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Irinotecan as first-line chemotherapy in patients with advanced hepatocellular carcinoma: A multicenter phase II study with dose adjustment according to baseline serum bilirubin level

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ABSTRACT

This study assessed the clinical activity and safety of irinotecan (CPT-11) in patients with advanced hepatocellular carcinoma (HCC) using dose adjustment according to baseline serum bilirubin level. Patients with advanced HCC received CPT-11 at a dose of 350 mg/m^2 when total bilirubin level was $\leqslant$1.5 times upper limit of normal (ULN) (group A), or 200 mg/m^2 when total bilirubin level was between 1.51 and 3 ULN (group B). No objective response, one minor response and 12 disease stabilizations were observed in the 29 patients (group A, 23; group B, 6) enrolled. Median time to progression and overall survival were 3.1 months (95% confidence interval [CI]: 2.0–4.0) and 7.4 months (95% CI: 3.9–12.0), respectively. Grade 3–4 adverse events (mostly neutropenia [47%], anaemia [24%], and diarrhoea [17%]) were more frequent in group A (74%) than in group B (33%) ($P = 0.086$). This study found favourable toxicity profile using dosage adjustment to the baseline total bilirubin level in patients with bilirubin level comprised between 1.51 and 3 ULN. However, the antitumour activity of single agent CPT-11 was not significant in advanced HCC.

1. Introduction

Only few patients with hepatocellular carcinoma (HCC) are eligible for radical treatments with curative intent (i.e., surgical resection, liver transplantation) or percutaneous ablation, because of the tumour extent and/or underlying decompensated cirrhosis.[1] Chemoembolization, which has been shown to improve survival in selected patients, is not feasible in case of portal vein thrombosis or extrahepatic spread.[2] Objective response rates achieved with systemic chemotherapy, even with combination regimens, remain desperately low.[3] Furthermore, cirrhosis may reduce the capacity of the liver to

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metabolize and excrete cytotoxic agents and thereby enhance toxicity. A careful adjustment of chemotherapy doses according to liver function could circumvent this limitation.

Topoisomerase-I inhibitors including irinotecan (CPT-11), a camptothecin derivative, have been shown to exert activity in HCC in vitro.[4,5] Only one phase II study assessing CPT-11 in HCC has been published, using a fixed starting dose of 125 mg/m^2/week.[6] One partial response (PR) was observed among 14 evaluable patients, but frequent adverse events (AEs) required dose adaptation in most of the patients. One case report of complete response (CR) after high-dose CPT-11 and surgery has also been published.[7] In our previous phase I study assessing CPT-11 in patients with liver dysfunction, six patients with HCC were enrolled. One PR and one minor response were observed. The recommended dose of CPT-11 for patients with serum bilirubin between 1.51 and 3 times upper limit of normal (ULN) was 200 mg/m^2 every 3 weeks, whilst the standard dose of 350 mg/m^2 was recommended for patients with bilirubin values $\leqslant$1.5 ULN.[8] Pharmacokinetic analyses showed that systemic exposure to CPT-11 and its active metabolite SN-38 increased proportionally with increasing bilirubin and alkaline phosphatase levels.[8,9]

On the basis of these data and of previous hints of clinical activity, we embarked on a phase II study to further assess the clinical activity of CPT-11 delivered with a once-every three-week schedule in patients with advanced HCC. Two different doses were assigned to patients according to their baseline bilirubin levels, in order to improve the safety profile in patient with underlying cirrhosis and liver dysfunction, and to validate the previously recommended dose adaptation schedule.[8]

2. Patients and methods

2.1. Eligibility criteria

Patients who were not suitable for surgical resection, liver transplantation, or local ablation techniques, with either histologically proven HCC, or combination of liver cirrhosis, radiologically documented hypervascular liver tumour and alphafetoprotein level $\geqslant$400 ng/mL, were eligible to this open-label, phase II study.[1] Other eligibility criteria were: bidimensionally measurable disease; age 18–75 years; World Health Organization (WHO) performance status (PS) 0–2; neutrophils $\geqslant 1.5 \times 10^9$/L, platelets $\geqslant 100 \times 10^9$/L, haemoglobin $\geqslant$100 g/L, creatinine clearance $\geqslant$1 mL/s, bilirubin $\leqslant$3 ULN, aminotransferases <20 ULN, normal prothrombin time, and fibrinogen $\geqslant$1.5 g/L. Main exclusion criteria were: Child-Pugh $\geqslant$10 (class C) cirrhosis; previous systemic chemotherapy; chemoembolization or embolization performed within the last 8 weeks; and concomitant antitumour therapy including tamoxifen. Patients provided written informed consent.

2.2. Treatment schedules

CPT-11 (Campto™, Sanofi Aventis, Paris, France) was given as a 30–90-min intravenous (i.v.) infusion every 3 weeks, at a starting dose of 350 mg/m^2 when baseline bilirubin was $\leqslant$1.5 ULN (group A), or 200 mg/m^2 when bilirubin was between 1.51 and 3 ULN (group B).[8] Subsequent doses were to be adapted according to the bilirubin value of the day, irrespective of the initial dose. Further dose reductions were planned according to pre-established guidelines in case of febrile neutropenia, grade 4 neutropenia lasting $\geqslant$7 days, grade $\geqslant$3 thrombocytopenia, grade $\geqslant$3 diarrhoea, or other non-haematological AEs, except for cholinergic syndrome or non-optimally controlled nausea or vomiting. Treatment was to be pursued until disease progression, unacceptable toxicity, patient's refusal or toxicity-related delay >2 weeks. Prophylactic atropine (0.25–0.5 mg subcutaneously) for cholinergic symptom, and i.v. methylprednisolone and granisetron were given before CPT-11 infusion.

2.3. Efficacy assessments

Tumour response (CR, PR, stable disease (SD), or progressive disease (PD)) was assessed every three cycles by computed tomography scan or magnetic resonance imaging according to WHO criteria.[10] For patients with PR or CR, a second radiological assessment was required four weeks later to confirm the response. All radiological tumour assessments were reviewed by an independent response review committee.

2.4. Toxicity assessments

Toxicity was graded according to the National Cancer Institute – Common Toxicity Criteria (NCI-CTC) version 2.0. Complete blood cell and platelet counts were performed every week. Physical examination and bilirubin were performed before each cycle. All patients who received at least one dose of study medication were considered evaluable for safety.

2.5. Statistical analysis

A two-stage Gehan's design with a 5% risk of wrongly rejecting an actual response rate $\geqslant$20% was used.[11] If no objective tumour responses were observed among the first 14 evaluable patients, the study had to be discontinued. Otherwise, enrollment had to be continued to better estimate the response rate. The time to disease progression was calculated from the start of therapy until tumour progression or death. Survival time was calculated from the start of therapy to the date of the death. Time-to-event parameters were analyzed using Kaplan–Meier product limit estimates.

3. Results

3.1. Patient characteristics

Overall, 29 patients (group A, 23; group B, 6) were enrolled between November 2000 and July 2001 (Table 1). A PR in the first 14 patients led to extend accrual until the final number, but was ultimately deemed as a minor response by the external review committee. All patients were evaluable for safety, and 25 (86%) were evaluable for response. All but two patients had a good PS of 0–1. Most patients had alcoholic and/or hepatitis B-related, Child A liver cirrhosis, and 15 (52%) were not pre-treated. Most patients (79%) had tumour-related

Table 1 – Patient baseline characteristics

	Group A N = 23	Group B N = 6	All N = 29
Median age (range) years	59 (24–76)	59 (48–74)	59 (24–76)
Gender M/F	19/4	5/1	24/5
Performance status 0/1/2/missing	12/8/2/1	2/4/0/0	14/12/2/1
Cirrhosis origin[a]			
Hepatitis B	4	2	6
Hepatitis C	0	0	0
Alcohol	10	4	14
Other	5	1	6
Missing	7	0	7
Child-Pugh class			
A	17	4	21
B	4	2	6
Missing	2	0	2
Median time from HCC diagnosis (range) (months)	3.7 (0.4–66.8)	3.5 (0.4–48.9)	3.7 (0.4–66.8)
Previous therapies[b]	11	3	14
Hepatic resection	4	0	4
Chemo-embolization	5	1	6
Percutaneous ethanol injection	2	0	2
Other[c]	4	3	7
Median time from last therapy (range) months	2 (0–62)	4 (0–14)	2 (0–62)
Target lesions by patient			
Liver	23	6	29
Lung	4	1	5
Abdominal lymph nodes	2	1	3
Other	2	1	3
Patients with tumor symptoms	18	5	23
Elevated aminotransferases	17	6	23
Elevated alkaline phosphatase	13	6	19

Group A: bilirubin $\leqslant$1.5 ULN; Group B: bilirubin, 1.5–3 ULN.
a Some patients with two possible causes.
b Some patients with more than one prior therapy.
c Hormone therapy: 2; cryotherapy: 1; intrahepatic radiation therapy: 1; brain radiation therapy: 1; experimental therapy: 3.

symptoms. Baseline liver function tests showed that 23 patients (79%) had elevated aminotransferases (including four patients with grade 3 elevated aminotransferases, as allowed by inclusion criteria), 19 patients (66%) had elevated alkaline phosphatase (including six patients with grade 2 increase), and 13 patients (45%) had elevated bilirubin. The baseline bilirubin levels of the six patients assigned to group B were 1.6, 1.7, 2.1, 2.2, 2.5 and 3.0 ULN, respectively. None of the patients had biliary tract obstruction, or an isolated unconjugated hyperbilirubinemia suggestive of Gilbert's syndrome.

3.2. *Response and survival*

No CR or PR were observed. Thirteen SD, including one minor response (group A), were observed (median duration, 4.0 months; range, 1.8–8.9); 12 patients (41%) had PD. Four patients (14%) were not evaluable for response due to early study withdrawal (one early death, one patient's refusal, and two patients with cycle delays >2 weeks after two cycles). With a median follow-up of 7.4 months, the median time to progression was 3.1 months (95% confidence interval [CI]: 2.0–4.0) and the median survival was 7.4 months (95% CI: 3.9–12.0).

3.3. *Safety*

The median number of cycles per patient was three in both groups (range, 1–13). However, group B patients received fewer cycles than group A patients, as no patients in group B received more than six cycles, whilst four patients in group A received 7–13 cycles. After cycle 1, 14 dose reductions were needed in 10 patients (all in group A), and 15 cycles were delayed by more than 3 days in 12 patients (all but one in group A). Median CPT-11 cumulative doses and dose intensity were 1078 mg/m^2 (range: 343–4674) and 104 mg/m^2/week (59–117) in group A, and 597.5 mg/m^2 (199–1216) and 66 mg/m^2/week (62–68) in group B. All patients experienced at least one AE thought to be related to study treatment. Grade 3–4 AEs were more frequent in group A than in group B (17 [74%] versus 2 patients [33%], $P = 0.086$). The most frequent AEs were those usually reported with CPT-11 (neutropenia, gastrointestinal toxicity, fatigue), and were more frequent in group A: 13 patients in group A (57%) experienced grade 3 ($n = 4$, 17%) or 4 neutropenia ($n = 9$, 39%), versus only one patient in group B (grade 4, 17%) ($P = 0.099$). Febrile neutropenia or neutropenic infection (including one fatal septic shock) occurred in four patients of group A, versus none in group B. Grade 3/4 diarrhoea ($n = 5$, 22%), grade 3/4 vomiting despite antiemetic prophylaxis ($n = 5$, 22%), and grade 3/4 fatigue ($n = 4$, 17%) occurred in group A, versus none in group B. Three patients in group A and one patient in group B experienced transient elevation of aminotransferases and/or alkaline phosphatase, concomitant with other grade 3 or 4 AEs, which may be therefore related to study treatment. Study treatment was discontinued in four patients in group A (fatal neutropenic infection after the 7th cycle; persistent grade 4 neutropenia after the 6th cycle despite dose reduction; patient's refusal after severe toxicity; and cycle delay due to toxicity; one patient each) and one patient in group B (cycle delay due to toxicity). Four deaths occurred on study, due to septic shock during grade 4 neutropenia ($n = 1$), tumour haemorrhage ($n = 1$), hepatic encephalopathy ($n = 1$), and cardiac arrest ($n = 1$).

4. Discussion

To our knowledge, this trial is the first to prospectively assess the impact of CPT-11 dosage adjustment according to baseline bilirubin elevation, a surrogate marker for hepatic dysfunction and for CPT-11-induced toxicity,[8,9] as recommended in our previous phase I study,[8] in terms of tolerance and efficacy in patients with advanced solid cancer, namely advanced HCC. Patients enrolled in this study had usual characteristics of HCC patients included in clinical trials, in terms of good PS and of mild-to-moderate cirrhosis severity, and only differed significantly by the existence, and level, of hepatic dysfunction.

There is no standard systemic chemotherapy for advanced HCC as no drug or combination has been convincingly shown to improve survival over best supportive care.[3] In addition to intrinsic resistance, underlying liver cirrhosis most often precludes the use of several cytotoxic agents. In this study, no objective response was observed with CPT-11, and tumour stabilizations were short-lived. Anecdotal clues of clinical activity[6–8] have thus not been confirmed so far, and further development of CPT-11 single agent therapy in advanced HCC is therefore not warranted.

The safety profile in group A was similar to that observed in patients with advanced colorectal cancer receiving the same dose of CPT-11,[12,13] and comparable to that observed with the weekly schedule in patients with advanced HCC, despite less frequent dose attenuation requirement (100% with the weekly schedule).[6] However, group B patients experienced a lower incidence of grade 3–4 AEs. Especially, the 57% incidence of grade 3–4 neutropenia in group A was consistent with that reported in previous large phase II trials,[12,13] whereas only 17% were observed in group B. Since the degree of neutropenia is directly correlated to CPT-11 systemic exposure,[9] group B patients may have been exposed to a suboptimal dose. However, according to our previous report, the dose of 200 mg/m^2 in patients with bilirubin comprised between 1.51 and 3 ULN achieved the same exposure as the dose of 350 mg/m^2 in patients with total bilirubin level $\leqslant$1.5 ULN.[8] The fact that two out of six patients in the present study had borderline grade 2 bilirubin (1.6 and 1.7 ULN) might contribute to this discrepancy. Furthermore, in the present study, liver dysfunction mainly resulted from cirrhosis in all the patients, while in our previous study, the profile of hepatic abnormalities was typical of chronic cholestasis caused by liver metastasis in 27 out of the 33 patients included, whereas only six patients had primary liver tumours potentially associated with liver cirrhosis.[8] Thus, CPT-11 exposure may be different in patients with hyperbilirubinemia caused by either liver insufficiency or intrahepatic cholestasis, although both mechanisms are frequently associated in patients with cirrhosis and HCC. As the main metabolic pathways of CPT-11 predominantly take place in liver, it can be hypothesized that CPT-11 conversion into active metabolites by carboxylesterase and cytochrome P-450 enzymes may be impaired by cirrhosis-associated liver insufficiency leading to a decrease in SN-38 exposure,[14] whereas CPT-11 biliary excretion may be impaired in case of cholestasis leading to decreased clearance of irinotecan and increased SN-38 exposure.[8] As glucuronidation is belatedly altered in cirrhosis with liver insufficiency,[15] conjugation of SN-38 into inactive SN-38 glucuronide may not have been impaired in patients with compensated cirrhosis included in our study.

In conclusion, the antitumour activity of CPT-11 single agent is not significant in advanced HCC. The safety profile was that expected with the dose of 350 mg/m^2 and confirms that this dose can be delivered in patients with serum bilirubin up to 1.5 ULN. We also confirmed that the dose of 200 mg/m^2 is safe in patients with total bilirubin level between 1.51 and 3 ULN. The concept of drug dosage adjustment according to the existence and level of hepatic dysfunction (e.g., bilirubin level) warrants further investigation, and should be systematically discussed when designing therapeutic trials in patients with underlying liver disease.

Conflict of interest statement

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