A Randomized Phase III Study of Doxorubicin Versus Cisplatin/Interferon α-2b/Doxorubicin/Fluorouracil (PIAF) Combination Chemotherapy for Unresectable Hepatocellular Carcinoma

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Background: **Single-agent doxorubicin has been widely used to treat unresectable hepatocellular carcinoma (HCC), but the response rate is low (<20%) and there is no convincing evidence for improved survival. Cisplatin, interferon, doxorubicin, and fluorouracil (PIAF) used in combination, by contrast, has shown promise in a phase II study. We compared doxorubicin to PIAF in patients with unresectable HCC in a phase III trial. *Methods:* Patients with histologically confirmed unresectable HCC were randomly assigned to receive either doxorubicin or PIAF every 3 weeks, for up to six cycles. The primary endpoint was overall survival, and secondary endpoints were response rate and toxicity. Survival differences were calculated using the Kaplan-Meier method. Treatment groups were compared for differences in the incidence of adverse events using chi-square tests. All statistical tests were two-sided. *Results:* The median survival of the doxorubicin and PIAF groups was 6.83 months (95% confidence [CI] = 4.80 to 9.56) and 8.67 months (95% CI = 6.36 to 12.00), respectively (*P* = 0.83). The hazard ratio for death from any cause in the PIAF compared with the doxorubicin groups was 0.97 (95% CI = 0.71 to 1.32). Eighty-six of the 94 patients receiving doxorubicin and 91 of the 94 receiving PIAF were assessable for response. The overall response rates in the doxorubicin and PIAF groups were 10.5% (95% CI = 3.9% to 16.9%) and 20.9% (95% CI = 12.5% to 29.2%), respectively. Neutropenia, thrombocytopenia, and hypokalemia were statistically significantly more common in patients treated with PIAF than in patients treated with doxorubicin. *Conclusion:* Although patients on PIAF had a higher overall response rate and better survival than patients on doxorubicin, the differences were not statistically significant. PIAF was also associated with increased treatment-related toxicity. The prognosis of patients with unresectable HCC remains poor. [J Natl Cancer Inst 2005;97:1532–8]**

Hepatocellular carcinoma (HCC) accounts for 5% of cancer incidence worldwide and 10% in parts of Southeast Asia and China, where it is a common cause of cancer morbidity and mortality *(1,2)*. HCC is highly aggressive; only 10–20% of patients are candidates for curative surgery *(3,4)*. Reasons for tumor unresectability include coexisting advanced cirrhosis, large primary lesion, multifocal disease, invasion and thrombosis of major blood vessels, poor hepatic reserve, and extrahepatic metastases. For the approximately 80% of patients who have unresectable tumors, the prognosis is very poor, with a median survival of only 4 months *(5,6)*.

Treatment options for HCC patients with unresectable tumors may include locoregional *(7–13)* and systemic *(14,15)* therapy. Although locoregional treatments have been shown to be somewhat effective based on randomized controlled studies, only transarterial chemoembolization has been found to increase survival. Even then, these results have been based on highly selected patients, possibly limiting its generalizability to other patients with different clinical profiles *(7,8)*. In addition, only a minority of patients with unresectable tumors, namely those with small

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tumors (defined as less than 5 cm) and with excellent liver function, may benefit from these locoregional therapies *(14)*. Thus, for the majority of HCC patients with unresectable tumors, best supportive care and systemic chemotherapy remain the main options for palliative treatment.

Various clinical trials investigating the role of single-agent chemotherapy for patients with unresectable HCC have reported response rates varying from 0% to 20%. Among these agents, anthracyclines such as doxorubicin have been the most effective, yielding response rates of up to 20% and median survival of 4 months *(16–19)*. Another class of agents that have been reported to have a modest degree of activity in HCC is interferons *(20)*. Interferons have immunomodulatory and antiproliferative effects on tumor cells *(21)*, and in one randomized study, interferons were reported to be superior to doxorubicin in terms of survival, tumor response, and toxicity in patients with HCC *(20)*.

Combination chemotherapy including doxorubicin, cisplatin, and fluorouracil, with or without interferon, has also been studied *(22,23)*. Although individual reports on combination chemotherapy *(22,23)* have yielded higher response rates than those found for single agents *(17,19)* the two treatment regimens have not been compared in a prospective randomized trial *(14,16)*. Recently, we conducted a phase II trial to examine the efficacy of interferon with doxorubicin, cisplatin, and fluorouracil (PIAF) in combination and observed a response rate of 26% in 50 patients with unresectable HCC. Four patients showed complete response on surgical resection of the residual tumors. The median overall survival of the 50 patients was 8.9 months *(22)*.

To date, there is no convincing evidence from randomized trials that combination chemotherapy prolongs the survival of patients with unresectable HCC better than single agents. The primary objective of this study was to compare the survival of such patients treated with PIAF with survival of those treated with doxorubicin alone. The secondary objectives of this study were to compare the response rates to and tolerability of the two regimens.

Patients and Methods

The aim of this phase III prospective randomized trial was to compare the efficacy and tolerability of single-agent doxorubicin with those of combination cisplatin/interferon α−2b/doxorubicin/5-fluorouracil chemotherapy (PIAF group) in patients with histologically confirmed unresectable HCC. The primary endpoint was overall survival from the date of randomization. The secondary endpoints were overall response and toxicity. The protocol was approved by the Clinical Research Ethics Committee of the Chinese University of Hong Kong. The patients provided written informed consent to participate before study entry.

Entry and Exclusion Criteria

The study was open to accrual from February 1, 1999, to October 30, 2003. Patients were eligible if they had histologically confirmed unresectable or metastatic HCC, were older than 15 years of age but younger than 75 years of age, had Eastern Cooperative Oncology Group (ECOG) performance status of 0–2, had adequate hematologic function (white cell count > 3 × 10⁹/L, platelet count > 100 × 10⁹/L), had adequate hepatic function (total bilirubin ≤ 30 μmol/L), and had adequate renal function (creatinine clearance > 50 mL/min).

The exclusion criteria included a history of prior malignancy except nonmelanoma skin cancer; substantial concurrent medical illness, such as cardiac or renal disease; intractable ascites that could not be controlled by medical therapy; bone or brain metastasis; prior chemotherapy for HCC; and, for female patients, being pregnant or breast-feeding.

Treatment Groups

Patients were randomly assigned to receive single-agent doxorubicin (60 mg/m^2) on day 1 every 3 weeks for up to six cycles or to receive PIAF, which consisted of cisplatin (20 mg/m^2) on days 1 through 4, interferon α−2b (5 MU/m^2) on days 1 through 4, doxorubicin (40 mg/m^2) on day 1, and 5-fluorouracil (400 mg/m^2) on days 1 through 4 every 3 weeks for up to six cycles. Patients receiving PIAF were premedicated with corticosteroids as part of an antiemetic regimen from the start of chemotherapy, but patients in the doxorubicin arm received corticosteroids only if they developed considerable nausea and vomiting.

Dose Reduction Schema for Severe Toxicities

There was no dose reduction scheme. For patients who developed febrile neutropenia, grade 4 thrombocytopenia and/or bleeding, or grade 3 or higher nonhematologic toxicity, further chemotherapy was delayed. All toxicities were graded according to the National Cancer Institute Common Toxicity Criteria recommendations on acute and subacute toxicity of cancer treatment *(24)*. In the event of progressive disease or intolerable side effects, treatment was stopped.

Randomization

This was an open study, with both physicians and patients being aware of the treatment arms to which the patients were randomly assigned. Patients were not stratified prior to being randomly assigned.

Schedule for Tumor Evaluation and Response Assessment

A complete medical history was taken and physical examination, renal and hepatic function tests, complete blood count, and chest X-ray were performed before treatment. Computed tomography of the thorax, abdomen and/or pelvis and abdominal ultrasonography were also performed, with bone scintigraphy and other tests as indicated, within 4 weeks before the start of treatment. Evaluation of response by radiologic methods was carried out after three and six cycles of treatment. A patient had to receive a minimum of one cycle for response evaluation. Classification of response was based on the World Health Organization criteria *(25)*. Complete response was defined as no evidence of tumor by clinical and radiologic assessments, with normalization of alpha-fetoprotein (AFP; if raised prior to treatment) lasting more than 30 days after treatment. Partial response was defined as a decrease of at least 50% in cross-perpendicular dimensions of the largest tumor nodule for at least 30 days without the appearance of new lesions or progression of other measurable or evaluable lesions (as defined below). Stable disease was defined as any response less than a partial response for the largest tumor nodule or an increase in cross-perpendicular dimensions of less than 25% of any measurable or evaluable lesions, without the appearance of new lesions. Progressive disease was defined as an

increase of at least 25% of any of the measurable or evaluable lesions or the appearance of new lesions. The investigators who evaluated response were not blinded to the treatment that the patient had received.

Statistical Design and Analysis

The study was designed to include a total of 180 patients with unresectable HCC. The primary outcome comparison between the two treatment groups was overall survival, and differences in risk were assessed by the log-rank test. We determined that this design would have 80% power to detect a 1.53-fold increase in 1-year survival when using a two-sided test alpha value of 0.05. Analyses were performed according to the intent-to-treat principle.

Survival time was measured from the date of randomization to the date of death or last contact, and all data were censored on May 31, 2004. Survival differences were calculated using the Kaplan-Meier method (26). Treatment groups were compared for differences in incidence of adverse events using chi-square tests. All statistical tests were two-sided, and P values less then .05 were considered statistically significant.

Factors associated with survival were determined using stepwise Cox regression analysis. Two approaches were used to assess the validity of the proportional hazards assumption. First, the assumption was assessed by log-minus-log-survival function and found to hold. Second, to confirm the assumption of proportionality, time-dependent covariate analysis was used. The time-dependent covariate was not statistically significant, suggesting that the proportional hazards assumption is reasonable. Estimates for hazard ratios (HR) and 95% confidence intervals (CIs) were calculated from these regression models. Independent prognostic factors for response were studied by stepwise logistic regression analysis. Eighteen objective clinical variables relating to baseline status were selected for exploratory analyses. They included age; sex; ECOG performance score; AFP; total bilirubin; alanine transaminase; albumin and hemoglobin levels; prothrombin time; hepatitis B surface antigen seropositivity; anti-hepatitis C virus positivity; cirrhosis (either on histologic or radiologic findings); presence of ascites (on either clinical or radiologic findings); Child-Pugh's grading of cirrhosis (27); tumor size; vascular thrombosis or invasion (of the portal veins, hepatic veins, or inferior vena cava on imaging findings); distribution of tumor (solitary, solitary with satellites, or infiltrative); and Okuda staging (stages I and II or stage III) (28). Both the logistic and Cox regression analyses used stepwise procedures for binary and time-to-event endpoints, respectively. Each prognostic variable was included or excluded in a stepwise fashion and based on a P value of .05 for inclusion and a P value of 0.10 for exclusion, starting from the most statistically significant variable in each step.

Interim Analysis

A formal interim analysis was undertaken on April 23, 2002. The members of the Data Safety Monitoring Committee, none of whom had any formal association with the study investigators, included a medical oncologist from the University of Toronto, a hepatobiliary surgeon from Singapore, and a local radiation oncologist in another hospital in Hong Kong. The recommendation was to continue the study until the final analysis. Neither the study investigators nor any of the personnel had access to the results of the interim analysis.

RESULTS

Study Population

A total of 188 patients with unresectable HCC were enrolled in the study, and 94 patients were randomly assigned to each arm. Comparison of the clinical and demographic characteristics of the patients in the two treatment arms (Table 1) revealed no statistically significant differences in the distribution of these baseline characteristics. A total of 169 patients had baseline imaging assessment performed by computed tomography, and the rest had ultrasonographic imaging. A total of 11 patients were subsequently found to be ineligible for response assessment (four patients did not have measurable disease, and seven patients did not receive any chemotherapy); these patients were included in the analysis of overall survival on an intent-to-treat basis (Fig. 1). Four patients in the PIAF arm and three patients in the doxorubicin arm who had an initial bilirubin level at above the exclusion level that did not return to normal levels prior to the start of treatment were included in the study.

Efficacy

The median number of cycles of chemotherapy received was four in the doxorubicin group and three in the PIAF group. One

Table 1. Clinical and demographic characteristics at baseline of patients with unresectable hepatocellular carcinoma*

	Doxorubicin arm	PIAF arm
No. of patients (male: female)	94 (85:9)	94 (87:7)
Median age (years; range)	54 (19 to 72)	49 (26 to 71)
ECOG performance status†		
0	82	87
1	10	7
2	1	0
Baseline biochemistry		
T bilirubin (umol/L, range)	11.5 (5 to 46)	12 (3 to 40)
Albumin (g/L)	35 (25 to 47)	34 (22 to 46)
ALT (iu/L)	61 (13 to 316)	64.5 (16 to 317)
Prothrombin time (sec)	11.3 (9.3 to 14.7)	11.6 (9.0 to 14.7)
AFP (ng/mL)	1307.5 (1 to 840 000)	2947.5 (2 to 18 926 000)
HBsAg positive, %	80	82
Anti-HCV positive, %	8	4
Coexisting cirrhosis, %	48	44
Child grading		
A	82	78
B	12	16
Vascular involvement, %	43	54
Okuda staging		
I	8	8
II	82	82
III	4	4

*PIAF = cisplatin, interferon α-2b, doxorubicin, and 5-fluorouracil; ECOG = Eastern Cooperative Oncology Group; ALT = alanine transaminase; AFP = alpha feto-protein; HBsAg = hepatitis B surface antigen; HCV = hepatitis C virus.

†Information on performance status was missing for one patient in the doxorubicin arm.
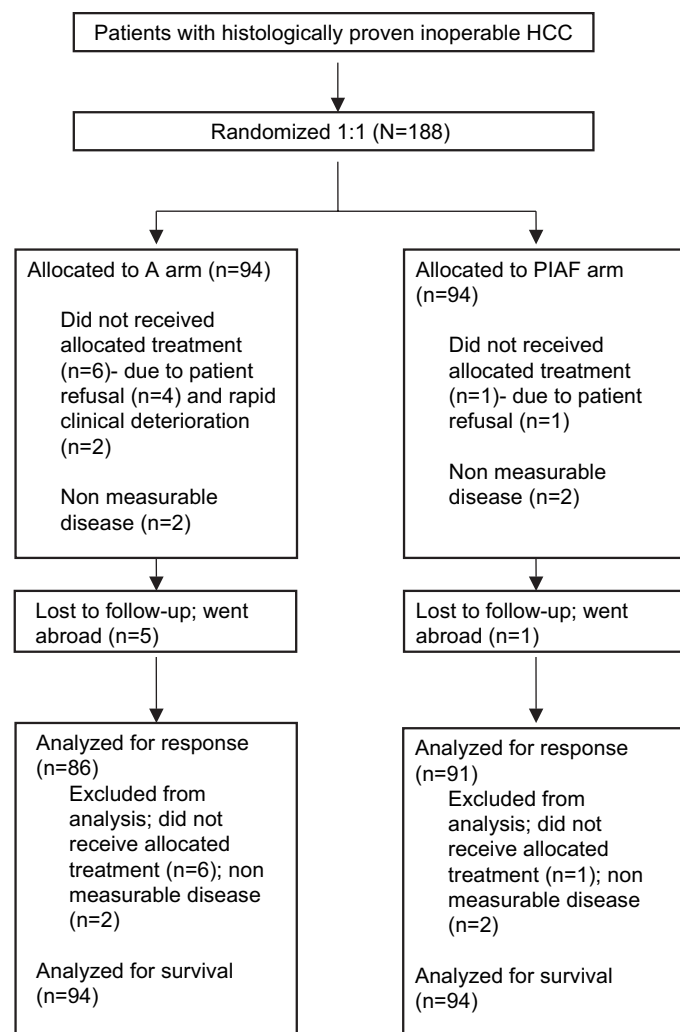
Fig. 1. Trial diagram of the phase III clinical trial comparing single-agent doxorubicin with cisplatin, interferon α-2b, doxorubicin, and 5-fluorouracil (PIAF) in combination for unresectable hepatocellular carcinoma.

Table 2. Evaluation of clinical response and overall survival by treatment arm*

Parameter	Doxorubicin arm	PIAF arm	P value†
Median no. of cycles	4	3	
Responses			
Complete response	0	0	
Partial response	9	19	
Stable disease	37	35	
Progressive disease	40	37	
Overall responses	10.5% (95% CI = 3.9 to 16.9%)	20.9% (95% CI = 12.5 to 29.2%)	.058
Median overall survival (mo.) based on intent-to-treat	6.83 (95% CI = 4.80 to 9.56)	8.67 (95% CI = 6.36 to 12.00)	.830

*PIAF = cisplatin, interferon α−2b, doxorubicin, and 5-fluorouracil; CI = confidence interval.

†Survival differences were calculated using the Kaplan-Meier method. All statistical tests were two-sided, and P values less than .05 were considered statistically significant.

hundred seventy-seven patients received at least one cycle of chemotherapy and were thus assessable for treatment response. Thirty-one patients did not receive further chemotherapy after the first cycle. The underlying reasons included treatment-related toxicities (*n* = 21 patients, including four who died of treatment-related complications), progressive disease (*n* = 4), and patient refusal (*n* = 6). Thirty-two of the 177 patients did not have their scheduled radiologic imaging for response assessment to chemotherapy. Thirty of these 32 patients received only one cycle of chemotherapy, one received two cycles, and one received four cycles. For these 32 patients, response assessments were based on subsequent radiologic assessment after the protocol-stipulated time period and/or on the combination of changes in AFP levels and clinical information.

Of the 86 assessable patients in the doxorubicin group, 9 patients had a partial response, 37 had stable disease, and 40 had progressive disease (Table 2). One patient did not have a follow-up imaging assessment to confirm the treatment response; however, the patient was included in the analysis as one of the responders. Ten patients in this group did not have their scheduled radiologic assessment; the responses in these patients, based on delayed radiologic or AFP/clinical assessment,

included stable disease (*n* = 1) and progressive disease (*n* = 9). Of the 91 assessable patients in the PIAF group, 19 patients had a partial response, 35 had stable disease, and 37 had progressive disease. Three patients initially classified as achieving a response did not have the response confirmed with a follow-up imaging assessment. Twenty-two patients did not have scheduled radiologic or AFP/clinical assessment; their responses, based on delayed assessment, included stable (*n* = 4) and progressive (*n* = 18) disease. The overall response rates were 10.5% (95% CI = 3.9% to16.9%) in the doxorubicin group and 20.9% (95% CI =12.5% to 29.2%) in the PIAF group (*P* = .058).

Among patients who responded to chemotherapy, four in the doxorubicin group and seven in the PIAF group subsequently underwent complete surgical resection of the residual tumors; one patient in each of the two groups was found to have complete response in the resected specimens. Five of these 11 patients also received postoperative adjuvant internal radiotherapy with I-131 *(29)*. Among the other responders, seven patients received other forms of second-line therapy (four patients underwent internal radiotherapy and three underwent further palliative chemotherapy) and three patients underwent third-line therapy with internal radiation or palliative chemotherapy.

A total of 163 patients, 79 in the doxorubicin group and 84 in the PIAF group, died during follow-up. The 1-year survival was 30% (95% CI = 20% to 39%) in the doxorubicin group and 39% (95% CI = 29% to 49%) in the PIAF group. The median survival was 6.83 months (range = 4.80 to 9.56) in the doxorubicin group and 8.67 months (range = 6.36 to 12.00) in the PIAF group. There was no difference in the HR of overall survival between treatment groups (HR = 0.97; 95% CI = 0.71 to 1.32) (Fig. 2).

Toxicity Profiles

Toxicities of grade 3 or above that were experienced by 3% or more of the studied patients are listed in Table 3. PIAF was associated with statistically significantly higher frequencies of neutropenia (82% versus 63%, *P* = .003), thrombocytopenia (57% versus 24%, *P*<.001), and hypokalemia (7% versus 0%, *P* = .007) than doxorubicin.
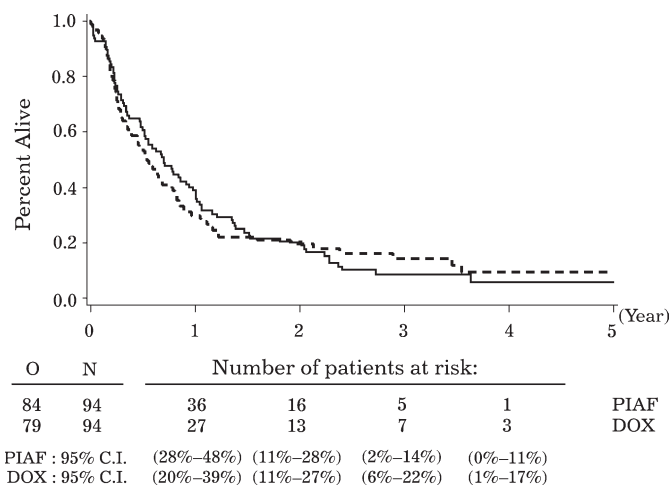
Fig. 2. Overall survival (OS) for patients with unresectable hepatocellular carcinoma treated with cisplatin, interferon α-2b, doxorubicin, and 5-fluorouracil (PIAF) in combination compared with single-agent doxorubicin. Median OS times were 8.67 months (range = 6.36 to 12.00) in the PIAF arm and 6.83 months (range = 4.80 to 9.56) in the doxorubicin arm (P_log rank = .83). The hazard ratio for death from any cause in the PIAF compared with the doxorubicin groups was 0.97 (95% CI = 0.71 to 1.32).

Number of patients at risk:

O	N					
84	94	36	16	5	1	PIAF
79	94	27	13	7	3	DOX

PIAF : 95% C.I. (28%–48%) (11%–28%) (2%–14%) (0%–11%)
DOX : 95% C.I. (20%–39%) (11%–27%) (6%–22%) (1%–17%)

Exploratory Analysis of Factors That Influenced Response and Survival

The only variable that was related to treatment response was albumin level (odds ratio for 1 unit change in albumin = 0.89; 95% CI = 0.81 to 0.97) (Table 4). A high albumin level was associated with improved survival (HR of death from any cause = 0.95; 95% CI = 0.92 to 0.99), whereas high total bilirubin level (HR = 1.04; 95% CI = 1.01 to 1.06) and high alanine transminase level (HR = 1.002; 95% CI = 1.00 to 1.01) were associated with poorer survival (Table 4). Although the treatment effect for response was of borderline statistical significance in favor of

Table 3. Toxicity profiles by treatment arm*

Toxicities	Doxorubicin arm		PIAF arm		P value†
	N	%	N	%	
Neutropenia	59	63	77	82	.003
Thrombocytopenia	23	24	54	57	<.001
Anemia	26	28	26	28	1.000
Febrile neutropenia	16	17	12	12	.412
Raised hepatic transaminase	12	13	16	17	.413
Hyperbilirubinaemia	15	16	12	13	.533
Diarrhea	7	7	11	12	.322
Vomiting	4	4	11	12	.059
Stomatitis	7	7	3	3	.193
Anorexia	3	3	7	7	.193
Abdominal pain	6	6	3	3	.305
Alkaline phosphatase	7	7	5	5	.550
Malena/gastrointestinal bleeding	5	5	5	5	1.000
Hypokalemia	0	0	7	7	.007
Hyponatremia	1	1	6	6	.054
Nausea	4	4	2	2	.406
Treatment-related mortality	3	3	8	9	.194

*PIAF = cisplatin, interferon α-2b, doxorubicin, and 5-fluorouracil.
†Treatment groups were compared for differences in incidence of adverse events using chi-square tests. All statistical tests were two-sided, and P values less than .05 were considered statistically significant.

Table 4. Stepwise Cox regression analysis for treatment response and overall survival adjusting for various prognostic factors

Factors	Hazard ratio (95% CI)*	P value
Associated with treatment response		
Univariate and multivariable analyses		
High albumin level	0.89 (0.81 to 0.97)	.0104
Associated with overall survival		
Univariate analysis		
High albumin level	0.95 (0.91 to 0.98)	<.001
High total bilirubin level	1.04 (1.02 to 1.06)	<.001
High alanine transminase level	1.006 (1.003 to 1.009)	<.001
Presence of ascites	2.35 (1.32 to 4.19)	.004
Child-Pugh grade A cirrhosis	0.52 (0.34 to 0.80)	.003
Presence of vascular involvement	1.53 (1.12 to 2.08)	.008
Okuda stage III	3.77 (1.83 to 7.77)	<.001
Multivariable analysis		
High albumin level	0.95 (0.92 to 0.99)	.006
High total bilirubin level	1.04 (1.01 to 1.06)	.001
High alanine transminase level	1.002 (1.002 to 1.008)	.001

*CI = confidence interval.

PIAF (P = .05) after adjusting for the prognostic factors, there was no association of PIAF with survival (P = .54). There was no treatment effect by covariate interaction under the final Cox regression model adjusted for statistically significant prognostic factors.

DISCUSSION

To our knowledge, the present study is one of the first prospective randomized trials to compare combination chemotherapy with single-agent chemotherapy for efficacy and tolerability in patients with unresectable HCC. The response rates for the doxorubicin and PIAF arms in this phase III study were within the range reported in previous phase II studies *(18,19,22)*, and patients on PIAF had a non-statistically significantly higher overall response rate than patients treated with single-agent doxorubicin. However, no difference in overall survival between the two treatment arms was observed.

There are a number of possible reasons for why no survival advantage was observed. One reason may be the higher-than-anticipated 1-year survival in patients treated with doxorubicin, which was nearly 30% in this study compared with 10–20% in other studies *(14,16)*. Another explanation may be that the broad patient inclusion criteria used to better reflect patients seen in clinical practice may have obscured any survival advantage associated with PIAF. Of note, better patient selection based on one of the newer prognostic classifications, such as the Cancer of the Liver Italian Program (CLIP) *(30,31)*, may have improved treatment outcome.

PIAF was also associated with a statistically significant myelotoxicity with increased frequency of neutropenia and thrombocytopenia in this phase III study, similar to what we reported in our phase II study *(22)*. However, in the present study, a PIAF-associated increase in neutropenic fever was not observed. We also observed liver dysfunction in HCC patients on both treatment regimens at similar frequencies, as measured by an increase in hepatic transaminase and hyperbilirubinemia. In fact, 15% of all patients developed severe hepatotoxicity. This hepatotoxicity may be due, in part, to coexisting chronic liver disease. In this geographical region from which our study participants were identified, over 80% of patients with HCC also have a chronic

hepatitis B virus (HBV) infection. HBV reactivation in HBV carriers receiving cytotoxic chemotherapy for solid tumors is a well-recognized phenomenon that has been related to varying degrees of liver damage (32,33).

A subprotocol to this study addressed this issue of HBV reactivation in HCC patients, and among the 102 patients studied, nearly 40% developed hepatitis that was attributable to HBV reactivation (34). Of those who had reactivation of their HBV infection, 30% died; there was no difference in survival in patients by treatment group. The only risk factor associated with HBV reactivation was elevated pretreatment ALT. Prophylactic use of the antiviral agent lamivudine has been shown to reduce HBV-related complications during chemotherapy and has also been suggested to decrease mortality during treatment (35).

We also conducted exploratory analysis of prognostic factors for response and survival. The only factor associated with better treatment response was high albumin level, whereas independent predictors for improved overall survival included high albumin level, low total bilirubin level, and low alanine transaminase level. These findings are consistent with those of previous reports (36–39), in which the two factors have been consistently associated with a better treatment outcome: the absence of cirrhosis and low bilirubin level (36). Another report, by Okada et al. (38), showed that age under 60 years, low bilirubin level, high albumin level, and absence of ascites were associated with improved survival of HCC patients after chemotherapy. Adequate liver function, as reflected by high albumin level, low or normal bilirubin level, and lower hepatic transaminase activity, may allow optimal cytotoxic delivery. Other factors that have been associated with better outcome in HCC patients undergoing chemotherapy were absence of AFP, absence of vascular involvement, and small tumor size (36–40).

Assessment of response to treatment based on conventional criteria that relies mainly on radiologic evaluation may not be reliable. Based on this criteria, a total of 28 patients achieved partial response after treatment with chemotherapy in this study. Eleven of these patients subsequently underwent surgical resection of the residual lesions, and two (one from each group) were confirmed to have complete pathologic responses with no HCC in the resected specimens. The results for these two patients illustrate that radiologic imaging may not provide information on pathologic status of the tumor and highlight an underlying problem with the conventional criterion used to assess response to treatment for HCC: residual tumor identified on radiologic imaging may merely represent necrotic or fibrotic tissues remaining after chemotherapy. In the absence of a definite survival advantage with the PIAF regimen, coupled with its considerable toxicity, we cannot recommend the PIAF regimen as standard therapy for patients with unresectable HCC. Nevertheless, our extensive experience with this regimen does confirm that it has clinical efficacy with an enhanced response rate that approached statistical significance when compared with single-agent doxorubicin.

It should be noted that optimizing study therapy may potentially avoid the premature termination of chemotherapy. However, based on the broad toxicity profiles reported in the current study, growth factor support alone would be unlikely to improve the tolerability of the treatment. Although the incorporation of dose adjustment was initially considered for this study protocol, our experience has been that HCC patients who suffer severe toxicities tended to experience a progressively poorer quality of life

over their limited remaining lifespan. Thus, without formal assessment on the impact of dose adjustments for severe toxicities and prophylactic therapies (such as lamivudine for HBV-related disease), the true efficacy of the PIAF regimen has not been fully evaluated and may warrant further investigation.

REFERENCES

(1) Parkin DM, Stjernsward J, Muir CS. Estimates of the worldwide frequency of twelve major cancers. Bull World Health Organ 1984;62:163–82.

(2) Hong Kong Cancer Registry. Cancer incidence and mortality in Hong Kong 1999–2000. Hospital Authority 2004. Available at: http://www.ha.org.hk/cancereg.

(3) Okuda K. Primary liver cancers in Japan. Cancer 1980;45:2663–72.

(4) Lai EC, Fan ST, Lo CM, Chu KM, Liu CL, Wong J. Hepatic resection for hepatocellular carcinoma. An audit of 343 patients. Ann Surg 1995;221:291–8.

(5) Pawarode A, Voravud N, Sriuranpong V, Kullavanijaya P, Patt YZ. Natural history of untreated primary hepatocellular carcinoma: a retrospective study of 157 patients. Am J Clin Oncol 1998;21:386–91.

(6) Calvet X, Bruix J, Gines P, Bru C, Sole M, Vilana R, et al. Prognostic factors of hepatocellular carcinoma in the west: a multivariate analysis in 206 patients. Hepatology 1990;12:753–60.

(7) Lo CM, Ngan H, Tso WK, Li CL, Lam CM, Poon RT, et al. Randomized controlled trial of transarterial lipiodol chemoembolization for unresectable hepatocellular carcinoma. Hepatology 2002;35:1164–71.

(8) Llovet JM, Real MI, Montana X, for the Barcelona Clinic Liver Cancer Group. Arterial embolisation or chemoembolisation versus symptomatic treatment in patients with unresectable hepatocellular carcinoma: a randomized controlled trial. Lancet 2002;359:1734–9.

(9) Kotoh K, Sakai H, Sakamoto S, Nakayama S, Satoh M, Morotumi I, et al. The effect of percutaneous ethanol injection therapy on small solitary hepatocellular carcinoma is comparable to that of hepatectomy. Am J Gastroenterol 1994;89:194–8.

(10) Rossi S, Buscarini E, Garbagnati F, Di Stasi M, Quaretti P, Rago M, et al. Percutaneous treatment of small hepatic tumors by an expandable RF needle electrode. Am J Roentgen 1998;170:1015–22.

(11) Sato M, Watanabe Y, Ueda S, Iseki S, Abe Y, Sato N, et al. Microwave coagulation therapy for hepatocellular carcinoma. Gastroenterology 1996;110:1507–14.

(12) Crews KA, Kuhn JA, McCarty TM, Fisher TL, Goldstein RM, Preskitt JT. Cryosurgical ablation of hepatic tumors. Am J Surg 1997;174:614–8.

(13) Lau WY, Ho S, Leung TW, Chan M, Ho R, Johnson PJ, et al. Selective internal radiation therapy for nonresectable hepatocellular carcinoma with intraarterial infusion of yttrium90 microspheres. Int J Radiat Oncol Bio Phys 1998;50:583–92.

(14) Johnson PJ. Hepatocellular carcinoma: is current therapy really altering outcome? Gut 2002;51:459–62.

(15) Leung TW, Johnson PJ. Systemic therapy for hepatocellular carcinoma. Semin Oncol 2001;28:514–20.

(16) Okada S. Chemotherapy for hepatocellular carcinoma. In: Okuda K, Tabor E, editors. Liver cancer. New York (NY): Churchill Livingstone; 1997. p. 441–8.

(17) Falkson G, Ryan LM, Johnson LA, Simson IW, Coetzer BJ, Carbone PP, et al. A randomized phase II study of mitoxantrone and cisplatin in patients with hepatocellular carcinoma: an ECOG study. Cancer 1987;60:2141–5.

(18) Nerenstone SR, Ihde DC, Friedman MA. Clinical trials in primary hepatocellular carcinoma: current status and future directions. Cancer Treat Rev 1988;15:1–31.

(19) Hochster HS, Green M, Speyer J, Fazzini E, Blum R, Muggia FM. 4′-Epidoxorubicin (epirubicin): activity in hepatocellular carcinoma. J Clin Oncol 1985;11:1535–40.

(20) Lai CL, Lau JY, Wu PC, Ngan H, Chung HT, Mitchell SJ, et al. Recombinant interferon- in inoperable hepatocellular carcinoma: a randomized controlled trial. Hepatology 1993;17:389–94.

(21) Elias L, Crissman HA. Interferon effects upon the adenocarcinoma 38 and HL-60 cell lines: antiproliferative responses and synergistic interactions with halogenated pyrimidine antimetabolites. Cancer Res 1988;48:4868–73.

(22) Leung TW, Patt Z, Lau WY, Ho KW, Yu CH, Chan TC, et al. Complete pathological remission is possible with systemic combination chemotherapy for inoperable hepatocellular carcinoma. Clin Cancer Res 1999;5:1676–81.

(23) Lee J, Park JO, Kim WS, Park SH, Park KW, Choi MS, et al. Phase II study of doxorubicin and cisplatin in patients with metastatic hepatocellular carcinoma. Cancer Chemother Pharmacol 2004;54:385–90.

(24) National Cancer Institute Common Toxicity Criteria, version 2.0. Bethesda (MD): National Cancer Institute; 1998.

(25) World Health Organization. WHO handbook for reporting results of cancer treatment. Geneva (Switzerland): World Health Organization; 1979.

(26) Kaplan EL, Meier P. Nonparametric estimation from incomplete observations. J Am Stat Assoc 1958;53:457–81.

(27) Okuda K. Primary liver cancers in Japan. Cancer 1980;45:2663–72.

(28) Pugh RNH, Murray-Lyon IM, Dawson JL, Pietronia MC, Williams R. Transection of the oesophagus for bleeding oesophageal varices. Br J Surg 1973;60:646–9.

(29) Lau WY, Leung TWT, Ho SKW, Chan M, Machin D, Lau J, et al. Adjuvant intra-arterial iodine-131-labelled lipoidal for resectable hepatocellular carcinoma: a prospective randomised trial. Lancet 1999;353:797–801.

(30) The Cancer of the Liver Italian Program (CLIP) Investigators. A new prognostic system for hepatocellular carcinoma: a retrospective study of 435 patients: the Cancer of the Liver Italian Program (CLIP) investigators. Hepatology 1998;28:751–5.

(31) Grieco A, Pompili M, Caminiti G, Miele L, Covino M, Alfei B, et al. Prognostic factors for survival in patients with early-intermediate hepatocellular carcinoma undergoing non-surgical therapy: comparison of Okuda, CLIP, and BCLC staging systems in a single Italian centre. Gut 2005;54:411–8.

(32) Yeo W, Chan PKS, Zhong S, Ho WM, Steinberg JL, Tam JS, et al. Frequency of hepatitis B virus reactivation in cancer patients undergoing cytotoxic chemotherapy: a prospective study of 626 patients with identification of risk factors. J Med Virol 2000;62:299–307.

(33) Yeo W, Zee B, Zhong S, Chan PKS, Wong WL, Ho WM, et al. Comprehensive analysis of risk factors associating with Hepatitis B virus (HBV) reactivation in cancer patients undergoing cytotoxic chemotherapy. Br J Cancer 2004;90:1306–11.

(34) Yeo W, Lam KC, Zee B, Chan PSK, Mo FKF, Ho WM, et al. Hepatitis B reactivation in patients with hepatocellular carcinoma undergoing systemic chemotherapy. Ann Oncol 2004;15:1661–6.

(35) Yeo W, Chan PKS, Ho WM, Zee B, Lam KC, Lei KIK, et al. Lamivudine for the prevention of hepatitis B virus reactivation in HBsAg seropositive cancer patients undergoing cytotoxic chemotherapy. J Clin Oncol 2004;22:927–34.

(36) Leung TW, Tang AM, Zee B, Yu SC, Lai PB, Lau WY, et al. Factors predicting response and survival in 149 patients with unresectable hepatocellular carcinoma treated by combination cisplatin, interferon-alpha, doxorubicin and 5-fluorouracil chemotherapy. Cancer 2002;94:421–7.

(37) Johnson PJ, Alexopoulos A, Johnson RD, Williams R. Significance of serum bilirubin level in response of hepatocellular carcinoma to doxorubicin. Hepatology 1986;3:149–53.

(38) Okada S. Chemotherapy in hepatocellular carcinoma. Hepatogastroenterology 1998;45:1259–63.

(39) Mondazzi L, Bottelli R, Brambilla G, Rampoldi A, Rezakovic I, Zavaglia C, et al. Transarterial oily chemoembolization for the treatment of hepatocellular carcinoma: a multivariate analysis of prognostic factors. Hepatology 1994;19:1115–23.

(40) Stuart KE, Ansand AJ, Jenkins RL. Hepatocellular carcinoma in the United States: prognostic features, treatment outcome and survival. Cancer 1996;77:2217–22.

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