Original Article

Phase II Trial of Gemcitabine in Combination with Cisplatin in Inoperable or Advanced Hepatocellular Carcinoma

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Abstract

Introduction: Advanced hepatocellular carcinoma (HCC) has a dismal prognosis and is notoriously chemo-resistant. We conducted a Phase II prospective study to evaluate the activity and tolerability of gemcitabine and cisplatin in chemo-naïve advanced hepatocellular carcinoma. The trial considered a "no further interest" response rate of 10% and a target response rate of 30%. Utilising a Simon's minimax two-stage design with a type I error of 0.05 and power of 80%, 25 subjects would be required. Fifteen patients would be needed in stage 1 and if fewer than 2 responses were observed, the trial would be stopped and lack of efficacy claimed. Materials and Methods: Patients with advanced HCC, diagnosed based on histology or by World Health Organization (WHO) criteria, were administered gemcitabine 1000 mg/m^2 and cisplatin 25 mg/m^2 on day 1 and day 8 of a 21-day schedule. Assessment of response based on computer tomography was performed after every 2 cycles of chemotherapy. Results: The trial was stopped early due to a lack of efficacy. A total of 15 patients were accrued. Twelve patients were hepatitis B positive and the other 3 patients were negative for both hepatitis B and C. Only 1 patient had a history of prior heavy alcohol use. Two patients had Child C liver cirrhosis, 5 patients had Child B cirrhosis, and the remaining 8 patients had Child A cirrhosis. This regime was well tolerated and there was only 1 patient who experienced grade IV toxicities. Only 5 of 15 patients experienced grade III toxicities (nausea and emesis, 1 patient; anemia, 1 patient; thrombocytopenia, 1 patient; and neutropaenia, 2 patients). Only 1 patient experienced a partial response to the combination of gemcitabine and cisplatin. A further 3 patients experienced stable disease and 11 patients progressed on chemotherapy. The median time to progression was 6 weeks. The progression-free curve showed a sharp descent in the initial part of the study, suggesting that many patients had disease progression after enrolment. The median overall survival was 18 weeks. Conclusion: The progression-free survival and overall survival in our study were extremely short. Based on the results of our phase 2 study, we are unable to recommend further studies utilising gemcitabine and cisplatin combination in patients with advanced HCC.

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Key words: Cisplatin, Gemcitabine, Hepatitis B, Hepatocellular carcinoma

Introduction

Hepatocellular carcinoma (HCC) has a high incidence rate in Asia. In Singapore, it is the third most common cancer amongst males, and constituted 8% of all cancers diagnosed between 1998 and 2002.[1] High incidences of HCC are also seen in Hong Kong, Taiwan, China and Japan, where hepatitis B infection is endemic. In contrast, many cases of HCC in western countries, arise from liver cirrhosis secondary to alcohol or chronic hepatitis C infections.

Currently, surgery offers the only chance of improved survival. Unfortunately, most patients with HCC present at an advanced stage of disease and less than 10% are operable.[2] For unresectable HCC, the prognosis is dismal, with a median survival of approximately 6 months. Until recently, with the presentation of the results of the SHARP trial evaluating sorafenib in advanced HCC, there was no single chemotherapeutic agent or combination that had been considered standard therapy for patients with inoperable or metastatic HCC.[3]

Gemcitabine is an antimetabolite that has shown activity against HCC in preclinical models.[4] In phase 2 studies, gemcitabine was associated with a response rate between 0% and 18%.[5,6] In addition, a combination of gemcitabine

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with cisplatin was also reported to have a response rate of approximately 20%.[7,8] We, therefore, undertook a study to determine the response rate of the combination of gemcitabine and cisplatin in our population.

Materials and Methods

This prospective, single-institution, open-label, non-randomised, phase 2 study was conducted between May 2002 and November 2004. The diagnosis of HCC was made either by histology or using a combination of radiology [computed tomography (CT) scan] and serum alpha fetoprotein level of >500ug/L or a combination of radiology (CT scan) and positive lipoidal uptake on angiography.

Eligibility Criteria

Eligibility criteria for this study included patients with no prior chemotherapy for HCC, tumours not amenable to surgery, radiological or clinically measurable disease, Eastern Cooperative Oncology Group (ECOG) performance status <2, age 18 to 65 years, adequate bone marrow, hepatic and renal function, [white blood count >3000/uL, absolute neutrophil count >2000/uL, platelet count >100,000/uL, haemoglobin level >9.0 g/dL, creatinine <150 umol/L and calculated creatinine clearance test >60 mL/min, alanine aminotranferease (ALT)/aspartate aminotransferase (AST) <5 times the upper limit of normal values (ULN), bilirubin <2 times ULN], and no evidence of hepatic encephalopathy. Patients who had previously received local therapy such as surgery or transarterial chemoembolisation (TACE) were included in the study, provided the local therapy had been carried out more than 2 months before enrolment into the trial. Informed consent from all patients were required before participation in this study. Patients were excluded if they had prior chemotherapy for HCC, prior malignant disease, serious co-existing medical illness or if their remaining life expectancy was estimated to be less than 12 weeks.

Study Design

Patients were scheduled to receive a maximum of 6 cycles of chemotherapy. Therapy consisted of 1000 mg/m^2 of gemcitabine over 30 minutes and cisplatin 25 mg/m^2 over 2 hours given on day 1 and day 8 every 21 days. Chemotherapy was administered in an outpatient clinic setting. Treatment was continued until disease progression or unacceptable toxicity.

Toxicity was evaluated weekly according to the NCI-CTC toxicity grading (version 2). Adjustments of dose for myelosuppression were based on haematological data from day 1 of each cycle as well as at the nadir. On day 1 and day 8, full doses of gemcitabine and cisplatin were given if granulocyte count was greater than 1500/uL, platelets greater than 75,000/uL, and if there was no grade 3 to 4 non-haematological toxicity. The dose of gemcitabine was reduced by 25% if the granulocyte count was between 1000/uL and 1499/uL or if platelet count was between 50,000/uL and 75,000/uL. Gemcitabine was withheld if granulocyte count was less than 1000/uL or if platelets was less than 50,000/uL. If the patient's calculated creatinine clearance was less than 40 mL/min or if the creatinine level was more than 1.5 times the ULN, cisplatin was withheld for that week.

The dose of gemcitabine in subsequent cycles was reduced by 25% if in the preceding cycle the platelet count fell to less than 25,000/uL, or if the platelet count fell to less than 50,000/uL with associated with bleeding. A similar dose reduction was made for a granulocyte count of less than 500/uL associated with fever of at least 38.5°C or with documented infection. Dose reductions were also made for elevation of bilirubin or AST/ALT more than five-fold above baseline, and any other grade 3 or 4 CTC non-haematological toxicity, with the exception of nausea, vomiting and alopecia.

Treatment was discontinued if patients experienced delays in administration of chemotherapy of greater than 2 consecutive weeks due to haematological toxicity. Prophylactic colony-stimulating factors were not allowed in this study.

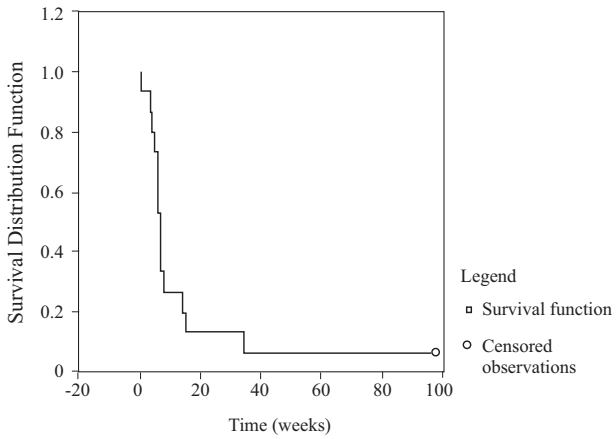

Fig.1. Progression-free survival.

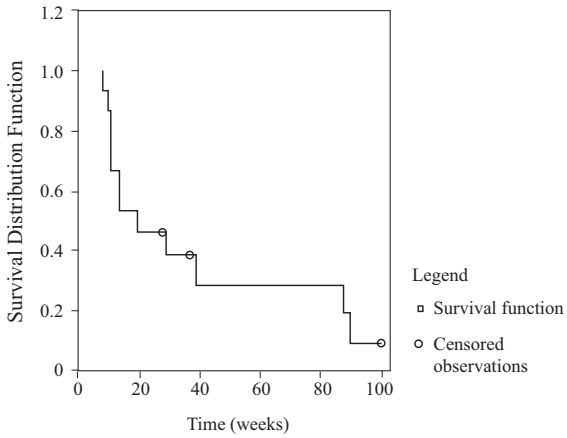

Fig. 2. Overall survival.

Treatment Assessment

Prior to enrolment into the study, all patients had provided a complete medical history and physical examination. EGOG performance status was also noted. A baseline CT scan was required and laboratory studies included a complete blood count, differential count, platelet count, biochemical liver and renal function tests. Hepatitis B surface antigen, E antigen and E antibody were performed at baseline. If the patient was Hepatitis B positive, a HBV DNA viral titre was assessed.

During treatment, patients were seen on day 1 and day 8 of each cycle, and body weight and ECOG performance status were noted. A complete blood count was performed before each chemotherapy treatment (D1 and D8). Liver and renal biochemistries were performed on day 1 of the therapy. CT scans were performed after 2 cycles of chemotherapy. Patients who were hepatitis B positive had their DNA titre quantified before each cycle of chemotherapy.

Statistical Consideration

Our study was an open-labelled, non-randomised and single-institution study.

The primary endpoint of the study was to assess the response rate according to the World Health Organisation (WHO) criteria. The secondary endpoints were the evaluation of progression-free survival and toxicity of chemotherapy at the dosages given.

A total of 25 subjects were to be recruited for the trial, which assumed a target response rate of 30% and no further interest in the combined agent if the response rate was 10% or lower. Using Simon (1989) two-stage design with a type I error of 5% and a power of 80%, 15 patients were to be enrolled in Stage 1. If 2 or more responses were observed, the trial will move on to Stage 2, with an additional recruitment of 10 patients. If at least 6 responses out of a total of 25 subjects were observed, the study would claim the treatment to be efficacious and recommend phase 3 trials.

Sample estimates and corresponding 95% confidence intervals were to be computed for the response rates. The confidence interval would be estimated using the Wilson method.[9] Progression-free survival and overall survival were estimated from Kaplan-Meier estimator on SAS 9.1.

Survivors are censored at the date of last follow-up or for those who were lost to follow-up, the date of last contact.

Results

Patient Characteristics

From May 2002 to December 2004, 15 patients were enrolled in the study. Baseline patient characteristics and clinical features are summarised in Table 1. The majority of patients were hepatitis B-positive and only 1 patient had a prior history of heavy alcohol use. With the exception of 1 female, the entire study group consisted of male patients and the median age of patients in our study was 51 years. Although the majority of patients had good ECOG performance status, half had poor hepatic function with Childs B or Childs C liver cirrhosis. In addition, two thirds of patients had large primary tumours (diameters of more than 10 cm) and approximately half of the patients enrolled had metastatic disease. Four patients had prior resection of HCC and 2 patients had prior TACE.

Toxicity

Chemotherapy was generally well tolerated (Table 2). Only 1 patient experienced a grade 4 toxicity. Four patients (27%) experienced grade 3/4 neutropenia, 2 patients (13%) suffered grade 3 thrombocytopenia and 1 patient experienced grade 3 anaemia. A total of 39 cycles of chemotherapy was administered and grade 3/4 neutropenia was observed in 15% of the total cycles administered. Thrombocytopenia and anaemia were seen in 5% and 2.5% of the total chemotherapy cycles administered.

The main grade 3/4 non-haematological toxicity was nausea and vomiting occurring in 5% of chemotherapy cycles administered. Grade 3/4 neuropathy was not seen. Elevated transaminases were commonly observed in patients even before enrolment into the study. No patients experienced hepatitis B flare (as defined by an elevation of AST or ALT more than 5 times the upper limit of normal). One patient however during chemotherapy, experienced an asymptomatic elevation of hepatitis B viral DNA titre to 127, 022 copies/mL. This patient was treated with lamivudine with complete suppression of hepatitis DNA titre to undetectable levels thereafter.

Five patients experienced dose delays because of chemotherapy-related toxicities. The main reason for discontinuing chemotherapy was progression of disease.

Response and Survival

There was no complete tumour response to chemotherapy and only 1 partial response was observed. Therefore the overall response rate was 6.7% [95% confidence interval (CI) 1.2% to 29.8%)]. As the response rate did not meet the Stage 1 criterion of Simon's minimax two-stage design, the trial had to stop. Three patients had stable disease and 1 of them decided to pull out from the study. The remaining 11 patients had disease progression.

One patient had a clinical disease progression after Cycle 1 and could not continue to Cycle 2. The tumour was not evaluated and no date was captured. The date used in the analysis for disease progression was the date when the patient had the clinical physical examination. The median follow-up time was 18 weeks (range, 7.4 to 96.7). Three patients were still alive at time of analysis; they were

Table 1. Patient Characteristics

Characteristic	No of patients	%
Male	14	93
Female	1	7
Median age (range) – y	51 (23-64)	
Performance status		
0	6	40
1	8	53
2	1	7
Hepatitis B positive	12	80
Hepatitis B/C negative	3	20
Childs classification		
A	8	53
B	5	33
C	2	14
Okuda stage		
I	4	27
II	9	60
III	2	13
AFP level (ug/L)		
<500	3	20
>500-10,000	6	40
>10,000	6	40
Tumour status		
Liver tumour >10 cm	10	67
Ascites	5	33
Main portal vein thrombosis	9	60
Distant metastasis	7	46
Diagnosis		
Histology	5	33
CT and AFP	9	60
CT and angiography	1	7
Previous treatment		
Surgery	4	27
TACE	2	13

AFP: alpha fetoprotein; CT: computed tomography; TACE : transarterial chemoembolisation

censored at 26, 35 and 96 weeks.

The Kaplan-Meier estimate of median time to progression was 6 weeks (95% CI: 5.1 to 7.0 weeks). The estimated median survival was 18 weeks (95% CI: 10.0 to 84.4) and the 6-month estimated survival rate was 46.7% (95% CI: 21.2% to 68.8%).

Discussion

Although many agents have been used in advanced HCC, there is still no recognised standard of care. One of the most frequently used single agents, doxorubicin, has a response rate of less than 20%. Single agents such as 5-fluorouracil, cisplatin, paclitaxel and irinotecan have been evaluated but all have shown disappointing results.[10,11] Combination chemotherapy regimens such as PIAF (cisplatin, interferon, doxorubicin, 5-fluorouracil) have also not shown to improve survival when compared to single-agent doxorubicin in randomised phase 3 studies.[12]

Table 2. Grade 3 and 4 Toxicity

Toxicity	No. of patients (%)	
	Grade 3	Grade 4
Neutropenia	3 (20)	1 (7)
Thrombocytopenia	2 (13)	0
Anemia	1 (7)	0
Nausea	1 (7)	0
Emesis	1 (7)	0
Fatigue	1 (7)	0

In our current study, although the gemcitabine and cisplatin combination was generally well tolerated, we did not observe any clinical efficacy in our study population. The study was terminated early after planned interim analysis in 15 patients showed the lack of efficacy. Only 1 patient (7%) had partial response and 3 patients (20%) had stable disease. The remaining 11 patients (73%) had progression of their disease. The median progression-free survival was 6 weeks and the median overall survival was 18 weeks. The sharp descent of the progression-free survival curve in the initial part of the study suggests that many patients had disease progression shortly after enrolment and chemotherapy.

Two other phase 2 studies exploring the use of gemcitabine and cisplatin combination in the same setting have reported contrasting findings. In the study by Parikh et al,[7] 30 patients with unresectable HCC were administered gemcitabine 1250 mg/m^2 on day 1 and day 8 of a 21-day schedule, with cisplatin 70 mg/m^2 given on Day 1. Out of 30 evaluable patients, 6 patients (20%) achieved partial response and 13 patients (43%) experienced disease stabilisation. The median time to progression was 18 weeks and the median overall survival was 21 weeks.

In the study by Yang et al,[8] 47 patients were administered gemcitabine at 1250 mg/m^2, and cisplatin 35 mg/m^2 on day 1 and day 8 for each 21-day schedule. The authors in this study observed 1 complete response and 9 partial responses (overall response rate, 21%). The progression-free survival was 3.2 months (approximately 13 weeks) and median overall survival was 6/4 months (26 weeks). This treatment was moderately toxic with 43% of patients experiencing grade 3/4 anemia, 30% patients having grade 3/4

neutropenia, and 26% grade 3/4 thrombocytopenia. In addition, there were 9 episodes of gastrointestinal (GI) bleeding during treatment but no deaths occurred.

It is difficult to explain the differences in response rate in our study as compared to the studies by Parikh et al and Yang et al. Although our study and the study by Yang et al use WHO criteria to determine response, simple bi-dimensional CT measurements may underestimate the benefit of chemotherapy as it does not take into account the degree of tumour necrosis which may not parallel the reduction in diameter of the lesion.[13] The duration of response is more important and in this respect, and in our study, patients' disease progressed rapidly despite chemotherapy indicating a lack of benefit of the combination. Interestingly, the median survival of patients in our study was not very far from the results obtained by Parikh et al (18 weeks versus 21 weeks).

The heterogeneity of HCC patients enrolled into chemotherapeutic trials also poses challenges to the interpretation of response rate and survival data. Oncologists treating patients with HCC in reality confront 2 diseases – chronic liver cirrhosis and liver cancer. It is often difficult to assess the benefit of a particular chemotherapy regimen when the chance of survival is determined not just by the efficacy of chemotherapy, but also intimately related to the degree of hepatic dysfunction. To confound matters further, there is also evidence that chemotherapy works less efficiently in patients with significant cirrhosis.[14]

Eighty-six per cent of patients in our study were hepatitis B-positive and 93% of them were males. This is in contrast to the study by Yang et al where only 70% of patients were hepatitis B-positive. Even though the majority of patients in our study had good performance status (only 1 patient had an ECOG of 2), more than half of them had significant hepatic impairment – 47% had Childs B and Childs C liver cirrhosis. The patients in our study also had large tumours (67% of tumours were more than 10 cm in diameter), and 60% had portal vein invasion. Forty six per cent of patients also had metastatic disease.

The scheduled dose intensity of gemcitabine and cisplatin in our study was lower than that in the other 2 studies, although the mean dose intensity administered in the other 2 trials were not available for direct comparison. In the study by Yang et al, gemcitabine was administered at 1250 mg/m^2 and cisplatin at 35 mg/m^2, both given on day 1 and 8 of a 21-day schedule. Although it would be tempting to speculate that the response rate may have been higher with an increased dose, it is possible that the increased toxicities would outweigh the marginal benefits of chemotherapy. In the study by Yang et al, the higher doses of chemotherapy were associated with higher toxicities as compared with our study (Grade 3/4 anaemia was 43% versus 7%, neutropenia was 30% versus 27%, thrombocytopenia was 26% versus 13% respectively). Even with the lower-dose chemotherapy dose intensity, one-third of our patients still experienced dose delays because of toxicities.

Conclusion

The progression-free survival and overall survival in our study were extremely short and may reflect both the aggressive biology of this cancer as well as the fairly advanced hepatic dysfunction in our study population. Based on the results of our phase 2 study, we are unable to recommend further studies utilising gemcitabine and cisplatin combination. New approaches utilising novel small molecule inhibitors and anti-angiogenesis agents should be actively pursued.

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