was more severe in the 5-FU/CDDP arm. Overall, seven treatment-related deaths (16%) were observed in the 5-FU/CDDP arm, none in the CDDP alone arm. Grade 3–4 toxicities were observed mainly with the combination, almost never with CDDP alone (Table 2). This could partly be explained by the intensive 3-week schedule we used. Indeed, the same combination given every 4 weeks is now commonly used in the pre-operative setting with substantially less toxicity.

Cerebrovascular accidents were clearly related to the administration of 5-FU/CDDP. It could not be predicted from the clinical status of the patients before chemotherapy nor from a previous history of cardiac or cerebrovascular event. Similar events have been described with 5-FU/CDDP-based regimens [14, 15]. Because 5-FU has been involved in cardiac arrests, which did not occur in our series and no similar toxicity was ever described with CDDP alone, it may be speculated that it is the combination of both drugs which is responsible for the increased incidence of cerebrovascular events. The hypothesis of a hypocoagulabillity status induced by chemotherapy has been suggested in patients with breast cancer [16]. Moreover, chemotherapy can lead to an increase in thrombin-like activity [17] and fibrinopeptide A [18] in plasma. This hypercoagulability status would also explain the acute ischaemic event of the lower limbs that was observed.

Weight loss before treatment appeared to be a major prognostic factor with a particularly poor survival for patients who lost more than 10% of their weight [19]. Only 17% of our patients had no weight loss and 36% had lost more than 10% of their weight. In that regard, our patients could have been a particularly poor prognosis group, and therefore had more severe toxicity and shorter survival. However, if this was the case, similar toxicities should have been observed in the CDDP alone arm. The randomised phase II design allows the real toxicity of the treatment to be observed, while excluding an effect of patient selection.

Chemotherapy, in the setting of patients with disseminated disease, does not appear to be of any benefit. Despite a higher response rate observed in the 5-FU/CDDP arm, it does not translate to any survival advantage. This might be related to the higher incidence of severe toxicity and treatment-related deaths observed in the 5-FU/CDDP arm. CDDP alone was well tolerated, had minimal toxicity but had only limited activity.

The present study demonstrates that the combination of 5-FU/CDDP is probably more active than single-agent CDDP. However, the severe side-effects induced by the combination suggest that, currently, no standard treatment can be recommended and that chemotherapy should not be given to patients with advanced squamous cell oesophageal cancer outside of prospective studies.

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