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Optimisation of 5-fluorouracil (5-FU)/cisplatin combination chemotherapy with a new schedule of hydroxyurea, leucovorin, 5-FU and cisplatin (HLFP regimen) for metastatic oesophageal cancer

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Abstract

To improve the efficacy and tolerance of the 5-fluorouracil (5-FU)/cisplatin combination in metastatic esophageal cancer, we designed a new therapeutic schedule, the HLFP regimen. 42 patients with metastatic oesophageal adenocarcinoma ($n=10$) or squamous cell carcinoma ($n=32$) were prospectively enrolled in the study. All had bidimensionally measurable disease. The HLFP regimen consisted of twice-monthly oral administration of hydroxyurea 1 g/m^2 on days 0, 1 and 2; a 2-h infusion of leucovorin 200 mg/m^2 and a bolus of 5-FU 400 mg/m^2 followed by a 22-h infusion of 5-FU 600 mg/m^2 on days 1 and 2; and, every two cycles, 80 mg/m^2 cisplatin on day 3. Relief of dysphagia and other symptoms were monitored, together with body weight changes. Major objective responses were observed in 24 patients (57%, 95% Confidence Interval (CI): 42–72%), including four complete responses (10%). The median progression-free survival and overall survival times were 8 and 12.7 months, respectively. Weight gain was observed in 48% of patients, and dysphagia improved in 76%. Grade 3-4 toxicity occurred in 40% of patients, with grade 4 neutropenia in 12% and grade 3 thrombocytopenia, vomiting and diarrhoea in 7–9% of patients. There were no treatment-related deaths. These results suggest that the HLFP regimen is an active and well-tolerated chemotherapy for metastatic oesophageal carcinoma. © 2002 Published by Elsevier Science Ltd.

Keywords: Metastatic Oesophageal carcinoma; Chemotherapy; Hydroxyurea; 5-Fluorouracil; Cisplatin

1. Introduction

There are more than 12 000 new cases of oesophageal cancer per year in the United States and more than 4500 in France. Long-term treatment results are disappointing, with 5-year survival rates of only 5–10%. Surgery alone is a standard of care for stage I, stage II or even stage III oesophageal carcinoma, but around 70% of patients are ineligible for this treatment. Moreover, even when surgery is feasible, the 5-year survival rate is still only approximately 20%. New multimodality therapeutic strategies are thus needed to improve long-term survival in this setting [1–3]. At least 40% of patients have metastases at initial presentation, and most patients with localised disease will develop metastases despite potentially curative local therapy [4,5]. Numerous single-agent chemotherapy regimens are active in this setting, including cisplatin, 5-fluorouracil (5-FU) and mitomycin. The 5-FU/cisplatin combination is a standard for both squamous cell carcinoma and adenocarcinoma of the oesophagus, with response rates of approximately 30% in metastatic disease [4,6]. Grade 3-4 toxicity occurs in between 46 and 70% of patients with the standard 5-days-a-month schedule, and treatment-related deaths have been reported [7,8]. To improve efficacy and toxicity, we designed a new regimen

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based on improved dosage and biomodulation. The HLFP regimen, combining hydroxyurea, LV5-FU2 (leucovorin, bolus and continuous infusions of 5-FU, 2 consecutive days every 2 weeks) and cisplatin, was developed at our institution on the basis of the following observations. The LV5-FU2 regimen, which has a better therapeutic ratio than the North Central Cancer Treatment Group (NCCTG)-Mayo Clinic regimen in advanced colorectal cancer [9], is also active in gastric cancer [10]; 5-FU and hydroxyurea are synergistic [11,12]; and hydroxyurea enhances cisplatin cytotoxicity by inhibiting repair of cisplatin-induced DNA damage [13]. In addition, the synergy between 5-FU and cisplatin is well described and may be optimal when cisplatin is administered after 5-FU [14]. Finally, the HLFP regimen has proven active and well tolerated in advanced gastric and pancreatic carcinomas [15,16].

2. Patients and methods

2.1. Eligibility criteria

Eligibility criteria were as follows: pathologically-proven oesophageal carcinoma (adenocarcinoma or squamous cell carcinoma), first-line treatment for metastatic disease, World Health Organization (WHO) performance status 0, 1 or 2, life expectancy more than two months, age between 18 and 75 years, no previous malignancies, no central nervous system metastasis, initial evaluation less than 2 weeks before therapy, normal renal function, neutrophil count $>1.5\times10^9$ cells/l and platelet count $>100\times10^9$ cells/l. Written informed consent was required from all the patients. The HLFP regimen has been approved by the institutional research ethics committee for gastric cancer [15] an extension was obtained for oesophageal cancer to perform this study. Between January 1994 and June 1998, all patients with metastatic oesophageal cancer referred to our institution for medical treatment were prospectively considered for this study.

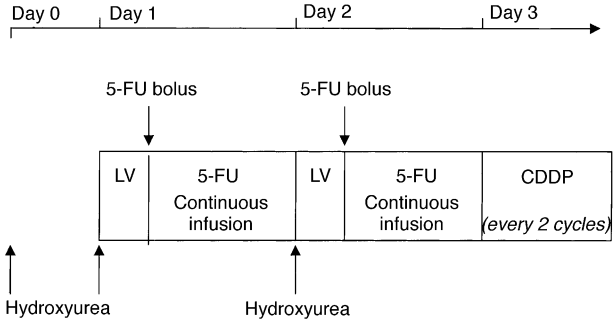

Fig. 1. The HLFP regimen. 5-FU, 5-fluorouracil; LV, leucovorin; CDDP, cisplatin.

Pretreatment evaluation included a physical examination, upper gastrointestinal endoscopy or endoscopic ultrasound when required, thoracic and abdominal computed tomography, and tumour marker assays (carcinoembryonic antigen (CEA) and squamous cell carcinoma (SCC)).

2.2. Treatment schedule

The HLFP regimen consisted of oral hydroxyurea 1 g/m^2 on days 0, 1 and 2; a 2-h infusion of leucovorin 200 mg/m^2 and a bolus of 5-FU 400 mg/m^2 followed by a 22-h infusion of 5-FU 600 mg/m^2 on days 1 and 2, as previously described in Ref. [7]; and, every two treatment cycles, a 30-min infusion of cisplatin 80 mg/m^2 on day 3, preceded and followed by hydration (Fig. 1). Treatment was repeated every 2 weeks if the neutrophil count was above 1.5×10^9 cells/l and the platelet count above 100×10^9 cells/l; the serum creatinine had to be below 120 μmol/l when cisplatin was used. Patients who responded or had stable disease received the full treatment for at least 12 cycles. Cisplatin administration during subsequent courses depended on the patient's condition. The 5-FU boluses on days 1 and 2 were reduced by 25% if grade 4 haematological toxicity occurred. Treatment was discontinued in case of progression, repeated grade 3-4 toxicity, or patient refusal. Second-line chemotherapy was permitted if the investigator considered it warranted.

2.3. Assessment of responses and clinical benefit

Bone metastases and pleural/peritoneal effusion were not considered as evaluable metastatic sites, but were taken into account when assessing progression. The response to treatment was evaluated every six cycles by Computed Tomography (CT) scan, or earlier if there were clinical signs of progression. WHO criteria [18] were used to define responses and their duration: a complete response (CR) was defined as a complete disappearance of all assessable disease; a partial response (PR) was defined as a decrease of at least 50% in the sum of the products of the two largest perpendicular diameters of measurable lesions lasting at least 4 weeks; stable disease (SD) was defined as a decrease of less than 50% or an increase of less than 25% in tumour size; progressive disease (PD) was defined as a greater than 25% increase in the sum of the products of two perpendicular diameters of at least one tumour, or the appearance of a new lesion. Major objective responses were confirmed by a second evaluation 4–8 weeks later. Body weight, performance status and clinical manifestations such as appetite loss, dyspnoea, ascites and pain were recorded initially and before each cycle. Dysphagia was assessed every month by the patient himself, using the Mellow and Pinkas modified score [17], in which a score of 0 denotes the ability to eat a normal diet; 1 the

ability to eat some solid food; 2 the ability to eat semi-solids only; 3 the ability to swallow liquids only; and 4 complete dysphagia.

2.4. Toxicity evaluation

Toxicity was recorded according to the National Cancer Institute (NCI) criteria. Physical examination, a full blood count and serum creatinine assay were performed before each cycle (every 2 weeks), by the physician in charge of the patient. Patients were questioned specifically about nausea and vomiting, mucositis, diarrhoea, malaise, appetite and ototoxicity. All patients who had received at least one course of chemotherapy were considered as evaluable for toxicity.

2.5. Statistical analysis

The end-point of this phase II trial was the overall response to the HLFP regimen. The maximum response rate considered of low interest, on the basis of the experience reported in the literature was 20%. The minimum response rate considered of interest, because of the demanding design of the regimen was 40%. The sample size was calculated with a type I error of 5% and a test power of 80%. The target enrollment was estimated to be 42 patients. Results are expressed as means ±standard deviation or range, as appropriate. The prognostic analysis was performed with the SAS 6.11 software (SAS Institute), using the Cox proportional hazards model. Prognostic factors for response and for survival were investigated. Follow-up started from the outset of treatment. The censoring event for response was the start of disease progression. The censoring event for survival was the date of death. Univariate analysis was performed first, and a multivariate model was then fitted using the covariates associated with endpoints with P values <0.10 in the univariate analysis. Survival curves were plotted with Splus 4.5 software, using the Kaplan–Meier method.

3. Results

Between January 1994 and June 1998, 93 patients with advanced oesophageal cancer were referred to our department for medical treatment. 12 patients had metastatic disease, but a poor performance status inconsistent with chemotherapy, 37 patients had locally advanced disease, and 2 had pleural effusion without bidimensionally measurable disease; the remaining 42 patients had evaluable metastatic disease and were prospectively included in the study. Their characteristics are summarised in Table 1. Median age was 61 years (39–75 years). Only 5 of the 42 patients were women. 32 patients had squamous cell carcinoma and 10 patients had adenocarcinoma. 8 patients (19%) had undergone attempted curative oesophagectomy at least 6 months before inclusion in this study. 2 of these 8 patients had received radio-chemotherapy (cisplatin alone) before surgery. All the patients were assessable for toxicity and for response (bidimensionally measurable disease).

Table 1
Baseline characteristics of the patients

Histology	Squamous cell carcinoma	Adenocarcinoma	Total
Number of patients	32	10	42
Median age (years) (range)	59 (39–74)	65 (57–75)	61 (±8.2) (39–75)
Male/female	28/4	9/1	37/5
Performance status (WHO)			
0	10	2	12
1	15	5	20
2	7	3	10
Tumour location			
Upper third	17	–	17
Middle third	8	0	8
Lower third	7	10	17
Site of metastases			
Liver	13	3	16
Lymph nodes	28	8	36
Lung	7	3	10
Other	4	4	8
Prior therapy			
0	26	9	35
Oesophagectomy (neoadjuvant radiotherapy/chemotherapy)	6 (2)	2 (–)	8 (2)
Patients with dysphagia (%)	84	70	81

WHO, World Health Organization.

3.1. Response to treatment

Responses to the protocol therapy are summarised in Table 2. The overall response rate was 57% (95% Confidence Interval (CI): 42–72%), with four CR (10%) and 20 PR (47%). SD was observed in 13 patients (31%) and PD in 5 patients (12%). The differences in the response rates between adenocarcinoma and squamous cell carcinoma were not significant. The median duration of response was 5.4 months (range 1–35 months). The four complete responders had metastatic lymph nodes with no visceral involvement. One of these patients developed a metachronous head and neck cancer 35 months later. Among the 20 patients with partial responses, the median duration of response was 5 months (range 1–14 months). In univariate analysis, only liver and lung metastases were predictive of the response to chemotherapy. Both were independent predictive factors of the response to chemotherapy in the multivariate analysis (hepatic metastasis: $n=16$; response rate: 55%, relative risk (RR): 2.48; CI: 1.0–6.1, $P=0.05$; lung metastasis: $n=10$; response rate: 80%, RR: 3.1; CI: 1.2–7.9, $P=0.02$). Age, sex, histology, tumour location, other visceral metastases, and toxicity were not associated with the response.

3.2. Clinical benefit

34 patients (81%) had dysphagia before treatment. None had previously received symptomatic therapy, and all were assessable for changes in dysphagia during therapy. 26 (76%) of these patients experienced a significant improvement or resolution of dysphagia during treatment. During follow-up, 5 patients (12%) underwent endoscopic dilation for recurrent dysphagia. Major weight gain (>10%) was observed in 9 patients (21%) during the treatment, and minor weight gain (5–10%) was observed in 11 patients (26%). The median time to symptom improvement was 6 weeks (range 3–10 weeks).

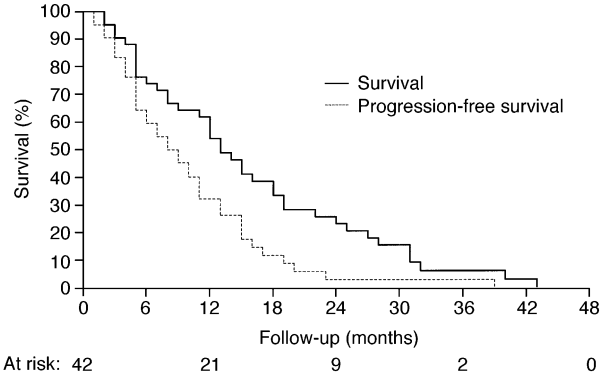

Fig. 2. Overall and progression-free survival.

3.3. Survival

The median overall follow-up was 53 months (range 10–85 months). The median progression-free survival time was 8 months (range 1–39 months) and the median overall survival time was 12.7 months (range 2–43 months) (Fig. 2). There was no difference in median survival between patients with squamous cell carcinoma and those with adenocarcinoma ($P=0.4$). Among the 4 patients who had a CR, the mean progression-free survival time was 21.2 months (range 8–39 months) and the overall survival time was 33.7 months (range 28–43 months). Univariate analysis selected four covariates for multivariate analysis, namely performance status ($P=0.08$), hepatic metastasis ($P=0.02$), 'other visceral metastasis' (excluding lung, liver and nodes) ($P=0.0008$), and the response to treatment ($P=0.04$). Multivariate analysis showed that 'other visceral metastasis' (excluding liver, lung and lymph nodes) (RR: 3.2; 95% CI: 1.3–8.1; $P=0.012$) was significantly associated with poor outcome. The response to treatment was a significant protective factor (RR = 0.5; 95% CI: 0.25–0.98; $P=0.04$). Age, sex, histology, tumour location and toxicity were not associated with survival.

11 patients received second-line chemotherapy, consisting of HLFP reintroduction after progression ($n=2$), HLFP without cisplatin ($n=2$), vinorelbine ($n=6$), or mitomycin-C ($n=1$). 3 patients received third-line chemotherapy with mitomycin-C. 6 patients were irradiated after the completion of chemotherapy (5 to local recurrences and 1 to the supraclavicular region).

3.4. Toxicity

A total of 419 cycles were administered, with a median of 10 cycles per patient (range 3–22 cycles). Toxicity

Table 2
Response to treatment

Response	All patients *n* (%)	Squamous cell carcinoma *n* (%)	Adenocarcinoma *n* (%)
Complete response (CR)	4 (10)	4 (13)	0 (0)
Partial response (PR)	20 (48)	17 (53)	3 (30)
Stable disease (SD)	13 (31)	9 (28)	4 (40)
Progression	5 (12)	2 (6)	3 (30)
Total	42 (100)	32 (100)	10 (100)

Table 3
Treatment-related toxicity per patient

Toxicity (WHO scale)	Grade 1 *n*	Grade 2 *n*	Grade 3 *n*	Grade 4 *n*	Grade 3-4 (%) *n*
Leucopenia	1	12	4	5	9 (21)
Thrombocytopenia	3	5	2	1	3 (7)
Anaemia	12	6	2	1	3 (7)
Alopecia	10	4	–	–	–
Diarrhoea	14	4	3	–	3 (7)
Nausea/vomiting	20	8	4	–	4 (10)
Stomatitis	12	3	–	–	–
Neurological	8	2	–	–	–
Hand–foot syndrome	2	–	–	–	–
Renal	2	–	–	–	–
Maximum/patient	12 (28)	14 (33)	11 (26)	6 (14)	17 (40)

WHO, World Health Organization.

data were available for all the patients (Table 3). No treatment-related deaths occurred. Grade 3/4 toxicity occurred in 17 patients (40%). Haematological toxicity was the most common toxicity, followed by gastrointestinal effects. Grade 3/4 neutropenia was observed in 9 patients (21%) but only 6 cases of febrile neutropenia warranting hospitalisation occurred (1.4% of courses); haematopoietic growth factors were not used because of the transient nature of the neutropenia. No bleeding events occurred in patients with thrombocytopenia. Gastrointestinal toxicity was mild to moderate and never necessitated hospitalisation. A 25% reduction in the 5-FU bolus was necessary in 13 patients (31%), who had no further severe toxicity.

4. Discussion

The prognosis of patients with metastatic oesophageal cancer remains extremely poor, with median survival not exceeding 6 months [1]. Although no randomised trials have been published comparing chemotherapy with best supportive care alone, chemotherapy seems to be the treatment of choice for metastatic disease. Combination chemotherapy can yield response rates of between 35 and 55% [4,6]. One of the most widely studied regimens is the monthly combination of 5-FU and cisplatin, with response rates of 25–33% in metastatic disease [6]. In a European randomised phase II study comparing high-dose 5-FU + cisplatin every 3 weeks with cisplatin alone in advanced squamous cell oesophageal cancer, the authors did not recommend the combination, which had severe side-effects including the treatment-related deaths of 16% of patients in this arm [7]. This high toxicity was probably due to the design of the schedule, with high-dose 5-FU and a short interval between two treatment cycles. A better therapeutic index should be obtained with a less toxic schedule of folinic acid-modulated 5-FU, as in the HLFP regimen. With an overall response rate of 57%, a CR rate of 10%, a median response duration of 5 months, manageable haematological and gastrointestinal toxicity, no treatment-related deaths and only 6 patients (14%) hospitalised for treatment-related toxicity, our results compare very favourably with those of previous 5-FU/cisplatin combination schedules, although a comparison between two phase II studies is limited. Moreover, 76% of our patients had a significant improvement or resolution of dysphagia, and 48% gained weight during therapy. These symptomatic effects appeared rapidly during the first weeks of treatment. Moreover, the HLFP regimen can be delivered to outpatients with 5-FU infusors. Thus, our patients only had to be hospitalised for 24 h every month, for the cisplatin infusion.

The same HLFP regimen has been used in two multicentre phase II trials involving patients with advanced gastric or pancreatic carcinoma [15,16]. Similar efficacy/toxicity profiles were observed in these studies, with grade 3-4 toxicity in 36 and 40% of patients, respectively.

The emergence of new cytotoxic drugs during the last decade has led to numerous phase II studies in metastatic oesophageal carcinoma. Topoisomerase I inhibitors, gemcitabine, raltitrexed and taxanes have recently been evaluated in single-agent or combination chemotherapy trials [19–24]. Gemcitabine and topotecan alone are particularly disappointing, without no objective responses [20,22]. The combination of irinotecan with cisplatin gave results very similar to those of our HLFP regimen [19]. Paclitaxel has been widely tested, and docetaxel recently showed interesting activity in metastatic oesophageal cancer [23,24]. Response rates ranged from 23 to 32% in single-agent trials; they increased to 44–55% in combination with cisplatin, but there was also a marked increase in toxicity [23–25]. Although it is not possible to compare the results of phase II studies, our HLFP regimen seems to be at least as promising as other combinations with new agents. Moreover, the HLFP regimen is less costly than regimens including these new drugs.

The HLFP regimen therefore appears to be well-tolerated and to provide good palliation for patients with metastatic oesophageal cancer, and should now be tested in a randomised phase III trial.

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