Pirarubicin, UFT, Leucovorin Chemotherapy in Non-embo-
lizable and Transcatheter Arterial Chemoembolization-Failed
Hepatocellular Carcinoma Patients; A Phase II Clinical Study

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**Purpose:** Hepatocellular carcinomas are one of the most common malignancies in the world. However, no effective therapeutic modality has been proven to prolong the survival of patients in an inoperable stage. The purpose of this study was to determine the response rate and the toxicities of a combination of pirarubicin, UFT and leucovorin in patients with non-embolizable hepatocellular carcinomas, or who had progressed during their transcatheter arterial chemoembolization treatment.

**Materials and Methods:** Of 23 patients with a hepatocellular carcinoma, 11 had progressed during a transcatheter arterial chemoembolization, with the other 12 being transcatheter arterial chemoembolization-naive. All the patients were treated with pirarubicin (70 mg/m² i.v., day 1), UFT (350 mg/m² P.O., day 1–21), and leucovorin (25 mg/m² P.O., day 1–21).

**Results:** Twenty patients were able to be evaluated, with a partial response being achieved in four, giving an overall response rate of 20% (95% confidence interval, 7–44%). The median overall survival time was 6 months, and the median survival time of the transcatheter arterial chemoembolization-naive patients was significantly longer than that of those treated by transcatheter arterial chemoembolization (p=0.012). The most significant dose-limiting toxicity was leucopenia and thrombocytopenia.

**Conclusion:** The combination of pirarubicin, UFT and leucovorin therapies showed marginal antitumor activity and significant toxicity in patients with non-embolizable or failed transcatheter arterial chemoembolization hepatocellular carcinomas. (Cancer Research and Treatment 2002;34:280-283)

**Key Words:** Hepatocellular neoplasm, Transcatheter arterial chemoembolization, Chemotherapy

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**INTRODUCTION**

Hepatocellular carcinomas (HCC) are one of the most common malignancies in the world, especially in Asia and sub-Saharan Africa (1). About one million people are newly diagnosed HCC patients annually worldwide. In Korea, HCC is the second most common malignancy in men after gastric cancer, and are the leading cause of cancer mortalities (2). Despite screening for high risk populations by ultrasonography and serum alpha-fetoprotein (AFP) testing, the number of surgical candidates is limited due to the advanced state of the disease and/or the poor hepatic reservoir at the time of diagnosis. In the case of unresectable HCC, transcatheter embolization has long been used as a palliative treatment (3–5). However, considerable uncertainty remains about its effectiveness in terms of survival in patients with locally advanced or metastatic HCC (6), and many patients have refused further treatment after failure of locoregional treatment.

In most patients with HCC, the disease progresses to a far-advanced stage, for which non-surgical local treatments, such as TACE, percutaneous ethanol injection, cryotherapy, and radiation therapy are not feasible. With these treatments the response rates have not been satisfactory, leaving systemic chemotherapy as may be the only option for such patients. In one Thai study, treatment with systemic chemotherapy was found to give survival benefits to unresectable patients with good liver function (7), which encouraged the investigation of the effectiveness of this therapy for those with inoperable HCC with good liver function.

Although the role of chemotherapy in the treatment of pa-
tients with HCC remains controversial, a number of single chemotherapeutic agents and drug combination regimens have been given to patients with HCC in attempts to improve their dismal prognosis. However, HCC is only moderately sensitive to systemically administered single agents. Among these, the anthracyclines, including doxorubicin, and 4'-epidoxorubicin are the most active and commonly used, but the objective response rates from 14 published trials were less than 20% (8,9). Although its activity is somewhat inferior to that of the anthracyclines, 5-FU has also been frequently tried as a chemotherapeutic agent, but has shown a marginal effectiveness compared to untreated controls (10). UFT, the oral form of fluorouracil, is commonly used owing to its good pharmacokinetics, which are similar to protracted intravenous injection of fluorouracil, but with better toxicity profiles (11). In 1986, Okazaki et al. reported a response rate of 4% in hepatocellular carcinomas using UFT as a single treatment agent (12). Tanaka et al. reported a case involving the complete disappearance of multiple pulmonary nodules in a HCC patient following the oral administration of UFT (13).

In this study, pirarubicin, UFT, and leucovorin were chosen because of their single agent activity, lack of cross-resistance and their different toxicity profiles. The objective of the study was to determine the response rates and toxicities of the pirarubicin, UFT and leucovorin combinations in the treatment of unresectable, non-embolizable HCC.

MATERIALS AND METHODS

1) Patients

All the patients in this study were referred to the Division of Hemato-Oncology, the Department of Medicine, the Korea University Hospital, Seoul, between January 1997 and December 1999. They had to be less than 75 years of age with an initially inoperable, non-embolizable or progressed HCC following previous TACE treatment for eligibility. The unresectable or non-embolizable disease was defined by a hepatic arteriography and a computerized tomographic scan. The diagnosis of HCC was made by histological examination of biopsied tissue, or imaging evidence of a space-occupying lesion in the liver, together with a serum AFP level greater than 500 ng/ml in patients at high risk of HCC. Other inclusion criteria included: - an Eastern Cooperative Oncology Group (ECOG) performance status of less than 2, Child-Pugh class A or B liver cirrhosis, a platelet count greater than 100,000/mm³, a WBC counter greater than 3,000/mm³ or a serum creatinine level of less than 1.5 mg/dl. The informed consent of the patient was a prerequisite. Patients were excluded if they had a concurrent systemic infection, cardiac disease, or had experienced recent upper gastrointestinal bleeding.

2) Treatment

The pirarubicin (70 mg/m²) was administered intravenously, on the first day of each cycle at the hospital, while the UFT (350 mg/m²) and the leucovorin (25 mg/m²) were administered orally from day 1 to day 21 on an outpatient basis. These cycles were repeated every 28th day, with no permitted dose escalation. If leucopenia or thrombocytopenia was present at grade III or more, the pirarubicin dose was reduced by 25% in the subsequent cycle. For a gastrointestinal toxicity of grade III or more, the subsequent UFT dose was also reduced by 25%. In cases of progressive disease, despite chemotherapy, the treatment was discontinued.

3) Evaluation of response and toxicity

Baseline CT scans were performed on entry to the trial, and repeated following every two cycles of treatment, to two-dimensionally measure the hepatic lesions. On day 1 of each cycle, serum AFP, ECG, serum biochemistry, and chest X-ray were performed, with hematological and liver function tests being performed between the 10~14th day of each cycle. Grading of the response evaluation was performed according to the WHO classification (14). The standard criteria included, the complete and partial responses, and the disease stability and progression. Toxicities were evaluated according to the National Cancer Institute criteria for clinical toxicity.

4) Statistics

Survival duration was calculated from the 1st day of chemotherapy. Actual survival was calculated by the Kaplan-Meier method, and the significance was determined by the Log rank test. A value of p<0.05 was regarded as significant.

RESULTS

1) Patients

The clinical features of the 23 patients enrolled this study between January 1997 and December 1999 are presented in Table 1. Of the 23 patients 19 were male and 4 were female.

Table 1. Clinical characteristics of 23 hepatocellular carcinoma patients

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>No. of patients</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male: Female</td>
<td>19:4</td>
<td></td>
</tr>
<tr>
<td>Median age in yrs (range)</td>
<td>50 (33~72)</td>
<td></td>
</tr>
<tr>
<td>Performance status (ECOG)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>20</td>
<td>87</td>
</tr>
<tr>
<td>2</td>
<td>3</td>
<td>13</td>
</tr>
<tr>
<td>Child-Pugh class</td>
<td></td>
<td></td>
</tr>
<tr>
<td>A</td>
<td>17</td>
<td>73.9</td>
</tr>
<tr>
<td>B</td>
<td>6</td>
<td>26.1</td>
</tr>
<tr>
<td>Previous treatment</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TACE+</td>
<td>11</td>
<td>47.8</td>
</tr>
<tr>
<td>None</td>
<td>12</td>
<td>52.2</td>
</tr>
<tr>
<td>Tumor status limiting local treatment</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Distant metastasis</td>
<td>13</td>
<td>56.5</td>
</tr>
<tr>
<td>Lung</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td>Bone</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Pelvic cavity</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Skin</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Local advancement</td>
<td>10</td>
<td>43.5</td>
</tr>
<tr>
<td>Main portal vein thrombosis</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>IVC^ thrombus</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Regional LN^ metastasis</td>
<td>1</td>
<td></td>
</tr>
</tbody>
</table>

^transcatheter arterial chemoembolization, ^ inferior vena cava, ^ lymph node
with an age range of 33 to 72 years with a median age of 50. Twelve were recently diagnosed as TACE naïve, and eleven had failed previous TACE treatment. Before the systemic chemotherapy was started, 17 patients had Child-Pugh class A, and 6 had class B, liver cirrhosis. Most of the patients (87%, 20/23) were ECOG performance status 1. Of the patients previously treated by TACE for their HCC, their median treatment number of those previously treated by TACE was 5 (range: 2–10).

2) Responses and survival

20 of the 23 patients were evaluated for their response to treatment. The remaining three discontinued their treatment before evaluation due to impending hepatic failure.

No patient achieved a complete response, but four had a partial response, this representing a 20% response rate (95% confidence rate 7–44%) for the 20 evaluated patients. Six patients had a stabilized disease, but 10 had a progressed disease.

The median survival for the 20 patients was 6 months (range: 3–27 months), but was significantly shorter for those treated by TACE than those receiving no treatment (p=0.021). The median survival durations of the patients in the two groups were 5 months (range: 3–9 months), and 6.5 months (range: 3–27 months), respectively (Fig. 1).

3) Toxicity

The treatment caused significant dose-limiting hematological toxicity, and of the 20 patients, 18 experienced WHO grade III-IV leucopenia and 15 had thrombocytopenia, so the subsequent pirarubicin dosage had to be reduced. Of the 79 courses of treatment, 52 of the dosages had to be subsequently reduced. Six patients developed unacceptable hepatotoxicity, so treatment was discontinued, but no toxic death occurred due to acute liver failure. Other treatment related side effects, including: anorexia, nausea, vomiting, oral mucositis and diarrhea, were mild (WHO grade I-II) and manageable. Thus, a reduction in the dosage of UFT was unnecessary.

![Graph](image.png)

**Fig. 1.** Survival curves of pirarubicin, UFT, leucovorin chemotherapy in patients with previous TACE treatment and TACE naïve patients.

**DISCUSSION**

Surgery offers the only hope of cure for patients with HCC, and those with an inoperable or metastatic disease have a dismal prognosis. Patients with extrahepatic metastasis, or a blocked portal venous system, are not usually candidates for the intra-arterial treatment, as it has not been shown, in randomized trials, to prolong survival, leaving systemic chemotherapy as the only remaining option for these patients (6). The antitumor activities of a number of chemotherapeutic agents have been evaluated as single agents in HCC patients, as well as in combination with other agents. In one study doxorubicin was shown to offer limited survival benefit as a single agent (15), but it still remains the most actively used drug against HCC. Its response rate, as a single agent, is only 10–20% and often its toxicity outweighs its benefit, leading to discontinuation of treatment. Pirarubicin, one of the anthracycline derivatives, has been shown to have the least hepatotoxicity and cardiotoxicity even at its maximum tolerated dose (16). Pharmacokinetically pirarubicin is superior to other anthracyclines due to its faster cellular uptake and disappearance from plasma, making it a better proposition for HCC patients with compromised liver function. However, little clinical data exists on the effectiveness and toxicity of chemotherapy in TACE-failed patients. In this study, we used pirarubicin as an anthracycline, in addition to UFT and leucovorin, which was shown to have a better toxicity profile than doxorubicin. 5-Fluorouracil (5-FU), the cornerstone of internal malignancy treatments, has been broadly administered to patients with HCC, and its significant antitumor activity, in combination with leucovorin, has been demonstrated in a former study (17). In this study, we aimed to improve the efficacy of systemic chemotherapy by examining the pirarubicin, UFT and leucovorin combinations, due to their known synergistic activity.

In our study, the overall response rate was 20%, which was no better than that found in the former phase II study using the epirubicin containing combined therapy (18). This can be partially explained by the frequent dosage reduction in pirarubicin required due to the myelosuppression. Only one of our four responding patient had previously been treated using TACE for his HCC. HCCs were shown to have an elevated MDRI gene expression, which encodes for P-glycoprotein, and their resistance to chemotherapy is believed to be related to the MDRI gene-mediated multidrug resistance (19). Moreover, during TACE treatment there is a possibility of developing anthracyline resistance, which would explain the lower effectiveness of the therapy in our TACE treated patients.

As for toxicity, our treatment regimen caused significant hematological toxicity, forcing us to frequently reduce the dosage of pirarubicin. HCC in patients are often associated with chronic viral infections and secondary hypersplenism, so may be more susceptible to myelosuppression. However, none of our patient suffered from sepsis induced by leucopenia. Hong et al experienced pegylated liposomal doxorubicin (PLD) in the treatment of advanced HCC, with severe hepatic dysfunction (20), but observed only minimal toxicities, including grade II stomatitis and moderate leucopenia. Safe and effective agents
of this type might be a novel attractive alternative compared to the initial use of anthracyclines or its derivatives. Excepting those who had treatment discontinued due to unacceptable hepatotoxicities after the first course, the main reason for discontinuation was a lack of response, rather than undesirable toxicity. 4 of the 6 patients (66.7%, 4/6) experiencing unacceptable hepatotoxicities had previously been treated by TACE. It is possible that these patients had liver function deterioration following TACE due to primary damage of the blood vessels feeding the bile ducts, even though they were the same Child-Pugh class as the TACE-naive patients.

CONCLUSIONS

The pirarubicin, UFT and leucovorin chemotherapies were found to be only marginally active, but tolerable for both TACE-treated and TACE-naive in advanced HCC patients. In view of the greater toxicities and the reduced effectiveness of this treatment in TACE-treated patients, we believe its role in TACE-failed patients should be proven in a controlled randomized study, by the comparison of patients receiving treatment with those who are given the best supportive care. Clinical trials of systemic chemotherapies using less toxic agents are warranted.

REFERENCES