7. Treatment of Advanced Hepatocellular Carcinoma

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Key words: hepatocellular carcinoma, chemotherapy, implanted port system

Introduction

Hepatocellular carcinoma (HCC) is one of the most common malignancies and over twenty thousand patients die because of HCC annually. As most HCC patients are associated with liver cirrhosis and multicentric carcinogenesis has been considered in HCC, surgical resection is limited and approximately 80% of HCC patients are treated non-surgically. Small HCC lesions of less than 30mm in diameter are mainly treated with percutaneous ethanol injection therapy (PEIT). Recent studies have indicated no difference in survival between patients treated with PEIT or surgical resection. Patients with advanced nodular lesions of HCC of over 30mm in diameter commonly receive transcatheter arterial chemoembolization (TAE) with Lipiodol®. TAE is, strictly speaking, not a curative treatment and supplementary therapies are needed. Our recent studies have shown that TAE combined with PEIT gives a better prognosis. In far-advanced HCC, arterial chemotherapy is usually indicated, however, at present, no extensive studies on the chemotherapy for HCC have been carried out. Thus, no good regimen has been established as yet. Current treatments for HCC are shown in Fig. 1.

Chemotherapy for far-advanced HCC

Advanced HCC is supplied only by arterial blood. Thus, it is well accepted that arterial infusion of anticancer drugs for advanced HCC is reasonable. For years, the procedure of a bolus injection of anticancer drugs has been administered by Seldinger’s method. However, this procedure is difficult to perform repeatedly and the therapeutic effects are limited. Recently arterial chemotherapy using a totally implanted injection port system has been widely used and therapeutic effects have been remarkably improved.

Anticancer drugs used for HCC

Anticancer drugs used for systemic chemotherapy in HCC are Adriamycin (ADR), Epirubicin, Mitoxantrone (MIT), 5-FU, Etoposide and Cisplatin (CDDP); their response rates to tumors are extremely poor (around 10%). Our preliminary studies using an injection port system indicated that the effective rate of CDDP, MMC and ADR used separately showed a poor response to tumors. However, CDDP, MMC or ADR combined with 5-FU showed a good response (Fig. 2). Among these combinations, CDDP+5FU appeared to be the most effective.

Fig. 1. Treatment of HCC. PEIT: percutaneous ethanol injection therapy, TAE: transcatheter arterial embolization.
Sensitivity test of anti cancer drugs

Chemotherapy would be more effective if sensitivity tests could be carried out in each case of HCC. However, biopsy is not usually performed in advanced HCC cases because of various disadvantages. In such a setting we have performed MTT or flow cytometry tests as a sensitivity test on HCC cell lines of various cell differentiation. The results of these studies showed that, CDDP, 5-FU, VP-16 and MIT have a relatively good response (Fig. 3); and finally CDDP, 5-FU and MIT were selected for clinical study.

Arterial chemotherapy using an injection port system for advanced HCC

Arterial chemotherapy was carried out using a port system, in 45 cases of advanced HCC. 5-FU combined with CDDP or 5-FU combined with CDDP+MIT was given five days a week for one month. The 2-year survival rate was 37%, which was significantly better than the non-treatment group (Fig. 4). No difference was noted between groups with MIT and without it. Further, no difference was seen between groups with advanced intravascular invasion and those without, suggesting that these combination therapies are also effective for the tumor thrombus. CDDP-5FU combination arterial chemotherapy using an injection port system seem to be effective for advanced HCC. This efficacy can be understood as a trial of biochemical modulation (1). Further efforts are necessary to achieve a better regimen by control studies and detailed indication criteria must be established for improved chemotherapy for HCC.

References


Fig. 2. Effects of anticancer drugs for hepatocellular carcinoma-comparison between unidrug and multidrug groups.

Fig. 3. Sensitivity test of anticancer drugs to various HCC cell lines.
8. New, Effective Treatment Using Proton Irradiation for Unresectable Hepatocellular Carcinoma

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**Key words:** proton irradiation, hepatocellular carcinoma, Bragg peak

In 34 hepatocellular carcinoma patients (44 lesions), proton irradiation was performed and assessed. Proton irradiation was effective for the nodular HCC in terms of tumor size reduction and histology and almost 100% local tumor control was obtained during the observation period of at least 2 years, which is still undergoing up to 4 years. This therapy is safe and has the merit of excellent QOL during the treatment without any complaints. Further, this method is feasible for patients of deep-seated tumors, and for those with serious complications. Due to the excellent local tumor control, the determining factor for the survival is not affected by the proton irradiation but by the associated complications such as liver cirrhosis.

**Background**

Conventional external radiotherapy has limited success in hepatocellular carcinoma (HCC), and is not always a recommendable approach among the treatment options. The reason is the severe adverse effects, such as hepatic failure, caused by irradiation accompanying cirrhotic liver. Thus, doses large enough to achieve anticancer effects cannot be accomplished. The proton beam has a Bragg peak that can limit distribution of the beam, which reduces radiation to the non-targeted area while increasing that hitting the target. Recently, we preliminary reported that a large quantity of protons can be safely...