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• *BRIEF REPORTS* •

Evaluation of HCPTd_1, d_{14}-double passaged intervening chemotherapy protocol for hepatocellular carcinoma

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Abstract

AIM: To establish a kind of standardization of the clinical chemotherapeutic prototypes for unresectable hepatocellular carcinomas (HCC).

METHODS: 10-Hydroxycamptothecin (HCPT) was applied through transcatheter arterial embolization (TAE) to HCC patients who were categorized into three groups: (1) test group: treatment with HCPT twice (HCPT d1 and 14) through TAE and portal venous embolization. (2) Control I: treatment with anticancer drugs without HCPT. (3) Control II: treatment with HCPT as a major component in anticancer drugs once (HCPT d1). A set of comparisons between test groups and control I and II groups were performed before and after the treatment to study the effectiveness of each treatment, in terms of tumor volumes, dynamic variations in serum alpha-fetoprotein (AFP), gamma-glutamyl transferase hepatoma-specific band (GGT-II), patient survival and adverse events.

RESULTS: The general effectiveness rate of the test group reached 62.1% (72/116), remarkably higher than that of control I (32.1%, 40/124) and control II (54.7%, 47/56), (P<0.01 and P<0.05, respectively). Especially, the reduction rate or disappearance of the portal vein tumor emboli was as high as 88.4% (61/69) in the test group, in contrast with 13.9% (10/72) in control I and 35.9% (18/51) in control II (P<0.01 and P<0.01, respectively). After treatment, AFP decreased or turned to negative levels at 52.3% (34/65) in control I, 67.3% (35/52) in control II, and 96.8% (60/62) in the test group. Also GGT-II declined or became negative at 37.8% (28/74) in control I, 69.5% (57/82) in control II, and 94.7% (89/94) in test group (P<0.01 and P<0.05, respectively).

CONCLUSION: We have designed a good protocol (test group) to treat HCC with excellent advantages of high efficiency, low cost, low toxicity and low adverse events and easy application. It could be recommended as one of the standardizations for HCC treatment in clinical practice.

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Key words: Hydroxycamptothecin; Transcatheter arterial embolization; Portal venous embolization; Hepatocellular carcinoma

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INTRODUCTION

Hepatocellular carcinoma (HCC) is one of the most common and rapidly spreading fatal malignancies worldwide, and has been ranked as the 2nd cancer killer in China since the 1990s, particularly in the southeastern provinces, including the inshore area of the Yangtze river[1-3]. Major risk factors for HCC in these areas are exposure to aflatoxin B1 and infection by hepatitis viruses[4,5]. HCC prognosis is poor and early detection is of utmost importance[6]. Treatment options are severely limited by the frequent presence of metastases. Recent studies of DNA isomerase inhibitors for clinical use have made some progress[7,8]. The direct injection of 10-hydroxycamptothecin (HCPT) into tumor vessels in primary hepatic carcinoma has proved promising due to its high efficiency and low toxicity[9-11]. However, treatment protocols differ greatly in drug-application routes, methods, doses and final results[12-14].

Since October 2000, we have used HCPT as a major component in chemotherapy in combination with 5-fluorouracil (5-FU) and cisplatin (CDDP). Drugs were administered through transcatheter arterial embolization (TAE) and subsequent portal venous embolization (PVE) to treat hepatic cancer on d 1 and 14, respectively. We compared this method (called test group) with chemotherapy protocols with and without HCPT through TAE d1 and reported here the excellent results.

MATERIALS AND METHODS

Study populations

We evaluated 326 HCC patients treated at Affiliated Hospital

of Nantong University, China. Patients were divided into three groups: test group, control I, and control II. All patients were confirmed by alpha-fetoprotein (AFP), gamma-glutamyl transferase hepatoma-specific band (GGT-II) serological examination[7], and by ultrasonography (US), computed tomography (CT) or magnetic resonance imaging, partly by pathological checking. The diagnosis of HCC was based on the criteria stipulated in 2001 Chinese National Conference on HCC[15]. The test group consisted of 116 HCC patients (91 males and 25 females) aged 30-68 years with an average age of 46.2 years. Among them, 12 were in stage I, 86 in stage II, and 18 in stage III, respectively; and the liver function was categorized according to the Child-Pugh scale with 46 cases of level A, 61 cases of level B, and 9 cases of level C, respectively.

Control I had 124 HCC patients, who received chemotherapeutic agents such as 5-FU, doxorubicin (ADM), CDDP without HCPT through TAE and were hospitalized at the same time as test group or earlier. Control II had 86 patients, who received chemotherapeutic agents HCPT, 5-FU, CDDP through TAE only on d 1.

HCC patients in the three groups had similar general conditions. Actually, mostly patients were at mid-late stage, often some of them already had metastasized cancerous emboli in portal vein or hepatic vein, and some even had remote lymph nodes affected according to the UICC criteria, most HCC belonged to T_{3-4} N_{0-1} M_{0-1}.

Treatment drugs

HCPT was purchased from Hubei Lishizheng Pharmaceutical Co., Ltd. HCPT 40-50 mg, 5-FU 750-1 000 mg, CDDP 60-80 mg, ADM 40-50 mg, lipiodol (LP) 10-30 mL, and gelatin sponge 1-2 pieces were used for treatment (one dose).

Therapeutical methods

Arterial embolization was performed according to Seldinger's procedure via the femoral artery. After the catheter was sent into the hepatic artery and right or left hepatic artery, arteriography was carried out for further confirmation of the characteristics, location and size of the tumor. The types and doses of drugs varied with the Child-Pugh grades of hepatic functional reserve, clinical stages and the number, size and extent of tumors. Usually a combination of full dose of 5-FU, 4/5 of HCTP, and 2/3 of CDDP was infused to attack the tumor. Then 1/5 dose of HCPT, and 1/3 of CDDP were mixed with LP or gelfoam to embolize the blood-providing arteries.

We selected a puncture site using the portal vein branch which supplied blood for tumor foci, or proximal to cancerous emboli. The drugs used were the same but half of the dose 3-6 mL of LP was used. The operation was performed on d 14 after TAE.

Blood and urine analysis were routinely checked twice a week, and the liver function and serum tumor markers (AFP, GGT-II) were determined once in every 2 wk. US and CT were also checked on d 21-28, to observe LP precipitates and variations in volume of tumor foci.

Statistical analysis

Differences between groups were assessed by the χ^2 test. The survival time was calculated according to the Lifespan method. $P<0.05$ was considered to be significant.

RESULTS

The therapeutic effects were evaluated with regard to tumor-emboli volume alteration, changes of serum tumor markers (AFP, GGT-II) changes and survival time, based on the Criteria of Diagnosis and Treatment of HCC proposed at Chinese National Collaborative Cancer Research Group[15].

Tumor-emboli volume alteration

The overall effective rate of the test group was 62.1% (72/116), much higher than that of control I (TAE without HCPT, 32.1%, $P<0.01$) and control II (TAE with HCPT d1, 54.7%, $P<0.05$) as shown in Table 1. Six patients had survived for over 3-6 years, repeated follow-up with US and CT showed no occupied lesions. More importantly, color Doppler reported high frequency of arteries or veins around tumors with a resistance index >0.50, mostly more than 0.60-0.80 in 59 of 66 partial response patients. After treatment with TAE and PVE, 42 cases reported disappearance of the high blood flow frequency, and the rest showed remarkable reduction of blood supply. Fifteen patients acquired complete removal of tumor by surgery, among them six were reported as having pathologically complete necrosis in the tumors with large amount of lymphocytes encircling and infiltrating around the tumors.

In test group, the reduction rate of cancerous emboli in portal vein reached 88.4%, which was much higher than that in control I (13.9%, 10/72) or control II (35.3%, 18/51) with statistically significant difference ($P<0.01$). In the eight cases in which the main portal vein was affected, the tumor emboli showed no change or even progress, so the portal vein branch I or II in the other site had to be chosen for infusion of chemotherapeutic agents.

Dynamic changes of tumor markers

In test group, 62 cases showed AFP>400 ng/mL, with 53.4% positive. After treatment, the concentration of serum AFP decreased in 60 cases, accounting for 96.8%, which was much higher than that in control I (52.3%, 34/65) and control II

Table 1 Tumor-emboli volume after treatment

	Tumor volume Cases/CR/PR/NC/PD Cases/Dis/Red/Un-ch/Prog					Portal vein emboli				
Test	116	6	66	43	1	69	8	53	6	2
Control I	124	1	39	76	8	72	1	9	38	24
Control II	86	1	47	36	2	51	2	16	21	12

CR: complete response; PR: partial response; NC: no change; Dis: disappear; Red: reduction; PD: progressive disease; Un-ch: unchanged; Prog: progression.

(67.3%, 35/52) with significant difference ($P<0.05$). AFP was termed negative in 25.8% (16/62) of test group, in 1.5% (1/65) of control I, and in 9.6% (5/52) of control II, respectively. Significant difference ($P<0.01$) was found between test group and control groups.

The number of GGT-II positive cases in test group was 94, accounting for 81.0%. After treatment, 89 cases turned negative or its concentration decreased, accounting for 94.7%, much higher than that in control I (37.8%, 28/74) and control II (69.5%, 57/82) with striking differences ($P<0.01$ and $P<0.05$), respectively (Table 2).

Survival time

The survival time was calculated according to the Lifespan method. The survival rates of 1, 2 and 3 years in test group were 94.6%, 65.9% and 39.1% respectively, which were significantly different from those in control I (65.1%, 36.3%, and 20.5%, respectively) and control II (80.6%, 52.4%, and 31.5%), respectively ($P<0.05$).

Adverse events

Almost all patients had nausea, vomiting, fever and hepatic pain to some extent after TAE treatment, i.e., "post embolization syndrome". Fever was relatively higher and lasted longer in groups with HCPT as a chemotherapeutic agent. In all three groups, digestive responses such as nausea and vomiting were slight and transient. Hepatic pain varied with the embolization state and the amount of LP and gelfoam used in the operation. Generally, in control I (without HCPT), the patient's temperature would rise to 39 ℃ 1 or 2 d after TAE, began to decrease on d 3, and returned to normal on d 5-7. In the group with HCPT, the temperature would rise to 39 ℃, decrease on d 4. Sometimes, it took 2 wk for the patients to recover.

The adverse events after PVE on d 14 were slight. Only a few cases reported a little bloating pain in the operated area. Nausea and vomiting were seldom reported. Fever was moderate and lasted shorter than 1 wk. No serious complications such as pneumothorax, and bleeding in the abdominal cavity were found.

Regular check of blood and urine routine showed that only nine cases in the test group had slight decrease in the WBC or platelet counting, and no bleeding was found. In control I and control II, 7 and 11 cases respectively showed slight decrease of WBC and platelet count. Statistical analysis showed no difference among the three groups ($P>0.05$).

DISCUSSION

HCPT has been in use for more than 20 years. Recently, the American FDA has approved two drugs, irinotecan and topotecan, which are HCPT analogs with similar molecular structure. Cellular and molecular biology has proven that this class of drugs belongs to DNA topoisomerase I inhibitors, which have strong anti-cancer activities, and wide-spread antagonizing spectrum, low resistance, low toxicity and the ability to induce differentiation of tumor cells and apoptosis[16,17]. The combined use of this drug with other kinds of drugs may enhance efficacy[18-20]. It is the common interest of many basic and clinical scientists to know how to reasonably standardize the application and maximize the efficacy of the drugs[21-23]. Therefore, international standardization remains a common focus. Based on the treatment of 326 cases of HCC patients with or without HCPT in our hospital, we systematically studied the application of this drug, and proposed our own standardized protocol.

In vitro drug sensitivity tests of tumor cell line showed that at low dose, HCPT played double roles in human liver carcinoma cell lines (HepG2, Bel-7402, and Bel-7404): inducing differentiation and inhibiting cell growth slightly. The greater the dose, the stronger the inhibitory action was, and the effects became stronger with time[9].

For the unresectable hepatic carcinoma patients who had wide ranges of foci together with high rates of portal vein emboli[24-26], we adopted double-passaged intervening chemotherapy with HCPT in combination with other drugs for treatment[27-29]. We emphasized three aspects in the treatment: drug dose, treatment time and continuous treatment. For drug applying routes, we utilized both artery and portal vein for tumors. Under the guidance of digital subtraction angiography of tumor and US, the needle was directed into supplying artery and veins, exerting high dose for close attack on cancerous area, followed by chemical embolization to keep the drug-LP mixture in the suffered area for a longer time.

The drug action period is no longer than several hours or several days, but lasting for weeks or months[30]. This method keeps the local drug concentration high, hundred times more than that by systemic intravenous drip[12]. It has been reported that after tumor arteries were blocked through TAE, portal vein branches increased remarkably[31]. Therefore, to perform PVE, 2 wk after TAE not only accorded with blood dynamics but also increased drug administration frequency. And at the same time, it struck an attack with high drug dose on portal vein cancerous emboli. Drugs accumulated at low concentration in normal tissue areas or organs. It has been reported that HCPT is not affected by multi-drug resistance protein and multi-drug resistance related proteins, therefore, it seldom has drug resistance. With the development of diagnostic techniques

Table 2 Hepatic cancerous marker alterations before and after treatment

	Hepatic cancerous marker							
	AFP				GGT-II			
	P	N	D	I	P	N	D	I
Test	62	16	44	2	94	29	60	5
Control I	65	1	33	31	74	6	22	46
Control II	52	5	30	17	82	8	49	25

P: positive; N: negative; D: decrease; I: increase.

and agents, super-selection ability of drugs greatly enhanced. It is a common practice in clinic that the catheter head is directed to the closest area of tumor artery to achieve segment embolization, thus greatly enhancing effectiveness. Some patients were able to achieve partial regression or even complete regression, known as "chemical resection". In our test group, PR+complete response (CR) reached 62.1%, among them six were CR, with portal vein cancerous emboli disappearance or reduction rate of 88.4%. In eight cases, cancerous emboli disappeared completely. Such a high efficacy was probably related to the above-mentioned pharmacology (our HCPT protocol in d 1 and 14) and methodology (by TAE and PVE)[32]. The earliest and most frequent passages for hepatic carcinoma metastasis are portal veins. Therefore, treatment through/on portal venous emboli is the key step to control its metastasis across the liver.

Pharmacological study indicated that the effectiveness of application of topoisomerase I and II inhibitors rely on the sequence of drug application. Subsequent administration of topoisomerase I and II inhibitors exerted co-operative effect; while co-administration of them antagonized each other[9]. The method of TAE or PVE is a way to apply drugs to tumor feeding vessels (veins or arteries); therefore, here we considered to use combined application of HCPT (topoisomerase I inhibitor) as a major component in the chemotherapeutic agents with 5-FU and CDDP, which are highly liver-specific drugs and act during S phase and S, G_1 or G_2/M phase respectively. HCPT exerted its action on DNA topoisomerase inhibitor I to directly suppress the DNA and RNA synthesis, and induced sister chromatid exchanges, distortions and breaks, so that it selectively killed S phase cells and induced G_2 arrest. In addition, both HCPT and CDDP can induce apoptosis. Drug dose and concentration, infusing speed, and emboli-forming rate for HCC patients were most important in all detailed manipulations based on the above-mentioned pharmacological features[33]. During 5-FU full dose attack, two major points should be emphasized: injection time and injection route. When 5-FU concentration is more than effective concentration in the blood, higher dose would only increase its toxicity, while elongation of injection time can remarkably enhance the effectiveness. Therefore, it is better to slow down the injection time, usually to longer than 30-40 min.

The route was dependent upon the tumor location or cancer emboli location[28]. For example, if tumor was located in the right liver lobe, then the passage route would be: (1) superior mesentery artery→superior mesentery vein→right portal vein→tumor location; (2) common hepatic artery→right hepatic artery→tumor location. If tumor was located in the left lobe of the liver, then pass through: (1) celiac trunk→splenic artery→splenic vein→left portal vein→tumor location; (2) common hepatic artery→left hepatic artery→tumor location. Since the hepatic artery provides blood to tumor center, while the portal vein provides blood to tumor surroundings, our protocol not only the whole tumor (center and surrounding) made double attacks on through arteries and veins, but also elongated the drug action time. On d 14, through PVE, the tumor and the cancerous emboli would receive the 3rd attack, which greatly enhanced local drug concentration and drug-acting time.

HCPT was marketed and used widely in 1970s; the number of patients receiving HCPT had accumulated to more than a thousand[11,14]. However, due to various reasons no formal phase I and II pharmacodynamic studies have been carried out.

We report here the so-called HCPTd_1, d_{14}-TAE, PVE double passaged tumor intervening chemotherapy for hepatic carcinoma. The local concentration of HCPT reached as high as 40-50 mg in hepatic artery +20-25 mg in portal vein, without observing dose-limiting toxicities like drastic bone marrow inhibition and diarrhea. There was a slight decrease in WBC and platelet counting in nine cases. No dramatic hematuria, skin rashes, but only self-limiting tumor necrotic fever and transient digestive response were observed. For those who acquired chances to be operated on, there were widespread necroses around tumor and large amount of lymphocyte infiltration[34]. Our protocol exhibited high efficiency and low toxicity. HCPT does not induce drug resistance. It has anti-infection activity and the ability to increase body immunity. It is inexpensive and convenient to use. Thereby, we recommend the protocol as one of the standardizations in treating liver cancer with HCPT.

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