Phase II Study of Gemcitabine in Patients with Advanced Hepatocellular Carcinoma

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BACKGROUND. The objective of this study was to evaluate the efficacy and toxicity of gemcitabine in patients with chemotherapy-naïve, advanced hepatocellular carcinoma (HCC).

METHODS. Twenty-eight patients with unresectable and nonembolizable HCC who had received no prior systemic chemotherapy and with objectively measurable tumors, adequate liver and renal function, and adequate bone marrow reserve were enrolled on this study. The therapy consisted of gemcitabine 1250 mg/m^2 intravenously over 30 minutes weekly in an outpatient clinic. One course of treatment included three consecutive weekly infusions of gemcitabine and a 1-week rest. Treatment courses were repeated every 4 weeks for a total of six courses unless there was prior evidence of progressive disease.

RESULTS. All 28 patients were evaluable for response and toxicity. A partial response (PR) was achieved in 5 patients, for an overall response rate of 17.8% (95% confidence interval, 2.7–32.9%). Seven patients had stable disease (25%), and 16 patients had disease progression (57.2%). The median survival for all 28 patients was 18.7 weeks, and, for those patients who achieved a PR, it was 34.7 weeks. The median time to progression was 12 weeks. National Cancer Institute Common Toxicity Criteria Grade 3–4 toxicity consisted primarily of leucopenia (10.7%), anemia (14.3%), thrombocytopenia (10.7%), and hepatotoxicity (14.3%). The spectrum of both hematologic and nonhematologic toxicity was mild, with thrombocytopenia constituting the dose-limiting side effect.

CONCLUSIONS. Gemcitabine shows marginal antitumor activity in patients with advanced HCC, although the response duration is short-lived. Gemcitabine seems to be particularly promising because of its low toxicity profile. Further studies in combination with other active agents are warranted. ***Cancer* 2000;89:750–6.**
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Hepatocellular carcinoma (HCC) is one of the most common cancers worldwide. Although it is far less common in Western countries, it is the most common malignant tumor in areas of Africa and Asia.[1,2] HCC is the leading cause of cancer-related death in Taiwan.[3] Although a wide range of therapeutic options is available, the efficacy of these methods and the prognosis of patients with HCC remain very poor.[4] Surgical resection represents the only possibility of cure. However, resection rates for patients with HCC remain low because of a high incidence of associated cirrhosis, the direct invasion of tumor into the portal or hepatic vein, or early spread to the entire liver. Many nonsurgical local treatments, such as cryosurgery and radiation therapy, have been proposed; however, considerable uncertainty remains about their effectiveness.[4] Eventually, in most patients with HCC, the

disease progress to a far-advanced stage for which effective local treatment is not available. These findings stress the pressing need for efficacious, systemic chemotherapy for patients with inoperable HCC.

However, the role of chemotherapy in the treatment of patients with HCC remains controversial.[2,5] Numerous single chemotherapeutic agents and drug combinations have been given to HCC patients in an attempt to alter their predictably short survival time. Unfortunately, the activity of a single agent is limited, with only a few drugs showing a response rate $> 10\%$. Moreover, combination chemotherapy has proven equally disappointing, because additional drugs have resulted in increased toxicity without any increased efficacy compared with single-agent doxorubicin therapy.[2,5] At present, there is no drug or protocol of treatment that can be recommended as standard therapy for this group of patients. Due to the lack of any effective systemic chemotherapy, there is an urgent need to investigate new drugs.

Gemcitabine is a novel nucleoside analog that has a broad spectrum of antitumor activity in preclinical murine leukemia and solid tumor models.[6,7] A range of Phase I trials with gemcitabine has been conducted, and most experience has been gained in Phase II trials with a weekly schedule. This treatment regimen consists of the administration of gemcitabine once weekly for 3 weeks followed by a 1-week rest. When it is given this way, the drug is extremely well tolerated, with the major forms of toxicity being myelosuppression, mild flu-like symptoms, and a reversible skin rash. The maximum tolerated dose on this once-weekly schedule was defined in the first Phase I trial as 790 mg/m^2, and short-lived thrombocytopenia was found to be dose limiting[8]; however, patients entering that trial had been heavily pretreated, and it is now clear that a higher weekly dose (at least 1250 mg/m^2) can be given safely to previously untreated patients.[9] The antitumor activity of gemcitabine in patients with advanced HCC is unknown. In an in vitro study, Graziadei et al.[10] demonstrated that gemcitabine has strong antitumor activity on human hepatoma HepG2 cells. This finding suggests that gemcitabine may be a promising substance for further evaluation in the treatment of patients with HCC. Herein, we report on this Phase II study that evaluated the efficacy of gemcitabine in the treatment of patients with advanced HCC.

MATERIALS AND METHODS

Eligibility Criteria

From September 1998 to April 1999, 28 patients with chemotherapy-naïve HCC were entered into this study. The eligibility criteria included 1) pathology proven primary HCC or α-fetoprotein $\geq$ 400 ng/mL, with a hepatic tumor highly suggestive of HCC by imaging studies; 2) unresectable tumor and patient was not a candidate for either transcatheter arterial chemoembolization (TACE) or percutaneous ethanol injection (PEI); 3) bidimensional measurable diseases; 4) no previous systemic chemotherapy; 5) age between 16 years and 75 years; 5) Eastern Cooperative Oncology Group performance status $\leq$ 2; 6) adequate liver function with serum bilirubin $\leq$ 3.0 mg/dL and cirrhotic status of Child class A or B; 7) adequate hematology function with white blood cell (WBC) $\geq 3000/\text{mm}^3$ and platelets $\geq$ 100,000/mm3; and 8) adequate renal function with serum creatinine $\leq$ 2.0 mg/dL. Patients with any active infection, concurrent major systemic disease, or history of any other malignancy (except for basal cell carcinoma of the skin) were excluded. Patients with brain metastasis or recent esophageal bleeding (within 1 month) also were ineligible.

Patients who had received local therapy, such as surgery, TACE, or radiotherapy, before were allowed, provided the indicator lesion was outside of the radiation port and at least 3 weeks had elapsed since the completion of local therapy. All patients gave written, informed consent.

Treatment Protocol

The therapy consisted of gemcitabine 1250 mg/m^2 in a normal saline 100 mL intravenous infusion over 30 minutes in an outpatient clinic. One course of treatment included three consecutive weekly infusions of gemcitabine and a 1-week rest. Treatment courses were repeated every 4 weeks for a total of six courses unless there was prior evidence of progressive disease (PD). No dose escalation was allowed. The use of antiemetic premedication was left up to the discretion of the treating physician.

Prior to entry into the study, all patients provided a complete history and physical examination, including performance status, recent weight loss, and concurrent nonmalignant disease and therapy. Laboratory studies included a complete blood count, differential count, platelet count, biochemical liver and renal function tests, electrolyte, chest X-rays, α-fetoprotein, triphasic liver computed tomographic (CT) scan, and bone scan if clinical symptoms indicated. Serum hepatitis B surface antigen (HBsAg), serum hepatitis C virus antibody (anti-HCV), and Child class evaluation also were performed before treatment. Histology or cytology was reviewed by the Department of Pathology at Chang Gung Memorial Hospital. Patients were seen by a physician on a weekly basis during treatment for a brief history taking, physical examina-

tion, and toxicity assessment. A complete blood count was determined before every gemcitabine treatment. Renal and liver functions and α-fetoprotein levels were examined every 4 weeks. The tumor was assessed by chest X-ray every 4 weeks and by triphasic liver CT scan every 8 weeks. Determination of the tumor response followed standard response criteria established by the World Health Organization (WHO).[11] Response was graded according to WHO criteria as complete response (CR), partial response (PR), stable disease (SD), or progressive disease (PD). Investigator-determined responses were reviewed subsequently by an independent panel of oncologists and radiologists. All patients who had evidence of disease progression or who died without documented progression were considered to have PD.

Treatment was continued until one of the following criteria was met: disease progression, unacceptable toxicity, patient refusal, chemotherapy needed to be delayed more than 2 weeks or dose had to be reduced below 600 mg/m^2, or completion of six courses of therapy. Treatment was stopped after six courses of therapy even if patients continued to respond. Patients who were refractory to gemcitabine were allowed to receive salvage chemotherapy at the physician's discretion.

Toxicity Evaluation and Dose Modification

Toxicity was evaluated weekly, with particular attention paid to skin rash, fatigue, leucopenia, and thrombocytopenia. These toxic events were noted prospectively and were evaluated according to the National Cancer Institute Common Toxicity Criteria graduation. Once toxicity was demonstrated in any patient during one cycle, prophylactic medication was allowed in subsequent cycles. This generally included phenothiazines and steroid for nausea and emesis and an antihistamine and steroid for skin rash. On Days 1, 8, and 15, full dose therapy was given if patients had WBC $\geq$ 2000/mm^3, platelets $\geq$ 100,000/mm^3, and $\leq$ Grade 2 nonhematologic toxicity. If patients had WBC = 1000–2000/mm^3 or platelets = 50,000–100,000/mm^3, then 75% of the planned dose was given. If patients had WBC $<$ 1000/mm^3 or platelets $<$ 50,000/mm^3, then therapy was held that day, and all subsequent doses were reduced by 25%. Treatment was held at the setting of $>$ Grade 3 nonhematologic toxicity with the exception of nausea and emesis, and the subsequent dose of gemcitabine was reduced by 25%. Liver toxicity was difficult to assess in our series. Because all patients presented with impaired baseline liver function, it is difficult to differentiate the causes of liver toxicity among gemcitabine toxicity, viral hepatitis exacerbation, and disease progression. For patients with transaminase elevation during gemcitabine therapy, whether or not to modify the dose was assessed by investigators.

Statistical Considerations

The primary end point of this study was the response rate of this selected group of patients. The Simon optimal, two-stage, Phase II clinical trial design was used.[12] In the first stage, the study would have been stopped if none of the first nine evaluable patients had responded. An additional 15 patients were to be enrolled in the second stage if there were objective responses in the first nine patients.

The time to disease progression was measured from the start of therapy to the date of disease progression. The response duration was defined as the interval from the onset of PR until evidence of disease progression was identified. The survival time was calculated from the start of therapy to the date of death, and survival curves were established by using the Kaplan–Meier method.[13]

RESULTS

Patient Characteristics

Baseline patient characteristics and clinical features are summarized in Table 1. Twenty-eight patients were entered into this trial, and all were found to be eligible for assessment of response and toxicity. All patients except three had raised serum α-fetoprotein levels (normal $<$ 20 ng/mL). HBsAg and anti-HCV were positive in 22 patients (78.6%) and 5 patients (17.8%), respectively, and 1 patient was positive for both. A history of alcohol abuse ($>$ 80 g/day) was noted in 3 patients, all of whom had the HBsAg marker. The diagnosis of HCC was made based on biopsy of liver tumor or metastatic tumor in 16 patients (57.1%) and was based on fine-needle aspiration cytology of liver tumors in 6 patients (21.4%). The remaining 6 patients (21.4%) were diagnosed by a marked elevation of serum α-fetoprotein level accompanied by a clinical picture and imaging studies indicating advanced HCC. In this study, there were 17 patients (60.7%) with huge liver tumors ($>$ 10 cm) and 19 patients (67.9%) with extrahepatic metastases (including 11 with lung metastasis, 6 with bone metastases, 3 with lymph nodes metastases, 2 with pleural metastases, and 2 with adrenal gland metastases). The causes of unfeasibility for TACE included 11 patients with main portal vein thrombosis, 19 patients with distant metastases, and 9 patients with diffuse bilateral lobe involvement. Of the 8 patients who had failed TACE before, 6 patients had distant metastases, and 2 patients had progression of liver tumor after TACE.

TABLE 1
Patient Characteristics

Characteristic	No. of patients	%
Male:female (total)	21:7 (28)	
Median age in yrs (range)	52 (33–74)	
Performance status		
1	18	64.3
2	10	35.7
Cirrhosis		
HBsAg (+)	22	78.5
Anti-HCV (+)	5	17.8
Alcohol abuse	3	10.7
Cryptogenic	1	3.6
Child classification		
A	16	57.1
B	12	43.9
Okuda stage		
I	3	10.7
II	23	82.1
III	2	7.2
Previous treatment		
Operation surgery	1	3.6
PEI	1	3.6
TACE	8	28.6
Radiotherapy for bone metastasis	2	7.2
Diagnosis		
Biopsy	16	47.2
Cytology	6	21.4
α-Fetoprotein and imaging	6	21.4
α-Fetoprotein (ng/mL)		
< 400	7	25.0
400–10,000	9	32.1
$> 10{,}000$	12	42.9
Tumor status		
Liver tumor > 10 cm	17	64.3
Ascites	11	39.2
Main portal vein thrombosis	11	39.2
Bilateral lobe involvement	9	32.1
Distant metastasis	19	67.9

HBsAg: hepatitis B surface antigen; HCV: hepatitis C virus; PEI: percutaneous ethanol injection; TACE: transcatheter arterial chemoembolization.

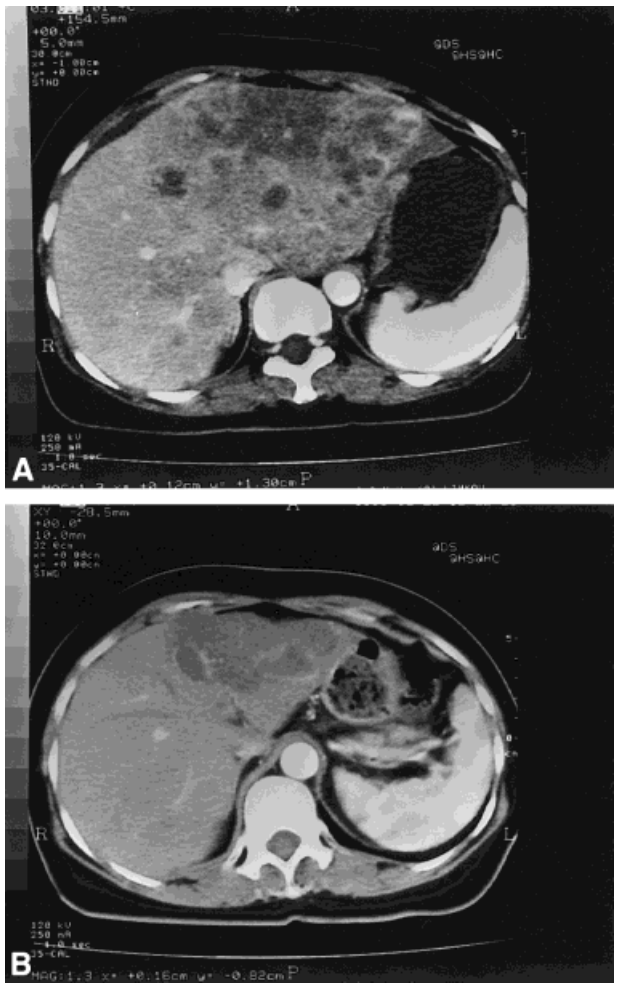

FIGURE 1. A case of hepatocellular carcinoma before treatment (A), and regression of the tumor after two courses of gemcitabine therapy (B).

Thus, almost all of our patients had far-advanced HCC.

Response and Survival

Response was evaluated in all 28 patients. Eighty-one courses of chemotherapy were administered. The median number of therapy courses was three (range, 1–6). Only three patients completed six courses of chemotherapy. All patient withdrawals from therapy were due to disease progression. Nine patients did not complete two courses of chemotherapy because of obvious disease progression or death, and the triphasic liver CT scan evaluation of response could not be taken. Two of these nine patients died of respiratory failure due to lung metastasis and hemoptysis, and chest X-rays revealed progression of lung metastasis. Another seven patients developed liver failure during gemcitabine treatment, and four patients had elevation of serum α-fetoprotein after the first course of chemotherapy. All nine patients were considered to have PD.

No patient achieved a CR, whereas five patients had a PR that lasted from 8.0 weeks to 15.1 weeks (Fig. 1). The median response duration was 13.4 weeks. This represents a 17.8% response rate (95% confidence interval, 2.7–32.9%) among the 28 patients in this series. Seven patients had SD (25%), and 16 patients had PD (57.2%). Among the eight patients who underwent TACE before, four had SD, and none achieved a PR. In addition, a decrease $> 50\%$ in α-fetoprotein level was found in 6 of 21 patients (28.6%) patients with pretreatment α-fetoprotein > 400 ng/mL.

As of November 1999, 22 patients had died, and 6 were still alive. The median survival for all 28 patients

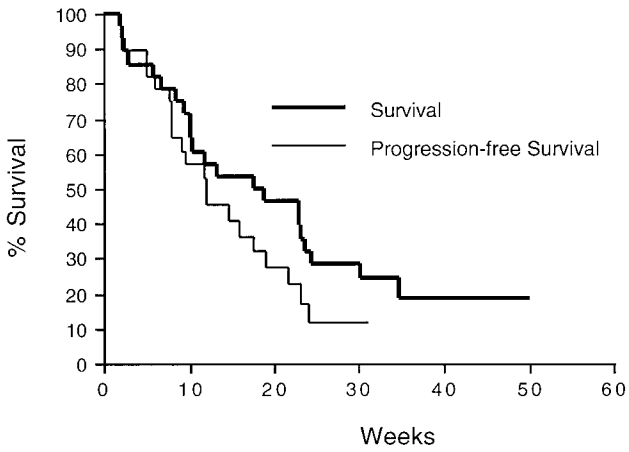

FIGURE 2. Survival and progression free survival curves.

TABLE 2
Maximum Severity of Toxicity (n = 28 patients)

	NCI common toxicity criteria grade					
Toxicity	**0**	**1**	**2**	**3**	**4**	**% of Grade 3 or 4**
Leucopenia	21	0	4	3	0	10.7
Anemia	12	9	3	4	0	14.3
Thrombocytopenia	12	4	9	2	1	10.7
Nausea	13	12	3	0	0	0
Emesis	19	4	5	0	0	0
Mucositis	23	3	2	0	0	0
Diarrhea	26	1	1	0	0	0
Alopecia	23	4	1	0	0	0
Hepatotoxicity	21	1	2	4	0	14.3
Skin rash	17	6	4	1	0	3.6
Fatigue	8	11	9	0	0	0
Infection	27	0	0	1	0	3.6

NCI: National Cancer Institute.

was 18.7 weeks, and, for those who achieved a PR, it was 34.7 weeks. The median time to disease progression was 12 weeks. The survival curves are shown in Figure 2.

Toxicity

Data on toxicity for all 28 patients are shown in Table 2. The toxicity recorded represents the maximum grade toxicity seen for a given patient for the entire course of therapy. Hematologic toxicity was mild: Only three patients (10.7%) experienced Grade 3 leucopenia. One patient was admitted to the hospital with febrile neutropenia and recovered rapidly. Two patients had Grade 3 and one patient had Grade 4 thrombocytopenia. There were no bleeding episodes. However, because platelets were relatively lower in patients with preexisting cirrhosis, thrombocytopenia was still the most important dose-limiting factor. Skin rash, gastrointestinal toxicity, and fatigue were frequent but usually were mild and were manageable in most patients. Four patients had 5-fold elevations of serum transaminase levels above the normal limiting value during treatment, but it was hard to differentiate the cause between gemcitabine toxicity, viral hepatitis exacerbation, or disease progression. One of the four patients developed acute liver failure and expired 1 week later due to hepatic encephalopathy. Chronic hepatitis exacerbation was considered in the other three patients because of an elevation $<$ 1-fold in the baseline serum transaminase level and because no symptoms were observed. These three patients continued chemotherapy without delay or dose reduction, and all of their serum transaminase levels returned to baseline levels within 1 month. Dose reduction or omission according to the protocol was administered in 14 patients. Most patients had to reduce the gemcitabine dose or had to omit a dose because of hematologic toxicity on Day 15. Due to Grade 3 or 4 toxicity, three patients had to reduce the dose on the subsequent treatment course. There were no drug-related discontinuations or toxic deaths.

DISCUSSION

Because the vast majority of patients with HCC are not candidates for curative surgery or other local therapy, systemic chemotherapy may be the only option. Unfortunately, HCC has generally been considered to be a chemoresistant tumor.[5] The antitumor activities of a number of chemotherapeutic agents have been evaluated in HCC patients, but most yielded poor results. The consensus is that no single agent or combination of agents given systemically leads reproducibly to a response rate $>$ 25% or has any effect whatever on patient survival. In addition, cytotoxic agents have lower response rates for patients with HCC and probably are associated with severe side effects. Therefore, many patients receive supportive care only.[5]

To improve the prognosis of patients with HCC, effective systemic chemotherapy must be developed. However, progress in treating HCC patients with chemotherapy has been disappointing. Doxorubicin remains the most active drug against HCC, with a single-agent tumor response rate of about 10–20%; however, the toxicity of doxorubicin often outweighs its benefit.[5,14,15] Doxorubicin still cannot be considered to be a satisfactory treatment for patients with this disease.[15] Chemotherapeutic agents other than doxorubicin have demonstrated even less activity.[5] New chemotherapeutic drugs, such as paclitaxel, raltitrexed, irinotecan, and nalatrexed, also have not demonstrated

encouraging results.[16–19] These new drugs exhibit some antitumor activity, but response rates rarely exceed 10%. Therefore, all patients with advanced HCC should be considered for joining well-designed Phase II trials with novel antitumor agents or regimens when patients can tolerate treatment. Because there was no previous Phase II trial of gemcitabine in patients with HCC, we commence this Phase II study to evaluate the efficacy of gemcitabine in the treatment of patients with advanced HCC.

The mechanism of the chemoresistant nature of most HCC is uncertain. One possibility may be related to a high incidence of multidrug resistance gene (MDR1) expression. More than 60% of tumors were positive for P-glycoprotein in patients with HCC.[20–22] In addition, cirrhosis, which usually is associated with thrombocytopenia and impaired liver function, can render patients unable to tolerate adequate doses of cytotoxic agents. Gemcitabine is a novel antimetabolite chemotherapeutic agent that is not refractory to MDR1, and its myelotoxicity is usually mild. Therefore, gemcitabine seems to represent a good opportunity for treating patients with advanced HCC.

In this Phase II study, gemcitabine was used to treat these far-advanced HCC patients. Despite the preentry selection of patients with favorable prognostic factors, only 19 of 28 patients (67.9%) completed two courses of gemcitabine treatment; therapy was stopped in all cases because of disease progression or death. Gemcitabine did show activity in these far-advanced HCC patients, and the toxicity was mild and acceptable. The response rate of gemcitabine against HCC was comparable to that of doxorubicin or any other single agent. The toxicity profile of this regimen was tolerated reasonably well compared with the doxorubicin regimen. However, the response duration was short-lived, and overall survival was not increased significantly.

Regarding toxicity, gemcitabine definitely was well tolerated. The spectrum of both hematologic and nonhematologic toxicity was mild. This regimen appears to be feasible for use in patients whose condition cannot tolerate doxorubicin treatment. Liver toxicity was difficult to assess in our series, because all patients presented with impaired baseline liver function. Despite the four patients who had marked increases in serum transaminase levels during gemcitabine therapy, these parameters usually worsened transiently and then recovered without dose reduction.

In conclusion, gemcitabine does show marginal activity in patients with advanced HCC, but the response duration is short- lived. Gemcitabine seems to be particularly promising because of its low toxicity profile. Considering the mild hematologic toxicity, this drug is a good candidate for combining with other cytotoxic drugs. The Phase II trial of combination chemotherapy with gemcitabine and doxorubicin is ongoing.

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