A Phase II Study of Irinotecan in Patients with Advanced Hepatocellular Carcinoma

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BACKGROUND. Advanced hepatocellular carcinoma has a poor prognosis. In a Phase II clinical trial, two academic centers assessed irinotecan, a topoisomerase-1 inhibitor with broad spectrum clinical activity, in patients who had advanced hepatocellular cancer.

METHODS. Patients who had had up to one prior chemotherapy regimen were eligible. Bidimensionally measurable disease, a good performance status, and adequate major organ function were required. At a starting dose of 125 mg/m^2, irinotecan was administered weekly for 4 weeks followed by a 2 week break, which constituted 1 treatment cycle. Patients were restaged radiologically after two cycles of therapy. Dose attenuations were made as indicated for toxicity.

RESULTS. Fourteen patients were enrolled over a 10-week period in 1997. There were ten males and four females. The median age was 58 years (range, 38–74 yrs). The Eastern Cooperative Oncology Group median performance status was 1 (range, 0–1). Two patients had prior chemotherapy (14%), and 1 patient (7%) had had radiation. A total of 30 cycles of therapy were delivered (median, 1; range, 1–6). Considerable toxicity was observed, mostly neutropenia, diarrhea, nausea, vomiting, and fatigue. All patients required at least one dose attenuation for toxicity. One partial response (7%; confidence interval, 0–20%) was noted to last 7 months. One patient had transient stable disease, and all others (86%) had progression of disease as their best response.

CONCLUSIONS. Irinotecan had modest activity in advanced hepatocellular cancer. Toxicity was substantial, presumably reflecting impaired underlying liver function or poor ability to metabolize and eliminate the drug. The current study indicated that continued new therapy assessment is warranted for this disease. ***Cancer* 2001; 91:101–5.** *© 2001 American Cancer Society.*

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Hepatocellular carcinoma is one of the most prevalent malignancies worldwide, occurring primarily in the Orient and Africa. In the United States of America (USA), the disease is relatively uncommon, with 15,300 new cases of hepatocellular carcinoma and intrahepatic bile duct malignancies anticipated in the year 2000.[1] About 13,800 people will die from these diseases in the USA this year. The natural history of hepatoma and predisposing factors vary between Eastern and Western Hemisphere populations. About 80% of hepatomas arise in the presence of cirrhosis, and the estimated lifetime risk of developing hepatoma in a patient with cirrhosis is about 4–20%.[2] In Asian populations, most cases of hepatocellular carcinoma arise from chronic hepatitis B infection. In the USA, hepatitis C now is the leading predisposing factor.[3,4] The prognosis for western patients who have advanced hepatocellular carcinoma is poor. The only known

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curative therapy is surgical resection or hepatic transplantation; however, for a significant percentage of patients, underlying liver function is compromised because cirrhosis and/or tumors are multifocal or diffuse and surgical intervention is not feasible.

Hepatocellular carcinoma has a significant propensity to develop metastases with major sites of spread to the liver, lymph nodes, lungs, bones, adrenal glands, and peritoneal cavity.[5,6] In patients with metastatic disease, treatment is palliative in intent. Even the current best standard therapies are of only minimal benefit, offering low response rates and no clear impact on survival. Clearly, new therapies are necessary to treat this disease.

Irinotecan is a water soluble, topoisomerase-1 inhibitor derived from a plant alkaloid, which results in single stranded breaks in DNA and inhibition of DNA repair enzymes leading to interference with DNA synthesis.[7] Irinotecan has been approved by the Food and Drug Administration for metastatic colorectal cancer in the USA, but also has broad activity against other malignancies, including nonsmall cell and small cell lung carcinomas, and ovary, breast, stomach, and esophageal cancers.[8] For several reasons, irinotecan was an attractive drug to assess in hepatomas and biliary tract malignancies. First, there is in vitro data suggesting the utility of irinotecan in a variety of gastrointestinal cell lines, including hepatocellular carcinoma.[9,10] Second, irinotecan undergoes activation in the liver to its active, minor metabolite, SN-38, which leads to high local concentrations of SN-38 in the biliary system.[11] SN-38 also undergoes enterohepatic recycling, which may further contribute to sustained local SN-38 levels in the hepatobiliary tree. Therefore, a Phase II clinical trial was conducted to determine the response rate, toxicity, and overall patient survival for irinotecan in advanced hepatocellular carcinoma.

PATIENTS AND METHODS

Eligibility

Patients who had locally advanced, recurrent, or metastatic hepatocellular carcinoma that was histologically confirmed were eligible. Patients were allowed to have up to one prior program of chemotherapy, provided it was not a topoisomerase-1 inhibitor. Bidimensionally measurable disease was necessary. Patients were required to be at least 18 years of age, to have an Eastern Cooperative Oncology Group (ECOG) performance status of 0–2, and to have adequate major organ function. Specifically, their bilirubin level had to be $\leq$ 2.0 mg/dL, aspartate transaminase (AST) $\leq$ 5 times the institutional upper limit of normal, and the serum creatinine had to be $\leq$ 2.0 mg/dL. Minimum hematologic parameters included a total white count $\geq 3.0 \times 10^9$/L and a platelet count of $\geq 75 \times 10^9$/L. Exclusionary criteria included a concurrent malignancy, $\geq$ 2 prior chemotherapy regimens, significant medical comorbidities, or an inability to give written informed consent. Patients from Memorial Sloan-Kettering Cancer Center in New York, NY, and the Beth Israel Deaconess Medical Center in Boston, MA, were eligible for enrollment.

Treatment Plan

Irinotecan was administered at 125 mg/m^2 for 90 minutes in an outpatient setting weekly for 4 weeks followed by a 2-week break. Each cycle consisted of 6 weeks. Premedication with dexamethasone 20 mg intravenously was given before each treatment. Granisetron and lorazepam were administered for refractory nausea or vomiting. Atropine 0.25–0.5 mg was given for cholinergic symptoms or for diarrhea that occurred during or shortly after treatment administration. Patients were restaged radiologically after a second cycle of therapy and, thereafter, every other cycle. Toxicity was assessed by using the National Cancer Institute's common toxicity criteria (URL: http://ctep.info.nih.gov/ctc3/ctc.htm). Treatment was held on the day of scheduled delivery for Grade II hematologic toxicity or Grade II diarrhea. The dose of irinotecan was attenuated by 25 mg/m^2 for Grade III neutropenia, thrombocytopenia, or diarrhea. Any Grade IV toxicity resulted in two dose level attenuations, i.e., by 50 mg/m^2. Diarrhea was managed aggressively by loperamide therapy.[12]

Assessment

Patients were staged radiologically within 4 weeks of initiation of therapy. When appropriate, α-fetoprotein levels were recorded. A complete history, physical examination, and documentation of bidimensionally measurable disease and performance status were performed at baseline. A complete blood count was drawn weekly. A full biochemistry panel, including liver function tests and bilirubin levels, was drawn at the start of each 6-week cycle. Patients were seen weekly for the first cycle, subsequently patients were assessed on Day 1 and Day 15 of each cycle.

Response Criteria

A complete response (CR) was defined as the disappearance of all clinical and radiologic evidence of disease and normalization of tumor markers for a period of at least 4 weeks. A partial response (PR) was defined as $\geq$ 50% decrease in the bidimensional tumor measurements, without the appearance of any new lesions or progression of any existing lesions. Progressive disease (PD) was defined as any of the following 1) a

TABLE 1
Patient Demographics

Characteristic	
Total number of patients	14
Males	10 (71%)
Females	4 (29%)
Age	
Median (range)	58 yrs (range, 38–74 yrs)
ECOG PS	
Median (range)	0 (range, 0–1)
Disease extent	
Locally advanced	6 (43%)
Metastases to lung, lymph nodes, bone	8 (57%)
Prior therapy	
None	11 (79%)
Doxorubicin chemotherapy	2 (14%)
Radiation	1 (7%)

TABLE 2
Maximum Toxicity Grade Per Patient

Toxicity	Grade II no. (%)	Grade III no. (%)	Grade IV no. (%)
Hematologic			
Neutropenia	4 (29)	6 (43)	—
Hemoglobin	4 (29)	—	—
Platelets	1 (7)	—	—
Gastrointestinal			
Nausea/vomiting	2 (14)	2 (14)	—
Diarrhea	3 (21)	4 (29)	—
Bilirubin	—	2 (14)	1 (7)
Fatigue	2 (14)	1 (7)	—

$\geq$ 50% increase in the sum of the products of all measurable lesions, 2) appearance of any new lesion, or 3) reappearance of any lesion that had disappeared. Stable disease was defined as tumor response that did not meet the criteria for CR, PR, or PD. The time periods to disease progression and survival were dated from the time of enrollment in the study.

Statistics

Fourteen patients were to be treated initially. If two patients were noted to respond to therapy in the first group of patients, then the option to expand enrollment to 25 patients existed, pending toxicity to the patients and the discretion of the principal investigator.

RESULTS

Patient Characteristics

Between August, 1997 and October, 1997, 14 patients were enrolled between the two participating centers. There were 10 men (71%) and 4 women (29%). Their median age was 58 years (range, 38–74 yrs). Their median ECOG performance status was 0 (range, 0–1). Two patients (14%) were of Asian origin, and the remainder was Caucasian. Two patients had received prior chemotherapy with doxorubicin, and one patient had received prior radiation therapy. A total of 102 individual irinotecan doses were delivered, which constituted 30 cycles of therapy. The median number of cycles administered was 2 (range, 1–6). The median bilirubin level was 1.15 ng/mL (range, 0.4–1.5). Demographic information is summarized in Table 1.

Toxicity

Toxicity was significant in this population of patients. The major toxicities were nausea, vomiting, neutropenia, diarrhea and fatigue, and poor tolerance for treatment. The maximum hematologic toxicity was as follows: Grade III neutropenia occurred in 6 patients (43%), Grade II thrombocytopenia in 1 patient (7%), and Grade II anemia in 4 patients (29%). The major nonhematologic toxicity was diarrhea with Grade III diarrhea occurring in 4 patients (29%), and Grade II diarrhea occurring in 3 patients (21%). Grade III nausea and vomiting occurred in 2 patients (14%), and Grade II nausea and vomiting occurred in 2 patients (14%) despite premedication with lorazepam, dexamethasone, and granisetron. Fatigue, Grade III, was noted in 1 patient (7%) and Grade II in 1 patient (7%). Every patient (100%) required at least 1 dose attenuation for toxicity, 4 patients (29%) required 2 dose attenuations, and 1 patient (7%) required 3 dose attenuations. Six patients (43%) had treatment delayed or omitted due to toxicity, primarily neutropenia and diarrhea. Progressive hyperbilirubinemia on treatment was documented in 4 patients, 3 Grade III (21%) and 1 Grade IV (7%). All episodes of elevated bilirubin were attributed to the underlying disease process and not to therapy but might have contributed to poor tolerance to treatment. Two patients (14%) were hospitalized with neutropenic fever. There were no treatment-related deaths during the current study. The toxicity data is summarized in Table 2.

Response and Survival

There were no complete responses. One patient (7%, 95% confidence interval, 0–20%) achieved a partial response to irinotecan that was sustained for 7 months. This responder required 2 dose attenuations for Grade III nausea and Grade III neutropenia but continued to respond at 75 mg/m^2. One patient (7%) had temporary stabilization of disease for 3.5 months, and 12 patients (86%) had progression of disease as their best response. For most of the patients, the time to progression of disease was the time of their initial

TABLE 3
Response Data

Response	No. (%)
Partial response	1 (7)
Stable disease	1 (7)
Progressive disease	12 (86)

reevaluation. Thirteen patients (93%) have died of progressive disease. One patient, the responder, is alive and is receiving further therapy. The median survival for the whole group was 8.2 months. Accrual was terminated after the initial fourteen patients because of low level activity and toxicity concerns. Response data is summarized in Table 3.

DISCUSSION

Advanced hepatocellular carcinoma that is not amenable to surgical resection or local ablative therapies has a very poor prognosis.[13] Few or, arguably, no chemotherapeutic agents have been shown to have any significant impact on survival.[14] 5-fluorouracil, floxuridine, doxorubicin, mitomycin, and cisplatin have been the mainstays of palliative chemotherapy for metastatic disease. Assessed response rates for these drugs are in the 5–25% range. Regional chemotherapeutic approaches also have been employed, resulting in slightly higher response rates, lower levels of systemic toxicity, and higher biliary toxicity. Given the lack of useful therapies for this disease, we chose to evaluate irinotecan in patients who had advanced hepatocellular carcinoma. Our rationale was based on irinotecan's broad spectrum of activity, its novel mechanism of action, its in vitro activity, and its active metabolite, SN-38, which is activated in the liver by carboxylesterases and undergoes enterohepatic recirculation.

At the time the current study was reported in preliminary fashion,[15] we were encouraged by the finding of one responder in the initial seven patients treated; however, with additional follow-up, the final results of this Phase II clinical trial are undoubtedly disappointing. Only one partial response of modest duration was observed, and the vast majority of patients demonstrated early progression of disease.

There are several observations worth noting, pertinent to this patient population. Most patients who had hepatocellular carcinoma also had underlying chronic liver disease, which almost certainly contributed to their poor tolerance of this drug. All patients (100%) required a dose attenuation, and more than half of the patients ($> 50\%$) required a treatment delay or an omission of a treatment because of toxicity. There were no treatment-related deaths or hospitalizations for life threatening toxicity, and an objective assessment of the toxicity as reported herein does not do justice to our clinical impression of irinotecan being poorly tolerated. However, in view of our strong clinical impression, we elected not to expand accrual of patients into the current study, even though 1 responder had been observed in the initial 14 patients treated. Early data that emerged from a North Central Cancer Treatment Group trial revealed similar findings in a Phase II study of irinotecan in advanced gallbladder and biliary tract cancers.[16] In that trial, significant toxicity occurred in the first group of patients enrolled, which resulted in an attenuation of the starting dose of irinotecan to 100 mg/m^2. Nonetheless, 3 of the next 7 patients that were treated at 100 mg/m^2 experienced Grade IV diarrhea, neutropenia, or vomiting. Because excess toxicity occurred despite dose attenuation, enrollment was terminated thereafter for patients with biliary tree malignancies. At the time that our study was initiated in 1997, data relating to hyperbilirubinemia and the risk of excessive toxicity from irinotecan was not fully known.[17,18] In retrospect, a bilirubin parameter of < 2.0 mg/dL as an enrollment criteria is probably too liberal for this patient population, albeit the median bilirubin level for our patients at entry to the current study was 1.15 ng/mL (range 0.4–1.5). A bilirubin level by itself may not express adequately the underlying degree of liver dysfunction. Alternatively, a more conservative starting dose of 100 mg/m^2 irinotecan might have resulted in better tolerance in this patient population, although the reason for choosing the full dose was that in most of the early Phase I studies of irinotecan most responders received higher dose levels.[12] Regardless, we think it reasonable to conclude that irinotecan has nominal activity and is difficult to administer at full dose in patients who have advanced hepatocellular carcinoma. Our findings are underscored by our recognition of the difficulties encountered when conducting a clinical trial in this patient population, where traditionally a small proportion of patients who have advanced hepatoma are able to participate, because of impaired performance status, thrombocytopenia attributed to portal hypertension and hypersplenism, as well as impaired hepatic function.

As with any cancer where the current best therapies are minimally effective, a strong emphasis on developing novel therapies for advanced hepatocellular carcinoma is necessary. Gemcitabine (2′, 2′ difluorodeoxycytidine) is one of the newer chemotherapeutic agents for treating advanced hepatomas that has shown some early promise and has a more favorable toxicity profile than older therapies.[19] Specula-

tively, gemcitabine combinations, or conventional cytotoxic therapies along with new biologic agents, may offer superior methods of disease palliation. Second or third generation topoisomerase-1 inhibitors that have greater in vitro potency and a more acceptable toxicity profile also may prove to have value in this disease.[20]

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