

Treatment of Advanced Hepatocellular Carcinoma (HCC) with the Combined Protocol of Chemotherapy 5-Fluorouracil and Traditional Medicine: Report of Ten Cases

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Abstract

Background: The global burden of Hepatocellular Carcinoma (HCC) is significant. In search for the effective approach of PHC, we had summarized the retrospective study of HCC under remission, with the combined protocol of chemotherapy and traditional medicine.

Methods: All ten patients with HCC were in progressive at hospitalization. The criteria of Complete Remission (CR) and/or Partial Remission (PR) is according to the rules where physician have in common with in clinics.

Results: Ten advanced hepatocellular carcinomas had been successfully treated using combination chemotherapy and traditional medicine. Six of ten HCCs (three patients with liver CT tumor 6.3×4.5 , 11.1×6.2 , 3.0×2.7 cm, respectively, one patient AFP 7500 ng/ml) obtained complete remission through 5-Fluorouracil and traditional medicine. Two HCCs (one patient AFP 200ng/ml, ascites +++, icterus index 100 u) obtained complete remission through cantharidine and traditional medicine. The main protocol of traditional medicine with adjuvant the antibiotics regimen and small dosage of dexamethasone (prednisone) administration was given in a primary hepatocellular carcinoma (AFP +, ascites +++, Jaundice +++, liver tumor 3.2×3.0). One acute promyelocytic leukemia complicated with metastatic hepatocellular carcinoma (7.0×4.5 cm) was in CR with All-Trans Retinoic Acid (ATRA) and traditional medicine. All ten patients with disease-free survival were 2,2,8,6,10,15,20,20 years, 18 months (died in HCC relapse), and 20 months (died in leukemia relapse) respectively.

Conclusion: In this paper we observed in detail the objective response of the combined protocol of chemotherapy (mainly 5-Fluorouracil) and traditional medicine in the treatment of Hepatocellular Carcinoma (HCC). Interesting, one case was only given All-Trans Retinoic Acid (ATRA) and traditional medicine. A Hepatitis B Virus (HBV) integration in a human steroid hap Retinoic Acid Receptor (RAR β) previously detected may involve in hepatocellular carcinogenesis, and ATRA use in this case. And also, an additional data indicate that human Hepatocyte Growth Factor (HGF) and HGF receptor (HGFR/metoncogenic receptor) act as a trigger for liver regeneration after partial hepatectomy and liver injury, even in (hepatocellular) carcinogenesis, which was also discussed.

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Introduction

The global burden of Hepatocellular Carcinoma (HCC) is significant. As the fifth most common malignancy and the third leading cause of cancer-related deaths, a high mortality rate as high as 70%, in worldwide^[1,2]. In Japan's group, A 95.4% of mortality rate occurs within 1 year in 1114 cases of HCC in 1976, and in China the average survival time 4.2 months in 2141 cases of HCC, stage II, III according to statistics analysis. HCC occurs most frequently in the setting of chronic liver injury and cirrhosis. Geographic variation in incidence is primarily related to patterns of infection with hepatitis B and hepatitis C. Although the incidence of HCC in Western countries is on the rise due to the impact of hepatitis C, an approximately 80% of Hepatocellular Carcinoma (HCC) cases occur in developing countries especially in Asian countries related to endemic hepatitis B^[3,4]. An additional data indicate that human hepatocyte growth factor (HGF) and HGF receptor (HGFR/met oncogenic receptor) act as a trigger for liver regeneration after partial hepatectomy and liver injury (Nakamura, et al, 1987), even in carcinogenesis^[5].

As to the therapy of Primary Hepatocellular Carcinoma (PHC), a 15 - 50% of earlier patients with a five years of disease-free survival was achieved undergoing surgical operation. In clinical situation only 5.3% of patients who were belonged to the indication of hepatectomy whereas 90% of them was conclusively the protocol of chemotherapy. One of this approaches, traditional medicine occupied its important role in the field of hepatocellular carcinoma treatment. In search for the effective approach of PHC, we had summarized the retrospective study of HCC under remission, with the combined protocol of chemotherapy and traditional medicine.

Methods and Results

All ten patients with HCC were in progressive at hospitalization. The criteria of Complete Remission (CR) and/or Partial Remission (PR) is according to the rules where physician have in common with in clinics. The detail results of ten patients described below.

Case reports

Case 1

A 52-year-old man was diagnosed as having Primary Hepatocellular Carcinoma (PHC), stage II in March 28, 1983 when he presented with both abdominal mass and abdominal pain for 2 months, complicated by progressive weakness, lethargy, weight loss and loss of appetite. At admission an enlarged hardens and nodular liver was felt 9 cm below the right costal margin. Investigations included normal serum bilirubin, serum r - glutamyl transpeptidase (r-GT) 240 u, serum α - fetoprotein (AFP) 7500 ng/ml, serum Alkaline Phosphatase (AKP) 16 u. Liver scan provided a diffuse infiltrate defect affecting both lobes of liver. Ascites negative. Treatment consisted of 500 mg of 5-Fluorouracil (5-Fu), 1 mg of Toyomycin, 1 mg of Vincristine (VCR) intravenously once a week. Partial Remission (PR) was obtained after 6 courses of the combination chemotherapy. In view of improvements in his general symptoms, a striking decrease in size of hepatomegaly, in comparison of the previous results on admission, receded to 3 cm below the right costal mar-

gin, and associated with further improvements of liver enzymes. Serum AFP was declined to 942 ng/ml. Serum r-GT 176 u. Serum AKP 8 u, and serum SGPT negative. The combination chemotherapy was continuous to be performed in September 1983 and in May 1984 respectively during the period of outpatient in addition to traditional medicine. On examination he presented a normal size of liver. Laboratory data that serum AFP was 50 ng/ml, serum r-GT 60 u, and serum AKP 4.2 u. A CR (disease-free survival) with 2 years was achieved and recovery of his job again.

Case 2

A 55-year-old man was admitted to hospital because of his PHC, stage II in November 18, 1976. An abdominal mass was slowly enlarged for 2 months, accompanied with abdominal pricking pain, abdominal distension, and further deteriorating followed by soft fluid diet. On examination showed that a palpable hepatomegaly (4 - 5 cm) associated with moderate harden and nodules in right upper abdominal quadrant. Abnormal liver enzyme presented serum AFP positive and serum r-GT 243 u. Liver scan demonstrated a filling defect. Ascites negative. 5-Fluorouracil (5-Fu) at 1000 mg once a week was administered intravenously, with adjustment of traditional medicine. In February 2, 1977, investigations provided, following the courses of eight weeks, serum AFP negative and serum r-GT 100 u. Repeat liver scan indicated the complete resolution of the hepatic lesion. A CR (disease-free survival) with 8 years was achieved.

Case 3

A 60-year-old man with PHC, stage III was admitted to hospital in July 25, 1979 because of abdominal distention and hemorrhagic ascites for 2 months, with a complaint of increasing whole body jaundice, loss of appetite, nausea and vomiting one month duration. Grossness he developed generalized hepatocellular jaundice. The abdomen was markedly protuberant. On examination an enlarged, harden and regenerating nodular liver was felt 4 - 6 cm below the right costal margin, and associated with the elevation of liver enzyme. Laboratory data showed serum icterus index 100 u, serum van den Bergh test (direct and indirect) positive, serum AFP 200 ng/ml, serum AKP 134 u, and serum r-GT 16.2 u. Ascites positive. Treatment consisted of 16 mg of (Demethyl) cantharidine daily added in 5% of saline solution infusion. Total dosage of cantharidine 1872 mg. A disappearance of ascites and jaundice was noticed. Laboratory data showed serum icterus index 12 u, serum van den Bergh test weak positive, serum AFP negative, serum AKP 27 u, and serum r-GT 5.4 u. He was discharged on October 6, 1979 and, as an outpatient, continued to undergoing the maintenance therapy of traditional medicine.

In May 10, 1983, physical examination revealed a moderate harden and receded liver to 2.5 cm in the comparison of her admission. The remainder of liver enzyme performed serum r-GT 13 u, serum AKP 2 u, and serum AFP < 50 ng/ml (negative). In the following years the patient with 6 years of disease-free survival remained well.

Case 4

A 37-year-old women was admitted to hospital because of her PHC, stage III in September 28, 1974. In clinical manifestation she developed an intermittent fever and right upper

quadrant tenderness. Prior to 40 days on admission there was histologically evidence of multiple subcutaneous metastatic nodules due to PHC in the lower of her left abdomen. About ten small nodules (1.5×1 cm, each pea size) were scattered through the subcutaneous of the chest and abdomen lesion. An enlarged (4 cm) and moderate harden liver was palpable in the right costal margin. Liver scan revealed a filling defect in the right liver lobe. She started on the therapeutical approach of a seven days course of 5-Fu at 1500 mg/day added in 1000 ml of 5% saline solution intravenously. After two courses of treatment, then a 1500 mg of 5-Fu was administered intravenously once a week, with adjustment of traditional medicine. Three months later her fever was recovered to normal temperature, and associated with complete disappearance of subcutaneous metastatic nodules. Repeated liver scan revealed a striking decrease in her liver defect. Another 1000 mg of 5-Fu infusion once a week associated with traditional medicine, which was repeatedly performed for three months. At the same period she took 0.25 mg t.i.d of cantharidine orally. Six months later liver scan showed almost resolution of hepatic lesion. In June 5, 1976, repeated liver scan presented available that right liver lobe defect was no longer seen, and continued on an outpatient basis. A 10-years of follow up she was well.

Case 5

A 26-year-old man was admitted into hospital because of the second relapse of his metastatic Hepatocellular Carcinoma (HCC), stage III in December 28, 1997. A naked mass with 6.3×4.5 cm was palpable in his upper abdomen, with the chief complaint of abdominal distention and the attack of abdominal pain. At admission on B ultrasound examination at second relapse showed a 6.2×4.0 cm liver nodular mass, with a 3×5 cm metastatic mass in his right breast. He had the operation of ascend colon cancer in abdomen one year ago. On CT examination and on B ultrasound examination at first relapse consistently showed a 3×4 cm liver mass and peritoneum posterior metastasis: 4.0×4.5 , 3.0×2.0 cm. A CR was obtained under intensive time sequential chemotherapy. A protocol of 5-Fu 1000 - 1500 mg/day infusion with other VCR, CTX and MMC drugs, and with the combination of traditional plant herbs. A disease-free survivor with 20 years was achieved. He had a history of cerebral infarction.

Case 6

A 30-year-old man was admitted into hospital because of his Primary Hepatocellular Carcinoma (PHC), stage III in April 18, 1997 when he was suffered from symptoms of intensive abdominal pain with distended abdomen. On B ultrasound and CT examination consistently showed a roundish mass of 11.1×6.2 cm and within mass many small nodules seen in colar structure in the right posterior lobular of his liver. A CR was obtained after intensive time sequential chemotherapy. A protocol of the continuous infusion of 1500 mg/day 5-Fu with other VCR, CTX and MMC drugs, and the addition of traditional medicine. In the follow up, he was remained well with a 20 years of disease-free survivor and was in recovery of his job again.

Case 7

A 39-year-old man was diagnosed as suspicion of earlier stage of PHC in May 12, 2002 when he had the symptoms of progressive weakness, facial jaundice, and moderate distended

abdomen after eaten. Laboratory data showed serum total bilirubin 31.7 umol/L (control 4 - 23.9 umol/L), indirect bilirubin 28.6 umol/L (control 2.56 - 20.9 umol/L), serum HBsAg (+), serum HbeAb (+), serum HBcAb (+), serum AFP slightly increased from 1.9 ng/ml in 1996 to 8.7 ng/ml in January 2002 (control 0 - 8.1 ng/ml). Immune index: CD4 27 (41 ± 5 %), CD8 26 (22 ± 6 %), CD4/CD8 1.0. He had a past history of jaundice (viral) hepatitis in 1993, and cholecystectomy due to cholesterol polyp of bile in April, 2002. He was given the combination therapy of cantharidine capsule with traditional medicine, with immune adjuvant injection of p-transfer factor, BCG drugs. Three months later, in view of improvements in his general symptoms, serum bilirubin was declined to normal, serum AFP was declined to 2.05 ng/ml. Liver scan showed a normal size of liver. 15-years of follow up he remained well.

Case 8

A 47-year-old man with Primary Hepatocellular Carcinoma (PHC), stage III was admitted to hospital in June 4, 2003 because of abdominal sharp pain, abdominal distention, accompanied with hemorrhagic ascites for 20 days, with a chief complaint of increasing whole body jaundice, icterus urine, loss of appetite, nausea and vomiting ten days duration. Grossness he developed generalized hepatocellular jaundice. The abdomen was moderately protuberant. On B ultrasound examination revealed a mass 3.2×3.0 cm in right anterior lobular of his liver, accompanied with liver cirrhosis and ascites. Abnormal liver enzyme presented serum AFP positive. Treatment was given the main protocol of traditional medicine with adjuvant the empiric antibiotics regimen and dexamethasone administration. With relief symptoms of abdominal pain, icterus was disappearance. In the following days the abdominal distention with much ascites relapsed due to the stop of traditional medicine. CR can be obtained through other traditional medicine. He was a survivor of 18 months.

Case 9

A 31-year-old man who entered hospital in October 16, 2003 because of fever, irritability and pallor 15 days duration. Physical examination revealed marked pallor, hepatosplenomegaly. Persistent fever reached to 39.5°C , Chest X-ray showed small amount of hydrothorax. Liver CT scan demonstrated an elliptical mass of 7.0×4.5 cm which was considered to secondary hepatocellular carcinoma (HCC). AFP negative. Hemoglobin concentration was 53 g/L. leukocyte count $3.4 \times 10^9/\text{L}$ with 20 per cent promyelocytes. The platelet count was $2.4 \times 10^9/\text{L}$. Bone marrow aspiration revealed normal cellularity. Approximately 77% of marrow cells were promyelocytes. The diagnosis of Acute Promyelocytic Leukemia (APL) complicated with hepatoma was made. Treatment consisted of 80 mg per day of All-Trans Retinoic Acid (ATRA) in conjunction with traditional medicine. Chemotherapy homoharringtonine 1mg intravenously per day for 5 days. After one month of therapy, he obtained Complete Remission (CR) of APL. He was continuous to the maintenance treatment of traditional medicine for three months. The liver scan showed the disappearance of hepatic tumor. The patient died in a relapse of APL with 94% of promyelocytes (with over-expression of oncogenic pml/RAR α fusion) in bone marrow aspiration in June 5, 2005, and the patient was resistant with 80 mg/day of ATRA within 7 days, but no tumor could be demonstrated in the liver at repeat liver scan.

Case 10

A 47-year-old woman was diagnosed as having metastatic Hepatocellular Carcinoma (HCC) in July 16, 2010 when she presented with both a marked abdominal distention and an abdominal sharp pain for 10 days, accompanied with loss of appetite. Abdominal sonography showed a 3.0×2.7 cm liver tumor. The patient also had a history of ovarian cancer. Ascites positive PR was obtained after 5-Fluorouracil injection $0.25 \text{ g / day} \times \text{total 5 bottles}$, Tegafur (fluorouracil) tablets (600 #) and traditional medicine for one month. On repeat liver scan showed a necrosis focus within liver tumor. Liver mass was receded to 2.3×2.2 cm. She was given on tap ascites relapse from the abdomen and two combination chemotherapy drugs, cisplatin and paclitaxel, a standard treatment for her advanced ovarian cancer^[6] (4.7×3.7 cm) in April, 2011 in other hospital. During follow up, she was over two years survivor.

Discussion

In earlier 1975 in china there was statistically investigation that ten percent of 700 liver cancers (HCC) the survival time was over one year with cantharidine. In 1981 Professor Yang BH in shanghai oncology conducted 1 year survival rate 35.4%, and 5 years survival rate 16.7% with combination chemotherapy and traditional medicine in middle and late stage HCC. Among unresectable HCC, none was over 5 years survivors, and 1 year survival rate 9.7%, with only chemotherapy. In this paper we observed in detail the objective response of the combined protocol of chemotherapy (mainly 5-Fluorouracil, 5-Fu)^[7-9] and traditional medicine in the treatment of Hepatocellular Carcinoma (HCC). As to our strong impression, a higher dosage of combination chemotherapy in conjunction with traditional medicine was beneficial to effectively killing malignant cells of HCC. Two primary Hepatocellular Carcinoma (HCC) had Complete Response (CR) with only cantharidine or/and traditional medicine. Another, Professor Yu erxin (unpublish data) had successfully conducted one complete remission with 5 years of advanced PHC with the combination of prolonged administration of Thiophosphoramidate (TSPA) 10 mg, intramuscle injection, 2-3/week, and traditional medicine. Moreover, an exploring area of research in the approach (activated LAK cells/natural IL-2) of PHC therapy remains to be under investigation.

Interesting in case 9 was only given All-Trans Retinoic Acid (ATRA) and traditional medicine. like translocated retinoic acid receptor α in leukemogenesis of acute promyelocytic leukemia^[10-14] previously isolated from a human hepatocellular carcinoma a Hepatitis B Virus (HBV) integration in a 147-bp cellular DNA fragment, later named hap in liver, which may relate to the hepatocellular carcinogenesis. Six out of seven hepatoma and hepatoma derived cell-lines express a 2.5 kb hap mRNA^[14]. And assignment of the human hap retinoic acid receptor RARb to chromosome 3^[15]. Moreover, It has been demonstrated that the RAR β gene has been shown to be rearranged as a result of insertion of HBV sequences^[14], and is autoregulated by Retinoic Acid (RA) as RAR β mRNAs increases 10-50-fold in RA-treated hepatoma cell-lines^[16]. *In vitro* the growth of SMMC - 7721 HCC line was markedly inhibited when culture in 10 u mol/L 13-cis-RA and all-trans-RA. Morphology of cell treated with RA reversed to normal phenotypes, and the inhibition of α -fetoprotein (AFP) synthesis and r-GT activity^[17]. The involvement of

hap retinoic acid receptor (RAR β) may explain why the disappearance of malignant hepatic tumor was obtained through the use of ATRA agent in this case. In addition, the diagnosis of liver cancer can be made through a variety of imaging methods such as ultrasound, CT, MRI, radionuclide scanning. Especially, the Digital Subtraction Thergiology (DSA) of liver artery including Long Time Low Rate Angiography (LTLRA)^[18] is considered more useful in raising the detecting ratio of sub-clinical liver cancer and the smaller tumors gain perfect coloration (the smallest lesion diameter 0.3 cm). Moreover, the DSA of liver also help to get a better understanding of hepatic vascular anatomy and lesion's artery blood supply. Therefore, LTLRA is of great value in detecting the small lesion of liver cancer. In this study, we experienced that a CR was a pivotal influencing factor in those longest survival patients, and traditional medicine was also recommended.

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