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Current status and future aspects on treatment of liver cancer*

Byung Soo Kim, Hyung Sik Yoo, Yong Jun Park, and John J. K. Loh

Yonsei Cancer Center, Yonsei University College of Medicine, Seoul, Korea

Summary. Among 80 patients with advanced hepatocellular carcinoma, treated by systemic chemotherapy, 19 patients (24%) achieved partial response or stable disease. The median survival time of responders was 20 weeks. Radioiodinated fatty acid esters ([^{131}I]lipiodol) are localized in hepatoma tissue for a considerable time. Taking advantage this phenomenon, there is a potential therapeutic effect of [^{131}I]lipiodol, since the radioactive oil can deliver a therapeutic dose of internal radiation. The response rate of patients who had a small hepatoma (less than 5 cm in diameter) was 80%. Among 25 responders, 12 cases are alive after more than 1 year. A pilot study of hyperthermia, using a heating device capable of delivering radiofrequencies, combined with radiotherapy or chemotherapy, demonstrated that this modality is safe and effective in the treatment of advanced hepatocellular carcinoma. Of the 19 patients treated, 47% showed partial remission or stable disease. The median survival time of 9 responders was 9 months. Among the 9 responders 3 patients survived for over 1 year.

Introduction

In Kangwha County in Korea 15 deaths from hepatoma per 100000 population occur annually. These neoplasms account for 6.7% of all cancer deaths [1].

Of various solid tumors, hepatoma is perhaps the most difficult to treat because of the frequently associated cirrhosis and advanced stage of the disease at the time of diagnosis in Korewa. The prognosis of patients with unresectable hepatoma is dismal, the median survival after diagnosis being 2–4 months in Yonsei Cancer Center.

In this article, we report our experiences with 80 patients with hepatocellular carcinoma treated by various chemotherapy regimens: 17 patients by transcatheter hepatic artery embolization, 60 patients by high internal radiation to the tumor with intra-arterial injection of the radioiodinated fatty acid ester ([^{131}I]lipiodol), and also the preliminary results of regional radiofrequency hyperthermia.

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Offprint requests to: Byung Soo Kim, Yonsei Cancer Center, C. P. O. Box 8044, Seoul, Korea

Materials and methods

Systemic chemotherapy. From 1980 through 1986, 101 patients with hepatocellular carcinoma were treated with systemic chemotherapy at Yonsei Cancer Center. The clinical records of all patients were reviewed; chemotherapy regimens, response to therapy, and survival were also noted. The chemotherapeutic regimens were 5-fluorouracil + adriamycin + mitomycin C, 5-fluorouracil + mitomycin C, and 5-fluorouracil + cisplatin. Because of a rapid deterioration in their condition, many patients received only a single chemotherapeutic agent (see Table 1).

Transcatheter intra-arterial therapy. From March 1985 to September 1985, transcatheter hepatic arterial embolization was performed in 17 patients with hepatocellular carcinoma. The materials used embolization were Ivalon (14 patients), absolute alcohol (2 patients) and Gelfoam (1 patient).

Radioiodinated fatty acid ester ([^{131}I]lipiodol) therapy. From 1985, 60 patients with primary hepatocellular carcinoma were treated with [^{131}I]lipiodol alone or in conjunction with embolization. There were 49 men and 11 women, whose ages ranged from 32 to 72 years. A small fraction of the stable iodine. (^{127}I) in lipiodol was replaced with radioactive ^{131}I by a simple exchange method. Volumes ranging from 5 ml to 15 ml [^{131}I]lipiodol were injected into the feeding hepatic artery for hepatoma. The total protracted radiation dose delivered to the tumor was aimed at 12000 rad. The response is defined as stasis or shrinkage of tumor over 6 months following the injection, measured by computed tomography.

Hyperthermia combined with chemotherapy and radiotherapy. From 1985, 19 patients with far advanced hepatocellular carcinoma have been treated with hyperthermia at this center. In each instance, the chemotherapy combined with hyperthermia consisted of adriamycin 40 mg/m^2 every 4 weeks, mitomycin C 8 mg/m^2 every 8 weeks and 5-fluorouracil 8 mg/kg twice weekly. These agents were administered 1 h prior to hyperthermia. Localized hyperthermia was administered by a heating device which delivered radiofrequencies (Thermotron RF-8) and treatment was started within 1 h after radiotherapy or chemotherapy. The heating period was 40–60 min after the temperature had reached 42° C above body temperature. The vital signs were monitored during the treatment.

Results

Systemic chemotherapy

A total of 101 patients with hepatocellular carcinoma received chemotherapy, but 21 had to be withdrawn from trial, leaving 80 patients evaluable. There are no complete responses. Nineteen patients showed a partial response or stable disease (Table 1). Response to treatment was associated with prolongation of survival. The median survival times of patients who showed a partial response or stable disease (19 patients) and no response were 20 weeks and 6 weeks respectively.

Transcatheter intra-arterial therapy

The devascularization of tumor vessles, as seen in a post-embolization hepatic angiogram, was complete in 6 patients and partial in 11. In the follow up computed tomography scan, 3 to 4 weeks after embolization, necrotic density was revealed in 8 patients. There are no differences in survival or objective tumor response between patients who received systemic chemotherapy and those treated by hepatic embolization. The complications were fever with temperatures higher than 38° C (92%), abdominal pain (72%) and nausea or vomiting (40%). These symptoms subsided within 7 days [2].

Radioiodinated fatty acid ester [^{131}I]lipiodol) therapy

[^{131}I]Lipiodol is localized in the hypervascular hepatocellular carcinoma for a considerable time following intra-arterial hepatic artery in injection, enabling the delivery of a high dose of internal radiation to the tumor. High-dose radiation (12000 rad) can easily be delivered to small hepatomas less than 5 cm in diameter in single or multiple injections with an 8-week interval. The response rates of patients who had small tumors (less than 5 cm), medium-size (5–10 cm) and larger tumors (larger than 10 cm) were 80%, 55% and 21.9% respectively. Among 25 responders, 12 cases are still alive after more than 1 year [4].

Hyperthermia combined with chemotherapy and radiotherapy

Of the 19 patients with advanced hepatocellular carcinoma, 10 patients were treated by hyperthermia combined with radiotherapy and 9 patients by hyperthermia combined by chemotherapy. The age of patients enrolled in this study ranged from 35 to 75 years. The follow-up periods after treatment ranged from 2 to 30 months. The response rates of patients who were treated by hyperthermia combined with radiation and chemotherapy were 55% and 40% respectively. The median survival times of the 9 responders among 19 patients was 9 months, and 3 of these survived for 14, 20 and 30(+)months. The median survival time of the 10 non-responder was 3 months. Only one patient among the non-responders survived for over 1 year. Complications during heating were a hot sensation and pain. No serious clinical problems were observed.

Table 1. Chemotherapy regimen for hepatoma

Regimen	Patients	PR+SD[b]
5-Fluorouvacil infusion	22	3
FAM[a]	48	12
5-Fluorouvacil mitomycin C	6	3
5-Fluorouvacil + cisplatin	4	1
Total	80	19 (24%)

[a] FAM, 5-fluorouvacil + adriamycin + mitomycin C
[b] PR, partial remission; SD, stable disease

Discussion

The prognosis of patients with unresectable hepatocellular carcinoma is dismal, median survival from diagnosis being only 2 months in Korea because most hepatomas arise in cirrhotic livers associated with the hepatitis B virus. Although the majority of our patients with hepatoma treated with systemic chemotherapy also died within a few months of diagnosis, we found that individual factors associated with improved survival included good performance status, lack of jaundice and response to chemotherapy. There has been a great deal of controversy about the role of hepatic artery embolization. In theory, it is an attractive concept, although the clinical effectiveness in terms of survival has not improved markedly because of the prompt development of collateral channels to the tumor tissue.

An oily contrast medium, lipiodol, injected into the hepatic artery was found to remain selectively in the vascular canals in the tissue of liver tumors for considerable time [3]. We elected to try radioembolization ([^{131}I]lipiodol) in the management of hepatocellular cancer. For small tumors, a cancercidal radiation dose (12000 rad) can be delivered by intra-arterial hepatic administration of [^{131}I]lipiodol with a minimal radiation dose to normal liver, lung and the whole body. The key point of intra-arterial injection of [^{131}I]lipiodol is to make the radioactive materials selectively retainable at high concentration in the tumor tissue for a prolonged period of time. We found a high tumor radioactivity, 15–20 times greater than that over the non-tumor bearing liver and lung.

Our pilot study demonstrated that radiofrequency hyperthermia treatment was potentially useful for hepatoma if combined with radiotherapy, and had negligible systemic side-effects.

Over 47% of the 19 patients with advanced hepatomas that were considered refractory to conventional treatment showed partial remission and stable disease. Although our results do not permit conclusions to be drawn concerning the influence of hyperthermia and a combined modality on survival, the data from patients among the responders suggest that there may be a substantial positive effect in killing hepatoma cells.

The quality of life in patients who achieved partial remission is excellent. A dramatic reduction in pain and fatigue was observed by all the patients responding to treatment. In patients whose tumors did not respond to hyperthermia, the survival time and quality of life were not compromised by the treatment itself.

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