Complete Pathological Remission Is Possible with Systemic Combination Chemotherapy for Inoperable Hepatocellular Carcinoma


ABSTRACT

The purpose of this Phase II study was to determine the response rate, the toxicity, and the effect on survival of the combination of cisplatin, doxorubicin, 5-fluorouracil, and α-IFN (PIAF) in advanced unresectable hepatocellular carcinoma. Fifty patients with either unresectable or metastatic disease were treated with PIAF: cisplatin (20 mg/m² i.v., days 1–4), doxorubicin (40 mg/m² i.v., day 1), 5-fluorouracil (400 mg/m² i.v., days 1–4), and α-IFN (5 MU/m² s.c., days 1–4). Treatment was repeated every 3 weeks to a maximum of six cycles. All patients were evaluable for response, toxicity, and survival. As assessed by conventional imaging criteria, there were no complete responses, but 13 patients (26%) had a partial response. Among the 36 patients who had an initially high α-fetoprotein level (>500 ng/ml), 15 (42%) had a >50% fall after therapy. Nine patients underwent surgical resection after achieving partial response and, in 4 of these patients, histological examination of the resected specimens revealed no viable tumor cells. All these nine patients are alive, and eight patients remain in complete remission at between 7.6 and 25.8 months at the time of analysis. The overall median survival was 8.9 months. Toxicity was mainly myelosuppression and mucositis. There were two treatment-related deaths due to neutropenic sepsis. PIAF is active in hepatocellular carcinoma despite considerable hematological toxicity. Complete pathological remission is possible with this systemic combination. Apparently, persistent radiological lesions may still represent complete pathological resolution of active disease.

INTRODUCTION

HCC is one of the most common malignancies worldwide. It is the second most common cancer in Hong Kong, with an age-standardized incidence rate of 47 per 100,000 (1). HCC is mainly associated with chronic hepatitis B and, less commonly, hepatitis C virus infection in Chinese populations. Surgical resection is the only treatment for HCC that consistently offers the hope of cure. However, only 9–27% of patients are suitable for resection (2, 3). Reasons for being inoperable are commonly the presence of advanced cirrhosis, large primary lesion, multifocal disease, invasion or thrombosis of major blood vessels, and poor liver function. Thus, the majority of patients present at an inoperable stage and have a dismal prognosis of median survival of only 4.1 months (4). HCC is only moderately sensitive to systemically administered single agents. Doxorubicin is commonly used, but the objective RRs from 13 published trials were <20%, and the median survival was only 4 months (5). Other active single agents include 5-FU (Ref. 6; RR, 17%) and cisplatin (Ref. 7; RR, 17%). The combination of doxorubicin and cisplatin by the intrahepatic-arterial route is more active (RR, 56%; Ref. 8).

IFNs are proteins produced by cells in response to viral infection and foreign antigens. They have immunomodulatory and antiproliferative effects on tumor cells. α-IFN has a modest degree of activity in HCC as a single agent and was reported to be superior to doxorubicin in one randomized study in terms of survival, tumor regression rates, and toxicity (9). IFN and 5-FU have synergistic activity both in cell lines (10) and clinically in colonic cancer (11). α-IFN was combined with 5-FU to treat advanced HCC in one study, and an objective RR of 18% was documented (12). More durable responses were seen in patients with a low serum AFP level in this study. However, a subsequent study involving 10 patients with HCC, and using the same combination of 5-FU and α-IFN, could not confirm these findings (13).

In this phase II trial, cisplatin, doxorubicin, 5-FU, and α-IFN were chosen because of the in vitro synergistic activity (between 5-FU and α-IFN), lack of cross-resistance and, except for the payment of page charges. This article must therefore be hereby marked advertisement in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.

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2 The abbreviations used are: HCC, hepatocellular carcinoma; RR, response rate; 5-FU, 5-fluorouracil; AFP, α-fetoprotein; PIAF, combination of cisplatin, doxorubicin, 5-FU, and α-IFN; CT, computed tomography; CR, complete response; PR, partial response; SD, static disease; PD, progressive disease; UR, unclassified response; SIR, selective internal radiation.
for bone marrow suppression, different toxicity profiles. This combination of drugs, which was initially designed and used at the University of Texas M.D. Anderson Cancer Center, was modified at The Chinese University of Hong Kong to a regimen that was suitable for out-patient administration. The objective of the study was to determine the RR and toxicity of PIAF for the treatment of advanced unresectable HCC and the effect on survival.

## PATIENTS AND METHODS

This was a single arm open label Phase II study. All patients were ethnic Chinese, referred to the Joint Hepatoma Clinic at the Prince of Wales Hospital (Hong Kong). Patients between 16 and 70 years of age with either inoperable or metastatic HCC were eligible. Inoperable disease was defined as either lesion too large for resection, regional lymph node involvement, presence of multifocal disease, or invasion of major blood vessels, including main portal vein thrombosis. The diagnosis of HCC was made either by histological examination of tumor tissue or imaging evidence of a space-occupying lesion in the liver together with a serum AFP concentration of above 500 ng/ml (normal value <10 ng/ml) in a known carrier of the hepatitis B virus surface antigen. Other inclusion criteria included: Karnofsky performance score >70%, platelet count >100 × 10^9/liter, WBC count >3 × 10^9/liter, total bilirubin <50 μmol/liter, creatinine clearance >50 ml/min, and informed consent. Patients were excluded if there was a history of prior malignancy, cardiac disease, or renal disease or if there was significant concurrent medical illness or ascites not controllable by medical therapy. The disease was required to have at least one site measurable in two dimensions by radiological means (CT scan, ultrasound, or plain radiograph). Patients with bone metastasis as the only site of disease were excluded. Previous treatment including surgery, radiotherapy, nonanthracycline-based chemotherapy, or chemoembolization did not exclude patients, provided they had a 1-month treatment-free period before entry.

### Treatment Plan

Patients were treated on an outpatient basis according to the regimen shown in Table 1. All i.v. treatment was given through a peripheral vein. Cisplatin (20 mg/m²) was given i.v. in 1 liter of normal saline solution over 1 h, daily for 4 days. 5-FU (400 mg/m²) was given as a short i.v. infusion daily for 4 days. Recombinant α-IFN-2b (5 M.U./m²; Intron-A, Schering-Plough Inc., Kenilworth, NJ) was given s.c. daily for 4 days. Doxorubicin was given on day 1 of each cycle at a dosage of 40 mg/m². Metoclopamide and dexamethasone were given before chemotherapy to control nausea and vomiting. Treatment was repeated every 3 weeks or delayed 1 week until the platelet count was >100 × 10^9/liter and WBC count was >3 × 10^9/liter. The maximum number of cycles was six.

### Evaluation of Response and Toxicity

A baseline ultrasonogram or CT scan was done on entry into the trial, after three cycles, and at termination of treatment to measure all of the lesions bidimensionally. Serum AFP levels were measured in all patients on the 1st day of treatment of each cycle and at the end of treatment. Complete blood picture, renal and liver function tests, were performed on day 1 of each cycle. Other symptoms were recorded on the days of blood sampling. Grading of toxicity was according to the WHO classification (14). The worst grading was taken as the overall toxicity grading.

### Definition of Objective Response

CR was defined as the complete disappearance of all known lesions on radiological grounds and normalization of the AFP level for at least 4 weeks. PR was defined as a decrease of 50% or more in the product of two perpendicular diameters of the largest tumor nodule for at least 4 weeks without the appearance of new lesions or progression of lesions. SD (static disease) was defined as a <50% decrease, or not more than a 25% increase, in the product of two perpendicular diameters of the largest tumor nodule. PD was defined as a >25% increase in the product of two perpendicular diameters of the largest tumor nodule or one of the measurable lesions, or the appearance of new lesions. Patients who did not survive to reassessment by radiological methods were considered to have UR. Calculation of RRs was based on the intent to treat.

### Statistical Methods

Simon’s (15) optimum two-stage Phase II design was used in this trial. Assuming the target and lower activity of the combination chemotherapy to be 25% and 10%, respectively, 21 patients are required in the first stage of accrual and, if there are more than two objective responses in the first stage, a total of 50 patients will be accrued. This gives a probability of 65% for early termination after the first stage when the true objective RR is ≤10%. Survival duration was calculated from the 1st day of chemotherapy. Actuarial survival was calculated by the Kaplan-Meier method.

### RESULTS

Fifty patients were entered into the trial from July 1996 to March 1998, and results were analyzed in August 1998. There were 46 male and 4 female patients, ages 30–67 years (median, 46). The median Karnofsky performance score was 90% (range, 80–100%). All patients were chemotherapy naïve, except for one who had failed a nonanthracycline Phase II agent. Thirty-five patients had evaluable disease in the liver only, whereas 15 patients also had extrahepatic disease. Forty-seven (94%) patients were hepatitis B surface antigen seropositive. All patients had an abnormal serum AFP level (>10 ng/ml), with a median value of 3,848 ng/ml (range, 19–1,922,300). The median largest tumor diameter was 10 cm (range, 0.5–22). There were 13 (26%) and 37 (74%) patients who had Okuda stage (4) I and II, respectively. A summary of the patients’ characteristics is shown in Table 2.

### Response

A total of 163 courses of PIAF were delivered, with a median number of three cycles per patient. Only 12 patients received the full six cycles, with the remainder receiving less due to intolerable toxicity (9 patients) or nonresponsive

### Table 1

<table>
<thead>
<tr>
<th>Treatment regimen</th>
<th>Days</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cisplatin (20 mg/m²)</td>
<td>1 2 3 4 21 (repeat every 3 weeks)</td>
</tr>
<tr>
<td>Doxorubicin (40 mg/m²)</td>
<td>1 2 3 4 21 (repeat every 3 weeks)</td>
</tr>
<tr>
<td>5-FU (400 mg/m²)</td>
<td>1 2 3 4 21 (repeat every 3 weeks)</td>
</tr>
<tr>
<td>α-IFN (5 M.U./m²)</td>
<td>1 2 3 4 21 (repeat every 3 weeks)</td>
</tr>
</tbody>
</table>
Chemotherapy for HCC

Surgical Resection after PR. Nine patients underwent surgical resection of residual lesions after achieving PR after chemotherapy. Reasons for being inoperable before PIAF were presence of extrahepatic disease (three patients), lesions too large for resection (four patients), and multifocal disease (two patients). All patients had received total of six cycles of PIAF. In four patients, histological examination of multiple sections through the resected specimens showed only necrotic tissue without any viable tumor cells. All patients were classified as having achieved PR on imaging grounds, but all had normalization of the serum AFP level after six cycles of chemotherapy. The other five patients had minimal residual disease on pathological examination. All nine patients who underwent surgical resection remain alive, and eight of them are in complete remission 7.6–25.8 months after the start of treatment. Pre- and posttreatment CT scans of one of the patients who underwent resection after chemotherapy are shown in Fig. 1, a and b.

Survival. At the time of analysis, 20 patients remained alive, including the 9 patients who underwent surgery. There were two defaults and 28 deaths. The median survival was 8.9 months. One of the patients, who had a complete pathological remission after chemotherapy and surgery, had the longest survival of 25.8 months from the 1st day of chemotherapy. The Kaplan-Meier actuarial survival curve for all patients is shown in Fig. 2.

Toxicity. The treatment carried with it considerable toxicity (Table 4). The majority of the patients had significant myelosuppression, especially leukopenia (grade 3 or more, 34%) and thrombocytopenia (grade 3 or more, 22%). Seventeen patients (34%) developed grade 3 or grade 4 leukopenia, resulting in two deaths from sepsis. Mucositis, drug fever, and vomiting were usually mild to moderate. Alopecia of grades 2 or 3 was commonly seen. Renal toxicity was mild, except in one patient who developed grade 3 toxicity.

DISCUSSION

Although surgery offers the only hope of cure for HCC, patients with inoperable or metastatic disease have a dismal prognosis (4). For disease confined to the liver, various locoregional treatments may offer useful palliation. These include intra-arterial infusion of combination chemotherapy (16, 8), chemoembolization (17, 18), and SIR treatment (19). Hepatic arterial infusion of floxuridine, leucovorin, doxorubicin, and cisplatin has produced an objective response in 41% of patients and a median survival of 12 months, but has significant toxicity, especially in patients with positive hepatitis serology (16). Carr et al. (8) used combination cisplatin and doxorubicin through an intra-arterial route, producing a RR of 50% and median survival of 15 months. Chemoembolization is widely practiced, but has not been shown to prolong survival in randomized trials (17, 18). SIR treatment with yttrium-90 microspheres treatment is quick, effective, and less toxic compared with other palliative modalities (19). However, this is only possible in selected cases, and delivery requires specialized facilities. Patients with extrahepatic disease, blocked portal venous system, are usually not candidates for intra-arterial treatment, and systemic chemotherapy is the only remaining option. However, single-agent chemotherapy has met with only very limited success. A study that randomized 60 patients to receive either no active treatment or chemotherapy has met with only very limited success. A study that randomized 60 patients to receive either no active treatment or chemotherapy has met with only very limited success. A study that randomized 60 patients to receive either no active treatment or chemotherapy has met with only very limited success. A study that randomized 60 patients to receive either no active treatment or chemotherapy has met with only very limited success. A study that randomized 60 patients to receive either no active treatment or chemotherapy has met with only very limited success.

α-IFN is used in the treatment of chronic hepatitis B and C infections. Its antiproliferative and immunomodulatory activity

### Table 2 Patient Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Number</th>
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</thead>
<tbody>
<tr>
<td>Total no. of patients</td>
<td>50</td>
</tr>
<tr>
<td>Male:Female</td>
<td>46:4</td>
</tr>
<tr>
<td>Median age (range)</td>
<td>46 (30–67)</td>
</tr>
<tr>
<td>HBsAg positive</td>
<td>47 (94%)</td>
</tr>
<tr>
<td>Median total bilirubin level (μmol/liter; range)</td>
<td>12.5 (3–45)</td>
</tr>
<tr>
<td>Median serum albumin level (g/liter; range)</td>
<td>33 (22–45)</td>
</tr>
<tr>
<td>Median AFP (range) ng/ml</td>
<td>3848 (19–1922300)</td>
</tr>
<tr>
<td>No. of biopsy-proven HCC cases</td>
<td>27</td>
</tr>
<tr>
<td>Median largest diameter of tumor (range) cm</td>
<td>10 (0.5–22)</td>
</tr>
<tr>
<td>Okuda staging</td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>13 (26%)</td>
</tr>
<tr>
<td>II</td>
<td>37 (74%)</td>
</tr>
<tr>
<td>AJCC* staging</td>
<td></td>
</tr>
<tr>
<td>II</td>
<td>4 (8%)</td>
</tr>
<tr>
<td>IIIA</td>
<td>3 (6%)</td>
</tr>
<tr>
<td>IIIB</td>
<td>5 (10%)</td>
</tr>
<tr>
<td>IVA</td>
<td>28 (56%)</td>
</tr>
<tr>
<td>IVB</td>
<td>10 (20%)</td>
</tr>
<tr>
<td>Site(s) of disease</td>
<td></td>
</tr>
<tr>
<td>Liver only</td>
<td>35</td>
</tr>
<tr>
<td>Lung metastases only</td>
<td>1</td>
</tr>
<tr>
<td>Pelvic recurrence only</td>
<td>1</td>
</tr>
<tr>
<td>Both liver and extrhepatic site(s)</td>
<td>13</td>
</tr>
<tr>
<td>Median no. of courses (range)</td>
<td>3 (1–6)</td>
</tr>
</tbody>
</table>

* AJCC, American Joint Committee on Cancer.

### Table 3 Tumor Responses

<table>
<thead>
<tr>
<th>Response</th>
<th>No. of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>PR</td>
<td>13 (26%)</td>
</tr>
<tr>
<td>SD</td>
<td>14 (28%)</td>
</tr>
<tr>
<td>PD</td>
<td>15 (30%)</td>
</tr>
<tr>
<td>UR</td>
<td>8 (16%)</td>
</tr>
</tbody>
</table>
has also led to indications in some hematological malignancies, including chronic myeloid leukemia, hairy cell leukemia, and low-grade lymphoma. It is also used in the treatment of pulmonary angiomatosi s because of its antiangiogenesis effects. α-IFN has been used as a single agent to treat advanced HCC and produced a RR of 31.4% and a small improvement in survival (9). However, the large dose of IFN (50 M.U./m², 3 times/week) used in this study resulted in significant toxicity.

In the light of these observations, the present study aimed to improve efficacy of systemic chemotherapy by combining four relatively active drugs that have synergistic activity. Patients with inoperable disease or extrahepatic disease, who were not suitable for regional intra-arterial treatment, were studied for efficacy and toxicity from this new combination. The treatment resulted in an objective RR of 26% and a median survival of 8.9 months that are comparable with, or better than, most Phase II systemic chemotherapy trials. Although the results look inferior to other series using regional intra-arterial treatment, the majority of the patients in the present study was not suitable for regional treatment due to presence of metastasis or portal venous obstruction.

A significant reduction of serum AFP levels (>50%) occurred in 42% of patients, although the objective RR by conventional radiological methods was less. It is possible that, in such cases, the tumor actually responds to treatment, but this is not reflected by conventional radiological changes. Thus, four

![Fig. 1](image)

**Fig. 1** A, pretreatment CT scan of a 42-year-old male with an inoperable HCC, 22 cm in diameter. The HBsAg status was positive, and the serum AFP was 71,000 ng/ml before treatment. B, posttreatment CT scan of the same patient after six cycles of chemotherapy. The patient achieved a PR, and the serum AFP fell to 1,029 ng/ml. This patient had PR after chemotherapy and received a partial hepatectomy 7 months after the initiation of chemotherapy. Residual disease was confined to the core of the lesion, whereas the rest of the lesion was largely necrotic.
patients had a complete pathological remission that was documented histologically after surgical resection of residual lesions. This suggests that the type of systemic chemotherapy used in the present study, as a single modality, is able to eradicate the disease. It also emphasizes that residual lesions, on conventional radiological grounds, may not represent active disease, an observation we have made previously after SIR (19). Additional studies are required to correlate tumor regression, reduction of serum AFP, and pathological response after chemotherapy. Using radiological regression as the sole criterion for response may have previously undermined some active agents or combinations of agents, especially when the serum AFP estimation could not be used to monitor response, due to low or negative pretreatment levels.

There were nine patients (18%) who initially had inoperable disease due to various reasons and subsequently underwent surgical resection of residual lesions after PIAF. All of them had achieved complete clinical remission after surgery, and eight of them had sustained remission from 7.6 months to as long as 25.8 months from start of treatment. Thus, the PIAF regimen was able to convert nearly 20% of inoperable lesions into operable. Because about 80% of HCC patients have inoperable disease at presentation (3), induction chemotherapy with PIAF may significantly increase the overall operability rate of HCC. In the case of hepatoblastoma in children, it is well accepted that preoperative chemotherapy with cisplatin or doxorubicin containing combinations can decrease the size of tumor. This facilitates surgical excision and leads to improved treatment results (21, 22). Using the PIAF combination, the treatment of HCC in the adults may follow the same path.

Even for patients who have operable disease at presentation and have their tumor successfully resected, there is still a high rate of early recurrence, giving a 5-year disease-free survival rate of 17% and an overall survival rate of 28% from a local study (23). Postoperative adjuvant PIAF may be an effective option to improve the outlook after operation, but this has to be further investigated by a prospective study.

We also observed that, in seven patients who had a PR, there was enlargement of the nontumorous liver after therapy and, together with regression of the HCC, resection became possible. Similar findings were observed in patients who responded to SIR treatment with yttrium-90 microspheres (19). In the latter study, four patients who received one course of SIR treatment had regression of tumor, followed by hypertrophy of nontumorous liver. They all subsequently underwent resection of the residual liver lesion, and two patients had a complete pathological remission (19). Thus, hypertrophy of the nontumorous liver seems to be a sign of effective treatment for both internal radiotherapy and chemotherapy.

The majority of the patients in this trial had very high pretreatment AFP levels and a large tumor size (maximum diameter, 22 cm). An earlier study using combination 5-FU and IFN found a lack of activity in these patients and suggested that a low serum AFP (<50 ng/ml) was a predictor of response (12). However, all of the responders in the present study had high pretreatment AFP levels, above 20,000 ng/ml in four cases. We have also separated the patients into two groups according to the median pretreatment AFP level and compared RRs and survival times. No differences were found in either end point. Thus, a high AFP level does not seem to be an adverse factor for response to treatment, at least in our Chinese population, where the mean AFP level is higher when compared with low-incidence HCC areas.

The toxicities of this combination were considerable. However, only 12 patients completed the planned six cycles of treatment. Among those patients who received less, the main reason was a lack of response after two to three cycles, rather than toxicity. Most of the patients who had a PR (12 of 13) completed the planned six cycles of therapy. It is possible that those patients who could tolerate the treatment may have had a biologically more favorable disease. There were two treatment-related deaths as a result of neutropenic sepsis. Therefore, close monitoring of cell counts and careful patient selection are very important in administering this regimen. The use of growth factors may be an option to reduce the degree of myelosuppression. As most of our patients had a positive hepatitis B serology (94%) and cirrhosis, they may have been more susceptible to the myelosuppressive effects of the cytotoxic drug regimen (16). This has been attributed to the inhibitory effect of the virus on bone marrow cells (16). The other possible explanation may be an altered hepatic metabolism of the cytotoxic drugs due to coexisting chronic liver disease and compromised liver function. Besides hematological toxicity, other toxicities were relatively manageable and tolerable.

In conclusion, PIAF is active in HCC despite moderate toxicities. The use of this therapy may result in the conversion of inoperable disease to operable disease and, in some cases,
may result in complete pathological remissions. The role of this combination in improving operability and overall survival warrants further study.

ACKNOWLEDGMENTS

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