Clinical Study

Role of Traditional herbal medicine in the treatment of advanced hepatocellular carcinoma (HCC): past and future ongoing

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Abstract

Objective: The global burden of hepatocellular carcinoma (HCC) is significant. In search for the effective approach of PHC, the objective of present study was to investigate in detail the objective response of the combined protocol of chemotherapy and traditional medicine in the treatment of hepatocellular carcinoma (HCC). **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:** Three of ten HCCs (two patients with liver CT tumor 6.3 x 4.5, 11.1 x 6.2, respectively) obtained complete remission using combination chemotherapy and traditional medicine. Three patient HCCs (one patient with AFP 7500 ng/ml) obtained complete remission through only 5-fluorouracil and traditional medicine. Two HCCs (one patient with AFP 200ng/ml, ascites +++, icterus index 100u) 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 x 3.0). One acute promyelocytic leukemia complicated with metastatic hepatocellular carcinoma (7.0 x 4.5cm) 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 study, traditional herbal medicine had been successfully conducted in treatment of ten advanced hepatocellular carcinomas. 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 (RARβ) 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 oncogenic HGF receptor (HGFR/met oncogenic receptor) act as a trigger for liver regeneration after partial hepatectomy and liver injury, even in (hepatocellular) carcinogenesis, which was also discussed.

Keywords: HCC, HBV, HCV, HGF/met or met oncogenic receptor, 5-fluorouracil,traditional herbal medicine

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 (Bosch et al., 2004; Irabor et al., 2009). 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 4.2months 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 (Giaglia et al., 2010; Chisari et al.,1987). An additional data indicate that

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human hepatocyte growth factor (HGF) and HGF receptor oncogenic signaling (HGFR/met oncogenic receptor) act as a trigger for liver regeneration after partial hepatectomy and liver injury (Nakamura et al, 1987), even in carcinogenesis (Konda et al., 1993).

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 were 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 harden and nodular liver was felt 9 cm below the right costal margin. Investigations included normal serum bilirubin, serum r-glutamyl transpeptidase (r-GT) 240u, serum α–fetoprotein (AFP) 7500ng/ml, serum alkaline phosphatase (AKP) 16u. Liver scan provided a diffuse infiltrate defect affecting both lobes of liver.

Treatment consisted of 500mg of 5-Fluorouracil (5-Fu), 1mg of Toyomycin, 1mg 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 3cm below the right costal margin, and associated with further improvements of liver enzymes. Serum AFP was declined to 942ng/ml. Serum r-GT 176u. Serum AKP 8u, 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. Traditional herbal medicine was consisted of *bupleurum scorzonerifolium* willd, *Angelica sinensis* (olive) diels, *Citrus reticulata* Blanco (orange peel), *Sparganium stoloniferum* bach. Han, *Curcuma phaeocaulis* val, *Impatiens balsamina* L, *Gallus gallus domesticus* Brisson. On examination he presented a normal size of liver. Laboratory data that serum AFP was 50ng/ml, serum r-GT 60u, and serum AKP 4.2u. 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 (4-5cm) associated with moderate harden and nodules in right upper abdominal quadrant. Abnormal liver enzyme presented serum AFP positive and serum r-GT 243u. Liver scan demonstrated a filling defect. Ascites negative.

5-fluorouracil (5-FU) at 1000mg 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 100u. 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 4-6cm below the right costal margin, and associated with the elevation of liver enzyme. Laboratory data showed serum icterus index 100u,serum van den Bergh test (direct and indirect) positive, serum AFP 200ng/ml, serum AKP 134u, and serum r-GT 16.2u. Ascites positive.

Treatment consisted of 16mg of (Demethyl) cantharidine daily added in 5% of saline solution infusion. Total dosage of cantharidine 1872mg. A disappearance of ascites and jaundice was noticed. Laboratory data showed serum icterus index 12u,serum van den Bergh test weak positive, serum AFP negative, serum AKP 27u,and serum r-GT 5.4u. 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 2.5cm in the comparison of his admission. The remainder of liver enzyme performed serum r-GT 13u, serum AKP 2u, and serum AFP<50ng/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 (1.5x1cm, each pea size) were scattered through the subcutaneous of the chest and abdomen lesion. An enlarged (4cm) 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 therapeutically approach of a seven days course of 5-Fu at 1500mg/day added in 1000ml of 5% saline solution intravenously. After two courses of treatment, then a 1500mg of 5-Fu was administered intravenously once a week, with adjustment of traditional medicine. Traditional herbal medicine was consisted of *Bupleurum scorzonerifolium* willd, *Citrus reticulata* Blanco(orange peel), *Cyperus rotundus* L, *Trionyx sinenesis* Wiegmann (turtle shell),*Curcuma phaeocaulis* val, *Eupolyphaga sinensis* walker (or steleophaga plancyl (Boleny)), *Scutellaria barbata* D. Don, *Oldenlandn diffusa* roxb. 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 1000mg of 5-Fu infusion once a week associated with traditional medicine, which was repeatedly performed for three months. At the same period she took 0.25mg 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 6.3x4.5cm 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 6.2x4.0cm liver nodular mass, with a 3x5cm 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 3x4cm liver mass and peritoneum posterior metastasis: 4.0x4.5,3.0x2.0cm. A CR was obtained under intensive time sequential chemotherapy. A protocol of 5-Fu 1000-1500mg/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 11.1x6.2cm 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 1500mg/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 31.7umol/L(control 4-23.9umol/L),indirect bilirubin 28.6 umol/L (control 2.56-20.9umol/L), serum HBsAg(+), serum HBeAb(+), serum HBcAb(+), serum AFP slightly increased from 1.9ng/ml in 1996 to 8.7ng/ml in January 2002 (control 0-8.1ng/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. Traditional herbal medicine was consisted of *Bupleurum scorzonerifolium* willd, *Angelica sinensis* (olive) diels, *Asparagus cochinchinensis* (lour) merr, *Citrus reticulata* Blanco (orange peel), *Zingiber officinale* Rosc, *Zizyphus jujuba* Mill (chinese date), *Glycyrrhiza uralensis Fisch* (Licorice), *Coix lachryma-jobi* L, *Artemisia capillaris* thunb, *Scutellaria baicalensis* geergi, *Astragalus memberanaceus* (fisch) bunge, *Lycium barbaium* L, *Chinemys reevesii* (Gray)(tortosis plastron), *Trionyx sinenesis* Wiegmann (turtle shell), *Curcuma phaeocaulis* val, *Scutellaria barbata* D. Don, *Oldenlandn diffusa* roxb. Three months later, in view of improvements in his general symptoms,

serum bilirubin was declined to normal, serum AFP was declined to 2.05ng/ml. Liver scan showed a normal size of liver. A 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 3.2x3.0cm 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 ℃, Chest X-ray showed small amount of hydrothorax. Liver CT scan demonstrated an elliptical mass of 7.0x4.5cm which was considered to secondary hepatocellular carcinoma (HCC). AFP negative.

Hemoglobin concentration was 53g/L. leukocyte count $3.4x10^9$/L with 20 per cent promyelocytes. The platelet count was $2.4x10^9$/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 80mg 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 overexpression of oncogenic pml/RAR α fusion) in bone marrow aspiration in June 5, 2005, and the patient was resistant with 80mg/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 3.0x2.7cm liver tumor. The patient also had a history of ovarian cancer. Ascites positive.

PR was obtained after 5-Fluorouracil injection 0.25g/day x 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 2.3x2.2cm. 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 (Kris etal,2010)(4.7x3.7cm) 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 unrespectable 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-Flourouracil, 5-Fu)(Link et al., 1977; Porta et al.,1995; Jiang et al.,1997) 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 were 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 (unpublished data) had successfully conducted one complete remission with 5 years of advanced PHC with the combination of prolonged administration of Thiophosphoramide (TSPA) 10mg, intramuscular 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 (de The et al., 1990; George Zhu,1992; 2013, 2016, 2017), de The (de The et al., 1987) 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 2.5kb hap mRNA (de The et al., 1987), and assignment of the human hap retinoic acid receptor RARb to chromosome 3 (Mattei et al., 1988). Moreover, It has been demonstrated that the RARβ gene has been shown to be rearranged as a result of insertion of HBV sequences (de The et al., 1987), and is autoregulated by retinoic acid (RA) as RARβ mRNAs increases 10-50-fold in RA-treated hepatoma cell-lines (de The et al.,1989). In vitro the growth of SMMC-7721 HCC line was markedly inhibited when culture in 10umol/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 (Ai et al., 1991). 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 thergiography (DSA) of liver artery including long time low rate angiography (LTLRA)(Zhang et al., 2009) 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 0.3cm). 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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