Cancer Chemother Pharmacol (2002) 50: 305–308
DOI 10.1007/s00280-002-0503-x

ORIGINAL ARTICLE

**Eveline Boucher · Stéphane Corbinais · Pierre Brissot
Karim Boudjema · Jean-Luc Raoul**

Treatment of hepatocellular carcinoma (HCC) with systemic chemotherapy combining epirubicin, cisplatinum and infusional 5-fluorouracil (ECF regimen)

Received: 26 February 2002 / Accepted: 8 July 2002 / Published online: 7 August 2002

Abstract *Purpose*: We tested the efficacy of a systemic chemotherapy regimen combining epirubicin, cisplatinum and infusional 5-fluorouracil (ECF) in a cohort of patients with hepatocellular carcinoma (HCC) who could not be given surgical, intraarterial or percutaneous treatment. *Patients and methods*: Between January 1998 and June 2000, 21 patients with metastatic and/or locally advanced HCC complicating a fibrous liver or a well-compensated (Child A) cirrhosis were given systemic chemotherapy with the ECF regimen. Tumor responses as assessed on CT scan and in terms of survival were studied. *Results*: Patients completed a median of five chemotherapy courses. Overall tolerance was good but eight patients developed grade 3-4 toxicity, mainly hematological, and one patient experienced a grade 4 renal toxicity. Median survival was 10 months. Actuarial survivals (±SD) at 6 months, 1 year and 2 years were 90.2±9%, 70.3±10% and 24.6±19%, respectively. Of the 21 patients, 13 died, 12 from their tumor and 1 from treatment-related renal failure. There were only three objective responses (14.5%; CI95 1–28%) but one of these corresponded to a pathological complete response. The delay to tumor progression was 5.9±4.7 months. *Conclusions*: Systemic chemotherapy using the ECF regimen gave a poor response and low survival rates. It would appear reasonable to pursue the search for potentially efficacious chemotherapy protocols using other drug combinations.

Keywords Hepatocellular carcinoma · Systemic chemotherapy · ECF regimen · Therapy

E. Boucher (✉) · S. Corbinais · J.-L. Raoul
Centre Régional de Lutte Contre le Cancer,
35062 Rennes, France
E-mail: boucher@rennes.fnclcc.fr
Tel.: +33-299-253180
Fax: +33-299-253250

P. Brissot
Service des Maladies du Foie,
Centre Hospitalier Universitaire,
35033 Rennes, France

K. Boudjema
Service de Chirurgie Digestive,
Centre Hospitalier Universitaire,
35033 Rennes, France

E. Boucher
Centre Eugène Marquis, 35062 Rennes,
France cedex, France

Introduction

Hepatocellular carcinoma (HCC) is one of the most frequent cancers worldwide [1]. The incidence in Western countries is among the lowest but has increased significantly. In France approximately 6000 persons die annually from HCC [2, 3]. Surgical (resection, transplantation) or percutaneous treatment (alcoholization, radiofrequency ablation) have curative potential, but can only be used in one-third of the patients [4, 5]. For more than 70% of the patients, the only currently recommended treatment is symptomatic palliation [6]. Either because of the severity of the underlying liver disease, or because intrahepatic dissemination precludes local treatment despite the patient's good general status or good liver function compatible with more aggressive treatment. The role of systemic chemotherapy in the treatment of HCC is very limited. Several agents have been assessed in single-drug or multiple-drug regimens and have given low response rates varying from 0 to 35% [7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19]. A few phase II trials have provided more interesting results, particularly with polychemotherapy regimens [8, 9, 10, 11, 18, 19]. The epirubicin-cisplatinum-5-fluorouracil (ECF) combination, currently the standard protocol for gastric adenocarcinoma, has given a response rate of 29% in a small cohort of seven patients [8]. We decided to test the efficacy of this treatment protocol in a larger cohort of patients with HCC.

Patients and methods

Between January 1998 and June 2000, 492 patients with newly diagnosed HCC were seen at the Pluridisciplinary Concertation Unit for liver tumors at the Rennes Comprehensive Cancer Center. For all these patients the diagnosis of HCC was based on: (a) histology or cytology findings, (b) the association of a tumor mass in a cirrhotic liver with elevation of alpha-fetoprotein (αFP), or (c) two contrast-enhanced examinations showing a hypervascularized liver tumor arising in a cirrhotic liver.

Usually, surgery or percutaneous treatments are proposed for patients having one tumor of 5 cm or less or at most three tumors of less than 3 cm. Transarterial treatments (intraarterial injection of iodine-131-labeled lipiodol) are proposed for patients without portal vein thrombosis and with one to five nodules < 6 cm in diameter. The ECF chemotherapy protocol was then proposed for patients not indicated for curative treatment or for locoregional palliative treatment but who had a good Karnofsky score of ≥70 indicating good general health status, preserved liver function (noncirrhotic liver or Child A cirrhotic liver), acceptable blood cell counts (neutrophil count $> 15{,}000/mm^3$, platelets > 100 g/l), normal renal function (serum creatinine < 110 μmol/l), and a measurable tumor target.

The ECF treatment schedule was: epirubicin 60 mg/m^2 on day 2, cisplatinum 50 mg/m^2 on day 2, and 5-fluorouracil 200 mg/m^2 administered as a continuous infusion from day 1 to day 21 (i.e. one course). Courses were repeated every 21 days. After three courses, treatment was interrupted for a period of 3 weeks.

Tumor response was the main goal of therapy and was assessed with computed tomography performed before treatment onset and then every 9 weeks. The tumor response was considered (WHO criteria) as objective for a decrease in tumor size of more than 50%, stable disease was defined as an absence of progression and a decrease in tumor size of less than 50%. An objective response had to be confirmed 4 weeks later. Progression was an increase in tumor size of more than 25%. The same definition was used for serum αFP levels to assess biochemical response. Patient tolerance was also assessed (NCI-CTC version 2.0). Side effects clinically expressed within 21 days following each treatment were recorded as acute side effects. Cause of death was also recorded. Patient survival was also evaluated as a secondary end-point.

Results

The ECF protocol was given to 21 patients, 17 men and 4 women (mean age 57.8 ± 10.7 years), during the study period from January 1998 through June 2000. The liver tumor was a fortuitous discovery in six patients, discovered at a regular 6-month check-up for known cirrhosis in five patients, revealed by tumor-related complications (pain, hemorrhage) in nine patients and by a cirrhosis-related complication (ascites) in one patient. The tumor developed in a noncirrhotic liver in five patients and in a cirrhotic liver in 16 patients (due to alcohol in ten, hepatitis B in four, hepatitis C in one, and genetic iron overload in one). The CLIP (Cancer Liver Italian Program) [20] scores were 0 ($n = 3$), 1 ($n = 7$), 2 ($n = 8$) and 3 ($n = 3$). There was a single tumor in nine patients, two to five lesions in five and multiple or diffuse tumors in seven. The mean tumor size was 84 ± 52 mm. Portal vein thrombosis was found in three patients and lung metastases in four. The patients received from 1 to 16 courses of chemotherapy (median 5).

Toxicity was graded using NCI-CTC criteria version 2.0. Overall tolerance was good. Eight patients developed signs of minor toxicity (grade 3 or lower) that resolved spontaneously without specific treatment. These toxicities were predominantly hematological but were not associated with clinical side effects. The main toxic effects are summarized in Table 1. One patient developed severe renal toxicity after the fourth course. This patient had been in a stable condition until that time and had not showed electrolyte disorders although his kidney function was borderline normal. There was no evident explanation for this acute adverse effect, but the patient did experience severe nausea after treatment limiting fluid intake. This patient died 7 weeks after the onset of the acute adverse effect despite slowly improving renal function. Dose reduction of 25% was allowed for nonhematological grade 3 or more side effects, and occurred in six patients (24%).

There was a tumor response in three patients (14.5%; CI95 1–28%). Nine patients were stable and nine had tumor progression. In one stable patient, an early objective tumor response was not confirmed later. The delay to tumor progression was 5.9 ± 4.7 months. Survival in the three patients who had an objective tumor response was long: one died after 28 months, one was still alive at the time of this report after 30 months with progression (the same chemotherapy had been successfully reinstituted). The third patient underwent surgical resection after five courses of chemotherapy. He was still alive at the time of this report without progression 14 months after surgery. The histological data were very interesting. Initially the patient had a multinodular 10-cm tumor of the right lobe. The surgical procedure was a right lobe resection. In the resected specimen, histological examination identified three nodules of 0.5, 3 and 4.5 cm without viable tumor cells defining a histological complete response. There was no vascular invasion nor capsule around the nodules.

The median survival of the treated patients was 10 months (range 3–30+ months). Actuarial survivals ($\pm$SD) at 6 months, 1 year and 2 years were $90.2 \pm 9\%$, $70.3 \pm 10\%$ and $24.6 \pm 19\%$, respectively. Nine patients died due to progression of their tumor, and one patient died from cisplatinum-related renal failure.

Discussion

Advanced HCC not amenable to surgical resection or percutaneous treatment has a very dismal prognosis [6].

Table 1. Toxicity of the treatment

Toxicity	Grade 3	Grade 4
Neutrophil count	4	1
Platelet	0	1
Mucositis	1	1
Vomiting	1	0
Fever	0	1
Renal	0	1 (death)
Asthenia	3	0
Glycemia	2	0
Alopecia grade 2	2	2

For disease confined to the liver, various locoregional treatments may offer useful palliation. These include intraarterial infusion of combination chemotherapy [10, 21, 22], chemoembolization [23] and iodine-131-labeled lipiodol [24, 25].

Different combination chemotherapy regimens have been proposed but with high toxicity for low efficacy. Single agents with a reproducible response rate of more than 10% are 5-fluorouracil, doxorubicin and cisplatinum. New agents such as paclitaxel, docetaxel or irinotecan have to demonstrate their activity against HCC. However, a higher response rate could be obtained by combining drugs that have synergistic activity, in particular combinations of 5-fluorouracil, anthracyclines and cisplatinum (ECF [8]) or combinations including interferon (PIAF [10, 18]). This latter protocol gave 16.8% response, and low toxicity [18], and for the few patients who underwent surgical resection after achieving a partial response, complete histological response was noted in one-third. These results led us to undertake a trial with the ECF regimen; we decided not to use interferon therapy.

In our series, the treatment resulted in an objective response rate of 14.5% (CI95 1–28%) and a median survival of 10 months (43 weeks). Only the three patients who had an objective response had a survival of long duration. As our group was small, we did not perform a statistical analysis to determine a predictive factor for response. However, our responders were either hepatitis C carriers or noncirrhotic, which are factors usually associated with a good response [18, 19]. Only one of the three responders had undergone a surgical resection. In the study of Leung et al. [18], it was possible to carry out a secondary resection in 11% of the treated patients after chemotherapy.

Our results are comparable with those of most phase II systemic chemotherapy trials. A median survival of 9 months and a 39% response rate with the association etoposide/cisplatin [7, 8], and a 16.8% response rate and a median survival of 30.9 weeks with the PIAF regimen [10, 18] have been reported.

In our study, the toxicity of the ECF combination was low despite the fact that more than 80% of the patients had cirrhosis. It is particularly noteworthy that patients with neutropenia due to hypersplenism did not exhibit excessive hematological toxicity and that there were no patients showing overt liver toxicity. There was one treatment-related death due to renal insufficiency caused by cisplatinum, in spite of correct hydration and normal serum creatinine level at treatment onset. However, we did not assess the quality of life using a written questionnaire in our patients. The quality of live was assessed before every course of chemotherapy by careful questioning.

In conclusion, treatment of HCC using the ECF protocol was well tolerated, but gave only a 14.5% objective response rate and a low survival time (10 months). This combination could not be recommended as a "standard" for HCC. It would appear reasonable to pursue the search for other effective chemotherapy schemes since this response rate is still quite insufficient. The potential contribution of new compounds (oxaliplatinum, irinotecan, taxanes) remains to be determined.

References

1. El-Serag HB (2001) Epidemiology of hepatocellular carcinoma. Clin Liver Dis 5:87–107
2. Arguedas MR, Fallon MB (2001) Prevention in liver disease. Am J Med Sci 321:145–151
3. Inoue H, Seitz HK (2001) Viruses and alcohol in the pathogenesis of primary hepatic carcinoma. Eur J Cancer Prev 10:107–110
4. Hemming A, Cattral M, Reed A, Van der Werf W, Greig P, Howard R (2001) Liver transplantation for hepatocellular carcinoma. Ann Surg 233:652–659
5. Curley S, Izzo F, Ellis L, Vauthey NJ, Vallone P (2000) Radiofrequency ablation of hepatocellular cancer in 110 patients with cirrhosis. Ann Surg 232:381–391
6. Llovet JM, Bustamante J, Castells A, et al (1999) Natural history of untreated non surgical hepatocellular carcinoma: rationale for the design and evaluation of therapeutic trials. Hepatology 29:62–67
7. Rougier P, Mitry E, Clavero-Fabri M (1998) Chemotherapy and medical treatment of hepatocellular carcinoma (HCC). Hepatogastroenterology 45:1264–1266
8. Ellis P, Norman A, Hill A, et al (1995) Epirubicin, cisplatin and infusional 5-fluorouracil (5-FU) (ECF) in hepatobiliary tumours. Eur J Cancer 31A(10):1594–1598
9. Bobbio-Pallavicini E, Porta C, Moroni M (1997) Epirubicin and etoposide combination therapy to treat hepatocellular carcinoma, a phase II study Eur J Cancer 33:1784–1788
10. Leung T, Patt Y, Lau W (1999) Complete pathological remission is possible with systemic combination chemotherapy for inoperable hepatocellular carcinoma. Clin Cancer Res 5:1676–1681
11. Ihde DC, Matthews MJ, Makuch RW, McIntire KR, Eddy JL, Seeff LB (1985) Prognostic factors in patients with hepatocellular carcinoma receiving systemic chemotherapy. Identification of two groups of patients with prospects for prolonged survival. Am J Med 78:399–406
12. Lai CL, Wu PC, Chan GC, Lok AS, Lin HJ (1988) Doxorubicin versus no antitumour therapy in inoperable hepatocellular carcinoma. A prospective randomized trial. Cancer 62: 479–483
13. Falkson G, Ryan LM, Johnson LA, Simson IW, Coetzer BJ, Carbone PP, Creech RH, Schutt AJ (1987) A random phase II study of mitoxantrone and cisplatin in patients with hepatocellular carcinoma. An ECOG study. Cancer 60:2141–2145
14. Cavalli F, Rozencweig M, Renard J, Goldhirsch A, Hansen HH (1981) Phase II study of oral VP-16-213 in hepatocellular carcinoma. Eur J Cancer Clin Oncol 17:1079–1082
15. Mani S, Schiano T, Garcia JC, et al (1998) Phase II trial of uracil/tegafur (UFT) plus leucovorin in patients with advanced hepatocellular carcinoma. Invest New Drugs 16:279–283
16. O'Reilly EM, Stuart KE, Sanz-Altamira PM, et al (2001) A phase II study of irinotecan in patients with advanced hepatocellular carcinoma. Cancer 91:101–105
17. Yang TS, Lin YC, Chen JS, Wang HM, Wang CH (2000) Phase II study of gemcitabine in patients with advanced hepatocellular carcinoma. Cancer 89:750–756
18. Leung T, Tang A, Zee B, Yu S, Lai P, Lau W, Johnson P (2002) Factor predicting response and survival in 149 patients with unresectable hepatocellular carcinoma treated by combination cisplatin, interferon-alpha, doxorubicin and 5-fluorouracil chemotherapy. Cancer 94:420–427

19. Okada S (1998) Chemotherapy in hepatocellular carcinoma. Hepatogastroenterology 45:1259–1263
20. The Cancer of the Liver Italian Program (CLIP) Investigators (2000) Prospective validation of CLIP score: a new prognostic system for patients with cirrhosis and hepatocellular carcinoma. Hepatology 31:840–845
21. Pat Y, Charnsangavej C, Yoffe B, et al (1994) Hepatic arterial infusion of floxuridine, leucovorin, doxorubicin and cisplatin for hepatocellular carcinoma, effect of hepatitis B and C viral infection on drug toxicity and patient survival. J Clin Oncol 12:1204–1211
22. Aguayo A, Patt Y (2001) Nonsurgical treatment of hepatocellular carcinoma. Clin Liver Dis 5:175–189
23. Groupe d'étude et de traitement du carcinome hepatocellulaire (1995) A comparison of lipiodol chemoembolisation and conservative treatment for unresectable hepatocellular carcinoma. N Engl J Med 332:1256–1261
24. Raoul JL, Guyader D, Bretagne JF, et al (1997) Prospective randomized trial of chemoembolisation versus intra arterial injection of 131-I-labelled-iodized oil in the treatment of hepatocellular carcinoma. Hepatology 26:1156–1161
25. Raoul JL, Guyader D, Bretagne JF, et al (1994) Randomized controlled trial for hepatocellular carcinoma with portal vein thrombosis, intra arterial iodine-131-iodized oil versus chemoembolisation. J Nucl Med 35:1782–1787