

## Long-term Clinical Outcome of Phase IIb Clinical Trial of Percutaneous Injection with Holmium-166/Chitosan Complex (Milican) for the Treatment of Small Hepatocellular Carcinoma

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**Abstract Purpose:** The purpose of this study was to evaluate the long-term tumor response after phase IIb clinical study and the safety of percutaneous holmium-166 (<sup>166</sup>Ho)/chitosan complex injection (PHI) therapy for small hepatocellular carcinoma as a local ablative treatment. <sup>166</sup>Ho is a radioactive isotope derived from natural holmium-165. We developed a <sup>166</sup>Ho/chitosan complex (Milican, Dong Wha Pharmaceutical Co., Seoul, Korea) using chitosan as a vehicle to retain the radioactive material within the tumor.

**Experimental Design:** Forty patients with single hepatocellular carcinoma <3 cm in maximal diameter were enrolled in this study. The patients either had refused surgery or were poor surgical candidates and were treated with only single session of PHI.

**Results:** Two months after PHI, complete tumor necrosis was achieved in 31 of 40 patients (77.5%) with hepatocellular carcinoma lesions <3 cm and in 11 of 12 patients (91.7%) with hepatocellular carcinoma <2 cm. Tumors recurred in 28 patients during the long-term follow-up period, of which 24 recurred at another intrahepatic site. The 1-year and 2-year cumulative local recurrence rates were 18.5% and 34.9%, respectively. The survival rates at 1, 2, and 3 years were 87.2%, 71.8%, and 65.3%, respectively. Transient bone marrow depression was serious adverse event requiring hospitalization in two patients.

**Conclusions:** PHI was found to be a safe and novel local ablative procedure for the treatment of small hepatocellular carcinoma and could be used as a bridge to transplantation. A phase III randomized active control trial is clearly warranted among a larger study population.

In spite of the high incidence of hepatocellular carcinoma, treatment options for patients are limited, and hepatocellular carcinoma remains a significant cause of cancer-related deaths. A number of modalities have emerged for the treatment of hepatocellular carcinoma using local ablative therapy. These include percutaneous ethanol injection therapy (PEIT; refs. 1, 2), hepatic cryotherapy (3), radiofrequency ablation (RFA; ref. 4), and laser photocoagulation (5). There are cases of cure in most of small tumors with these procedures; however, marginal recurrence might be expected, even if the entire tumor mass was included in the targeted area. To improve the efficacy

of local ablation, selective internal radiation therapy was attempted using radioisotopes, such as iodine-131 (<sup>131</sup>I)-lipiodol (6) or yttrium-90 (<sup>90</sup>Y) microspheres (7). In selected patients with hepatocellular carcinoma, treatment with <sup>90</sup>Y microspheres has given positive results (8). However, because the distribution of the isotope depended on tumor vasculature, leakage could occur in cases of arteriovenous shunts or difficult catheterizations. Therefore, it is important to verify biodistribution within the tumor and to quantify any systemic leakage.

To overcome the limitations that have been encountered in various ablative therapies, we have developed a novel therapy using another radioisotope, holmium-166 (<sup>166</sup>Ho). <sup>166</sup>Ho is a product of the neutron activation of holmium-165 and is predominantly a high-energy  $\beta$ -emitter ( $E_{\max} = 1.84$  MeV) with radiotherapeutic properties appropriate for ablation therapy. It also emits  $\gamma$ -ray photons (81 keV, 6.2%) detectable by scintillation imaging (9). Its relatively short half-life (26.8 hours; ref. 10) and proper mean penetration depth (2.2 mm) permit effective treatment without isolation, and it poses a very low risk of radiation hazard (11). Microspheres loaded with radioactive <sup>166</sup>Ho have been investigated in several preclinical studies and have been shown to be potentially useful agents for internal radiation therapy for hepatic tumors (12–14).

Our previous study using an animal model for hepatocellular carcinoma showed that the <sup>166</sup>Ho was effective in destroying

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tumor tissue without associated radiation damage to neighboring organs (15). In the current study, we examined a group of hepatocellular carcinoma patients who participated in a phase IIb clinical trial of the percutaneous  $^{166}\text{Ho}$ /chitosan complex ( $^{166}\text{Ho}$ /CHICO, Milican, Dong Wha Pharmaceutical Co., Seoul, Korea) injection (PHI). The purpose of this study was to evaluate the long-term therapeutic efficacy and safety of phase IIb clinical trial of PHI in patients with tumors <3 cm.

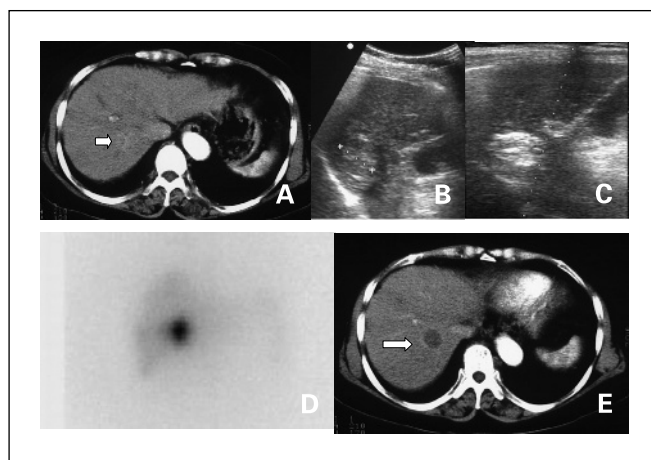
## Patients and Methods

**Patient selection.** Forty patients (27 men and 13 women) with hepatocellular carcinoma, ages 38 to 83 years (mean, 57.4 years), were enrolled in a phase IIb clinical study of Milican treatment at the Severance Hospital in Seoul, Korea, between July 1999 and September 2000. The diagnoses of hepatocellular carcinoma were based on histopathologic confirmation or radiological findings typical of hepatocellular carcinoma combined with elevated serum  $\alpha$ -fetoprotein (>200 ng/mL). Some of the patients were poor surgical candidates because of poor hepatic reserve function, comorbidity, age, or economic reason, and others rejected surgery because they did not want invasive management. All agreed to enter this study voluntarily. The criteria for exclusion were tumors >3 cm, age younger than 18 years, with evidence of extrahepatic metastasis, invasion of the portal vein or massive shunt, uncontrolled liver disease decompensation (total bilirubin  $\geq$  4.0 mg/dL, aspartate aminotransferase or alanine aminotransferase  $\geq$  150 IU/L, gastrointestinal bleeding, encephalopathy, refractory ascites), bleeding tendency (platelet count  $<60 \times 10^9$ /L after correction or prothrombin time <60%), low leukocyte count (<2,000/ $\mu\text{L}$ ), percutaneous injection not feasible owing to location of the tumor, compromised immune state, pregnancy or lactation, history of severe allergic reactions (especially to crab), renal failure, previous radiation treatment of upper abdomen, acute infection, treatment for hepatocellular carcinoma within 4 weeks, or inability to give informed consent.

Informed consent was obtained from all participants in this phase IIb clinical trial, which had been approved by the Investigation and Ethics Committee of the hospital and by the Korean Food and Drug Administration.

**Preparations of  $^{166}\text{Ho}$ /chitosan complex (Milican).** The  $^{166}\text{Ho}$  solution [ $^{166}\text{Ho}(\text{NO}_3)_3 \cdot 5\text{H}_2\text{O}$ ] was generated at the Korean Atomic Energy Research Institute (Taejeon, Korea). In this study, we used  $^{166}\text{Ho}$ /CHICO. Chitosan is a  $\beta$ -1,4-linked polymer of 2-deoxy-2-amino-D-glucose derived from the deacetylation of chitin (11) and was supplied by the Pharmaceutical Development Laboratory of Dong Wha Pharmaceutical (Kyunggi-do, Korea). On the day of the injection, the radiolabeled agent was added to nonradiolabeled agent and shaken vigorously for 2 to 3 minutes to form an injectable solution of  $^{166}\text{Ho}$ /CHICO. The mixture was allowed to stand at room temperature for 30 minutes. Based on the results of phase I clinical trial, the amount of  $^{166}\text{Ho}$ /CHICO required to administer a dose 20 mCi/cm tumor diameter was calculated on the day of injection, and this volume was injected percutaneously directly into the tumor under ultrasound guidance.

**Clinical methods.** The preparations for the PHI procedure were done according to the methods used for percutaneous needle aspiration biopsies. With ultrasonographic guidance to target lesion (Fig. 1A), a 21-gauge, four-holed needle was introduced into the tumor (Fig. 1B), and the  $^{166}\text{Ho}$ /CHICO was injected. The injection was verified by sonographic demonstration that the tumor lesion had become hyperechoic (Fig. 1C). Only a single session for each patient of PHI was planned in this study. On the day of the injection and the following day,  $\gamma$  scans were done to confirm the retention of the radioisotope in the tumor (Fig. 1D). The concentration of radioactivity in the blood was also checked at the time of  $\gamma$  scanning.



**Fig. 1.** Complete tumor necrosis in a 60-year-old female patient with hepatocellular carcinoma after treatment by percutaneous injection of  $^{166}\text{Ho}$ /CHICO. *A*, a nodule showing contrast enhancement similar to liver parenchyma was confirmed as hepatocellular carcinoma. *B*, the hyperechoic nodule with peripheral hypoechoic rim on sonography. *C*, the nodule showed increased echogenicity after the injection of  $^{166}\text{Ho}$ /CHICO. *D*, on Gamma scan taken on the day of injection, well-retained radioisotope confined to the tumor is noted at anterior view. *E*, the nodule had become a hypoattenuated lesion on arterial and delayed phase 2 months after the procedure, which was suggestive of hemorrhagic necrosis of the tumor.

Before the procedure and at 1, 3, and 6 months after the treatment, a complete blood cell count, routine chemistry, and urinalysis were conducted. All patients underwent abdominal sonography at 1 month and received a dual-phase liver spiral computed tomography scan at 2 months after the treatment (Fig. 1E). The ultrasonography was done to find out early treatment failure. The 2-month computed tomography scan was done to determine the initial tumor response. The tumor response was evaluated under WHO tumor response criteria with the European Association for the Study of the Liver modifications (16), estimating the reduction in enhanced viable tumor area by spiral computed tomography. Thereafter, until the end of the study or death, the patients were evaluated every 3 months with computed tomography scans, measurement of serum  $\alpha$ -fetoprotein, and routine blood tests to determine the long-term responses of the treatment and the recurrence of tumors.

The response to PHI was determined to be complete or partial necrosis or progression based on the findings of the spiral computed tomography scans at 2 months posttreatment. Tumor necrosis was defined as a necrotic portion of tumor that was not enhanced on either the arterial or portal phase of the spiral computed tomography scan. Local recurrence was diagnosed when enhancing foci were observed close to, along the edge of, or within the tumor area.

Size increase measured by ultrasonography after 1 month or incomplete tumor necrosis confirmed by the spiral computed tomography scan after 2 months was regarded as a therapeutic failure, and another therapeutic modality was selected, such as surgery or transcatheter arterial chemoembolization, for the continuation of treatment.

The side effects and complications of PHI were monitored during the procedure and for 6 months thereafter and were described according to the WHO toxicity criteria. In the case of initial abnormal grade at baseline, the difference between grading scales was regarded as severity. Toxicity was recorded at most severe state regardless of time.

**Statistical analysis.** The patients' baseline characteristics and follow-up results are presented as the median and range of the values. The rates of local recurrence, occurrence of new lesions, death, local tumor-free survival, and overall survival, as well as the cumulative local recurrence rates and the cumulative tumor-free time from the procedure, were calculated using the Kaplan-Meier method using SPSS 11.0 software (version 11; SPSS, Chicago, IL).

**Results**

The clinical characteristics of the patients are summarized in Table 1. The median tumor diameter was 2.45 cm (range, 1.3-3.0 cm), and the median follow-up duration was 26 months (range, 2-38 months). The median serum α-fetoprotein level was 160 ng/mL (range, 1.8-5,635.0 ng/mL) before treatment and 15.8 ng/mL (range, 0.57-2,479 ng/mL) 2 months after the procedure. The median injected dose of <sup>166</sup>Ho was 50.0 mCi (range, 30-60 mCi; Table 1). The distribution of risk factors for hepatocellular carcinoma was as follows: 28 patients (71%) were positive for HBsAg, seven patients (17.5%) had alcoholic liver disease, four patients (10%) were positive for anti-HCV, and one patient had no history of liver disease.

Of the 40 patients, 29 (72.5%) were treated as first-line therapy. The diagnoses of 16 patients were confirmed with biopsy, and the remaining patients were diagnosed based on typical radiological findings and elevated serum α-fetoprotein. The tumor locations were mainly in the right lobe (72.5%).

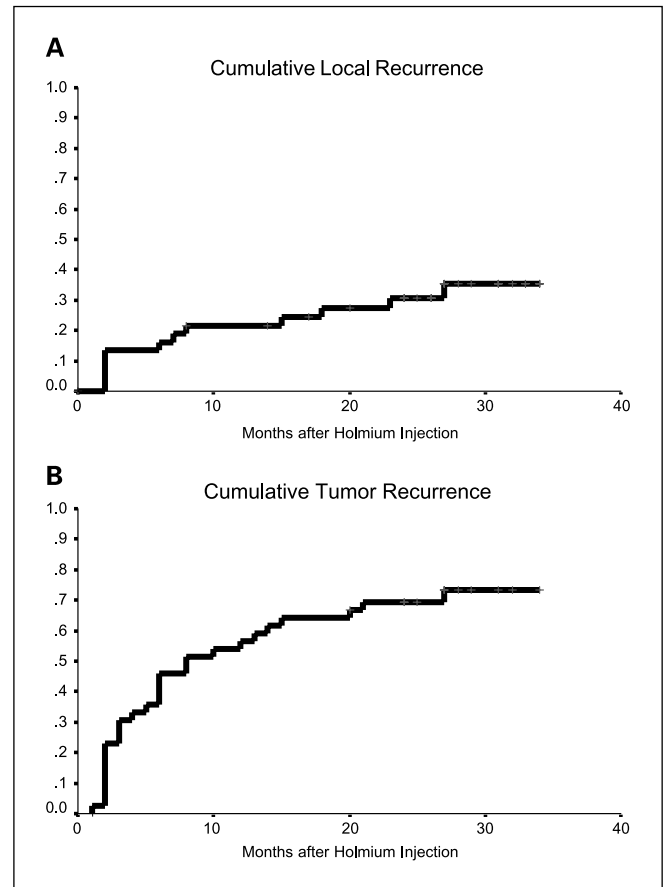
Generally, the PHI procedure was well tolerated in all patients. The short-term response, assessed on computed tomography scans done at 2 months after the PHI procedure, showed that 31 of 40 patients (77.5%) with hepatocellular carcinoma lesions <3 cm had complete tumor necrosis. Of 12 patients with hepatocellular carcinoma lesions <2 cm, 11 patients (91.7%) had complete tumor necrosis. A partial response was achieved in four patients (10%), and stable

**Table 1.** Clinical characteristics of the patients

| Characteristics                   | n = 40 (%) |
|-----------------------------------|------------|
| Sex                               |            |
| Male                              | 27         |
| Female                            | 13         |
| Age (y)                           |            |
| Median                            | 58.5       |
| Range                             | 38-83      |
| Tumor size (cm)                   |            |
| Median                            | 2.45       |
| Range                             | 1.3-3.0    |
| AFP before treatment (ng/mL)      |            |
| Median                            | 160.0      |
| Range                             | 1.8-5635   |
| AFP 2 mos after treatment (ng/mL) |            |
| Median                            | 15.8       |
| Range                             | 0.57-2479  |
| Dose of <sup>166</sup> Ho (mCi)   |            |
| Median                            | 50.0       |
| Range                             | 30-60      |
| TNM stage*                        |            |
| I                                 | 12 (30.0)  |
| II                                | 28 (70.0)  |
| Tumor location                    |            |
| Lateral segment                   | 9 (22.5)   |
| Medial segment                    | 2 (5.0)    |
| Right lobe                        | 29 (72.5)  |

Abbreviation: AFP, α-fetoprotein.

\*According to the modified Unio Internationale Contra Cancrum criteria.



**Fig. 2.** A, cumulative local recurrence rate at long-term follow up. B, cumulative intrahepatic recurrence rate at long-term follow-up.

disease was achieved in four patients (10%). One patient was lost to follow-up at the time of the short-term response evaluation.

To assess the long-term response, 31 patients for whom complete tumor necrosis was achieved were followed. Of these patients, 11 maintained a complete response status, one patient had a local recurrence, three patients had local and other intrahepatic recurrences, and 16 patients had other intrahepatic recurrences without local recurrence over 26.5 months of median follow-up duration (range, 9-36 months).

The 1-year and 2-year cumulative local recurrence rates of enrolled patients were 18.5% and 34.9%, and the 1-year and 2-year cumulative recurrence rates were 66.1% and 69.2% respectively (Fig. 2). The 1-year, 2-year, and 3-year survival rates were 87.2%, 71.8%, and 65.3%, respectively (Fig. 3).

Two patients required hospitalization due to transient bone marrow depression 1 month after the procedure. Minor side effects after the procedure were noted (Table 2), however, improved after simple medication or hospitalization with conservative management.

**Discussion**

Internal radiation therapy for hepatocellular carcinoma makes use of an internal radiation source that, owing to the characteristics of the delivery system, achieves a degree of

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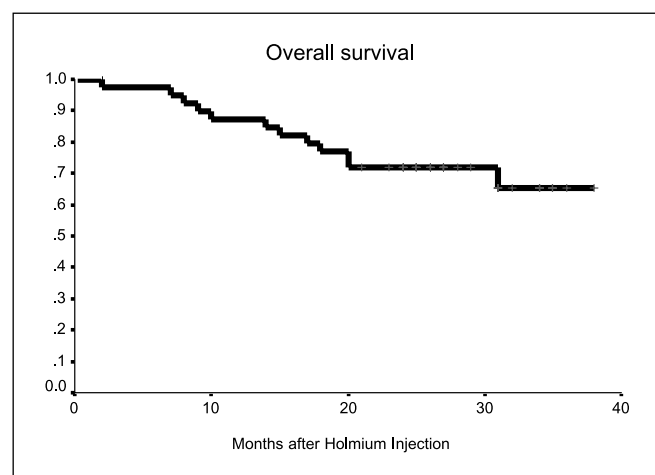


Fig. 3. Overall survival rate at long-term follow-up (Kaplan-Meier method).

selective uptake within liver tumors. This selective uptake permits a high dose of radiation to be delivered to the tumor tissue with little or no risk of serious radiation hepatitis, gastro-duodenitis, or pneumonitis.

We have previously presented the results of treatment with percutaneous injection of  $^{166}\text{Ho}$  microaggregates and compared them with those of treatment using segmental transcatheter arterial chemoembolization (17).

In this study, biodegradable chitosan, rather than microspheres remained persistently, was used as the vehicle to deliver and retain  $^{166}\text{Ho}$  at the tumor site. Chitosan, which is obtained from the exoskeletons of crustaceans, such as crab and shrimp, possesses the useful property of transforming from a liquid to a gel state depending on the pH of the surrounding environment. It is a polymer of 2-deoxy-2-amino-D-glucose and is readily dissolved in water to yield a clear solution under acidic conditions but is converted to the gel state under neutral or

basic conditions above pH 6 (18), such as those found in injected tumor tissues, thus effectively holding the bound holmium in place (19). By exploiting this unique property,  $^{166}\text{Ho}/\text{CHICO}$  was developed to prevent systemic distribution of  $^{166}\text{Ho}$ , and upon injection, it destroys tumors and pericapsular lesions while salvaging the surrounding normal tissue.

In the present study, after the percutaneous administration of  $^{166}\text{Ho}/\text{CHICO}$ , the concentration of radioactivity in the blood was low (data not shown), and the cumulative urinary and fecal excretions of the agent over the period from 0 to 72 hours were 0.53% and 0.54%, respectively. Suzuki et al. (9) has shown the suitability of  $^{166}\text{Ho}/\text{CHICO}$  for local injection by showing that at 24 hours after the injection, <1% of the total injected amount was detectable in tissues other than those at the injected site.  $^{166}\text{Ho}/\text{CHICO}$  diffuses from the injected site only minimally because it is transformed into a gel in the tissues, and because it has an appropriately limited half-life. In an evaluation of acute toxicity in mice after the i.v. injection of  $^{166}\text{Ho}/\text{CHICO}$ , the major effects of the injection of 1 mCi/kg were limited to the spleen, and the changes in the hematologic variables were reversible by day 14 after the injection (20).

Mechanism of tumor control by intratumoral injection of  $^{166}\text{Ho}$  was revealed in melanoma model. Using high-dose continuous irradiation with intratumoral injection, the main cell death mechanism in the central portion is necrosis. Peripheral tissue, which received a lower radiation dose, showed growth arrest, as in conventional radiation therapy. Therefore, growth arrest and necrosis were thought to be the main cell death mechanisms with this technique (21).

Several radionuclides are used for selective internal radiation therapy (i.e.,  $^{131}\text{I}$ ,  $^{90}\text{Y}$ , and  $^{166}\text{Ho}$ ). We believe that  $^{166}\text{Ho}$  has several distinctive features over the other currently used radionuclides. First,  $^{166}\text{Ho}$  can be produced from  $^{165}\text{Ho}$ , a naturally abundant element, by an uncomplicated process. In addition, because  $^{166}\text{Ho}$  emits  $\gamma$ -rays that permit image acquisition, it is also suitable for the confirmation of its accumulation at the targeted site and for quantitative dosimetric

**Table 2.** Frequency and grade of side effects during 2 months after the procedure using the Common Terminology Criteria for Adverse Effects version 3.0

| Toxicity            | No. patients with maximum toxicity grade (n = 40) |                                       |                                       |                                       |
|---------------------|---|---------------------------------------|---------------------------------------|---------------------------------------|
|                     | G <sub>1</sub> or 1 grade drop, n (%)             | G <sub>2</sub> or 2 grade drop, n (%) | G <sub>3</sub> or 3 grade drop, n (%) | G <sub>4</sub> or 4 grade drop, n (%) |
| Injection site pain | 1 (2.5)   | 22 (55.0)                             |                                       |                                       |
| Back pain           | 7 (17.5)  | 1 (2.5)                               |                                       |                                       |
| Fever               | 6 (15.0)  | 18 (45.0)                             |                                       |                                       |
| Nausea              | 7 (17.5)  | 6 (15.0)                              |                                       |                                       |
| Facial edema        | 1 (2.5)   | 1 (2.5)                               |                                       |                                       |
| Headache            | 4 (10.0)  | 4 (10.0)                              |                                       |                                       |
| Skin rash           | 5 (12.5)  |                                       |                                       |                                       |
| Hematuria           | 1 (2.5)   |                                       |                                       |                                       |
| Leucopenia          | 11 (27.5)   | 8 (20.0)                              | 1 (2.5)                               |                                       |
| Anemia              | 4 (10.0)  | 1 (2.5)                               | 1 (2.5)                               |                                       |
| Thrombocytopenia    | 11 (27.5)   | 6 (15.0)                              | 2 (5.0)                               | 2 (5.0)                               |
| AST/ALT elevation   | 3 (7.5)   | 2 (5.0)                               |                                       |                                       |
| Jaundice            | 1 (2.5)   |                                       |                                       |                                       |

Abbreviations: AST, aspartate aminotransferase; ALT, alanine aminotransferase.

studies. Third, <sup>166</sup>Ho has a shorter half-life of 26.8 hours than <sup>131</sup>I and <sup>90</sup>Y, making it possible to discharge the patient on the day after the procedure. Finally, the  $\beta$  emissions of <sup>166</sup>Ho have an adequate penetration range for the ablation of tumors, including pericapsular lesions, while avoiding damage to adjacent nontumorous tissue. <sup>166</sup>Ho deposits 90% of its energy within an area 2.1 mm in diameter, whereas the remainder is deposited within an area 2.1 to 8.7 mm in diameter (mean, 2.2 mm; ref. 19). Thus, the patients do not have to be isolated and need few special precautions.

Compared with other percutaneous ablative therapies, such as PEIT and RFA, PHI using <sup>166</sup>Ho/CHICO also has several merits complementing other established local therapies. PHI can be completed in a single session; it causes less pain and inflammatory reactions than PEIT, which usually requires multiple sessions. In addition, because necrosis occurs only after direct contact between the tumor tissue and ethanol, marginal treatment failure may occur more commonly in PEIT. In PHI, the penetration of radiation into the tissue surrounding the injected area can resolve this limitation. RFA has the advantage of causing necrosis in a large tissue volume in one session and destroying a predictable amount of tissue in a reproducible manner. However, RFA requires complex and expensive equipment and involves a more invasive injection procedure than either PEIT or PHI. It has been shown that the location of treatable tumors is more limited for RFA, especially for tumors near the gallbladder, with subcapsular location or adjacent to the hepatic hilum where running large vessels occur (22, 23). Precise puncture and insertion of the large-diameter radiofrequency electrode is technically more unfeasible than that of the fine noncutting needle used for PEI or PHI. Tumor seeding along the puncture tract has been reported for RFA (22), whereas no tumor seeding has been found in the puncture tract until now after PHI done at our institute.

In the same manner of other studies, tumor necrosis was considered where no enhancement was seen on computed tomography scan. Although there is no absolute proof of reliability for prediction of tumor necrosis, spiral computed tomography is recognized as the standard imaging modality for evaluating the response of hepatocellular carcinoma until now (24), and further histologic correlation with imaging is needed.

Initially, 40 patients were enrolled for the intention-to-treat analysis. Although 31 patients (77.5%) showed complete tumor necrosis after 2 months, four patients had marginal tumor recurrences during the long-term follow-up period.

Although no control group was in this one-armed phase II study, comparing with historical data of other therapy, PEIT achieves complete responses in 70% of patients with hepatocellular carcinoma lesions <3 cm and has been considered the gold standard treatment (25, 26). A recent study reported similar initial complete response rate (96%) to data in present study with hepatocellular carcinoma <2 cm and revealed significant relation between tumor size and complete response rate (27). The rate of complete response was higher in RFA-treated group by the same investigators comparing with PEI (90% versus 80%; ref. 28). In the present study, PHI was regarded having comparable response rates only after single session and could thus be another useful percutaneous therapeutic modality with the merits mentioned above. Further prospective comparative phase III clinical trial is in the pipeline.

In this study, no patients experienced treatment-related irreversible adverse events or mortality. However, decreases in leukocyte and platelet counts, in addition to allergic reactions to the chitosan component, were observed in some patients. Two patients (5%) admitted for cytopenia 1 month after the procedure and underwent bone marrow studies. Although the cellularity of marrow was decreased, it revealed normal maturation and normal cellular components. These two patients were completely recovered with conservative general care and administration of granulocyte macrophage colony-stimulating factor. Allergic symptoms and pain were easily improved following appropriate treatments. The blood radioactivity counts (data not shown) were found to have a correlation with the suppression of the hematopoietic system. Little amount of leakage through hypervascular tissue could be related. In recent study that analyzed 1,000 cases of RFA, major complications resulting in hospitalization or secondary procedure were observed in 4.0% of treatments, including neoplastic seeding (29). Deliberating on wide percent range of adverse rates after systemic chemotherapy, bone marrow depression in current study was acceptable to be safe.

In conclusion, the treatment of hepatocellular carcinoma with PHI is a relatively simple and effective procedure that can be done with a single, intratumoral injection given percutaneously. PHI also can be a bridge therapy to transplantation, as well as a novel local treatment modality. It causes very little discomfort and disruption of daily activities for most patients. A phase III randomized active control trial is clearly warranted for further testing of the safety and efficacy of PHI among a larger study population.

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