Chemotherapy for transarterial chemoembolization in patients with unresectable hepatocellular carcinoma

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Abstract

AIM: To compare the efficacy of different chemotherapeutic agents during conventional transarterial chemoembolization (cTACE) in the treatment of unresectable hepatocellular carcinoma (HCC).

METHODS: A retrospective review was undertaken of patients with unresectable HCC undergoing cTACE from May 2003 to November 2011. A total of 107 patients were treated with at least one cTACE session. Irinotecan (CPT-11) was used as a chemotherapeutic agent in 24 patients, gemcitabine (GEM) in 24 and doxorubicin in 59.

RESULTS: The time to progression and overall survival rates were significantly superior in patients treated with CPT-11 compared with the GEM or doxorubicin treated groups ($P = 0.022; P = 0.003$, respectively). There were no significant differences in adverse events among the three groups ($P > 0.05$).

CONCLUSION: For patients treated with cTACE, the chemotherapeutic agent CPT-11 was significantly associated with improved overall survival and delayed tumor progression compared with GEM or doxorubicin. There were no significant differences in clinical adverse events between the three agents. CPT-11 thus appears to be a promising agent when combined with cTACE for the treatment of HCC.

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Key words: Irinotecan; Gemcitabine; Transarterial chemoembolization; Hepatocellular carcinoma; Overall survival

Core tip: In the present study, we aimed to compare the efficacy of different chemotherapeutic agents during conventional transarterial chemoembolization (cTACE) in the treatment of unresectable hepatocellular carcinoma. Our study indicated that for patients treated with cTACE, the chemotherapeutic agent irinotecan (CPT-11) was significantly associated with improved overall survival and longer time to progression compared with gemcitabine or doxorubicin. There were no significant differences in clinical adverse events between the three agents. CPT-11 thus appears to be a promising agent when combined with cTACE for the treatment of hepatocellular carcinoma.

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INTRODUCTION

Hepatocellular carcinoma (HCC) is one of the most common malignant tumors worldwide. The annual incidence ranges from < 10 cases per 100000 persons in North America and Western Europe to 50-150 cases per 100000 persons in parts of Africa and Asia, where HCC is responsible for a large proportion of cancer-related deaths\[^{[2,3]}\]. The Barcelona Clinic Liver Cancer (BCLC) staging system directs therapy according to tumor stage, liver function status, physical status and cancer-related symptoms\[^{[3]}\]. However, over 60% to 70% of patients with HCC are diagnosed at a late stage and therefore curative therapies such as resection, liver transplantation or local ablation therapy are not appropriate\[^{[4]}\]. Transarterial chemoembolization (TACE) is the primary treatment used most frequently for unresectable HCC. TACE has been shown to improve survival when compared with best supportive care for unresectable HCC\[^{[5,6]}\]. The rationale for using TACE is that intra-arterial chemotherapy using lipiodol and chemotherapeutic agents followed by selective vascular embolization will result in a strong cytotoxic effect combined with ischemia (conventional TACE or cTACE)\[^{[7,8]}\].

However, there is a lack of data to support the use of one chemotherapeutic agent or combination of agents over another. Doxorubicin as a single agent is the most common chemotherapeutic agent used worldwide. In the United States, combination therapy is more often used, typically consisting of doxorubicin, mitomycin C and cisplatin. An adenosine triphosphate tumor chemosensitive assay system is a new promising regime as a single chemotherapeutic treatment for HCC. Cells of HCC are highly sensitive to various chemotherapy drugs: taxol 46%, CPT-11 (irinotecan) 44%, gemcitabine (GEM) 36%, mitomycin 14%, adriamycin 12%, cisplatin 8%, 5-fluorouracil oxalate (5-FU) 4%\[^{[9]}\]; the higher the percentage, the higher the sensitivity. Thus, it is indicated that CPT-11 might be a potential drug for the treatment of HCC and prolong survival time of HCC patients.

CPT-11, a drug used for the treatment of cancer, prevents DNA unwinding by inhibition of topoisomerase 1. It is a semi-synthetic analogue of the natural alkaloid camptothecin and is activated by hydrolysis to SN-38, an inhibitor of topoisomerase 1. Inactivation follows by uridine diphosphate glucoronosyltransferase 1A1 glucuronidation. The inhibition of topoisomerase 1 by the active metabolite SN-38 eventually leads to inhibition of both DNA replication and transcription. In 2007, Takeba et al\[^{[10]}\] suggested that the antitumor effects of SN-38 might include the mechanism of the mitochondria-apoptotic pathway inducing p53 activation. This newly discovered mechanism of action of CPT-11 might be useful as a treatment for patients with HCC. Currently, there are limited data available regarding the use of chemotherapeutic agents administered via cTACE in patients with HCC. This study evaluated the efficacy, tumor response, clinical adverse events, time to progression and overall survival benefit of three chemotherapy agents: CPT-11, GEM and doxorubicin.

MATERIALS AND METHODS

This study was approved by the ethics committees of the Dalian Medical University (No. 2013.012). As a retrospective medical records study, consents were not obtained. The records and personal information of all patients were anonymized prior to analysis.

Study design

This retrospective analysis was conducted on 107 patients with HCC who were treated with TACE-based therapy from May 2003 to November 2011 at the Second Hospital of Dalian Medical University of China. There were 95 men and 12 women with a mean age of 57 years (± 11 years). Hepatitis B virus was present in 81 of the 107 patients. The primary tumor was verified in all patients either by biopsy and histopathology or according to EASL criteria\[^{[11]}\]. Briefly, non-invasive diagnosis of HCC was verified if a nodule of more than 2 cm within existing liver cirrhosis appeared arterially hypervascularized and with an enhanced venous “wash-out” on one contrast-enhanced imaging modality, with an AFP level exceeding 400 ng/mL. In patients with AFP levels below 400 ng/mL, a tumor greater than 2 cm had to show the above-mentioned dynamics of the contrast agent in two different imaging modalities.

Data evaluation was performed retrospectively and data were reported according to the standards defined by the Society of Interventional Radiology\[^{[12]}\]. The study was performed in accordance with guidelines of the local institutional review board. A computed tomography (CT) scan was performed before the first chemoembolization to assess tumor size, multifocality, vascular invasion, morphological signs of liver cirrhosis and the presence of ascites. Etiology of liver cirrhosis, laboratory results including bilirubin, albumin, liver enzymes, prothrombin time (as Quick value or INR), thrombocytes, AFP and Eastern Cooperative Oncology Group status were retrieved from patient records. Based on these data, all patients were rated according to Child-Pugh\[^{[13,14]}\], The Model for End-stage Liver Disease (MELD)\[^{[15]}\], Cancer of the Liver Italian Program (CLIP)\[^{[16]}\] and the BCLC\[^{[17]}\]. Survival data were based on patients’ records from our institution and follow-up information from their families.

Chemotherapy regimen and dosage

CPT-11 and 5-Fu were used as chemotherapy agents in the CPT-11 group, GEM and 5-Fu in the GEM group, and doxorubicin and 5-Fu in the doxorubicin group. The doses were CPT-11 130-180 mg/m\(^2\), GEM 1000 mg/m\(^2\), doxorubicin 30-40 mg/m\(^2\), 5-Fu 500-600 mg/m\(^2\). Physical condition of patients was also considered in the determination of the final doses.

Chemoembolization procedure

Digital subtraction angiography (DSA, Multistar, Siemens, Wu J et al. CPT-11 in TACE for hepatocellular carcinoma
Erlangen, Germany) was performed before TACE to show vascular anatomy of the liver and to identify arterial feeders of the tumor. TACE was performed by selective catheterization of the hepatic segmental arteries nourishing the lesions. A 3-F coaxial microcatheter (TurboTracker 18; Boston Scientific, Cork, Ireland) was utilized. A co-
mixture of iodised oil (Lipiodol UltraFluid; Laboratories Guerbet, Aulnay-sous-Bois, France) and chemotherapeu-
tic agent (CPT-11, GEM or doxorubicin) with gelatine sponge particles (Spongostan Standard; Johnson and
Johnson Medical Limited, Gargrave, Skipton, United
Kingdom) was injected until a complete blockage of the
tumor feeding branch was demonstrated. The doses of
anticancer agent and lipiodol and the pieces of gelatine
sponge particles used for TACE were determined based
on the tumor size and extent of the lesions.

TACE was considered to be technically successful
when target lesions were fully embolized and a complete
blockage of the tumor feeding branch was demonstrated
in the absence of immediate technical complications
requiring treatment interruption. Complications were de-
defined according to the Society of Interventional Radiol-
ogy guidelines[18].

Follow-up
After the TACE procedure, patients recovered with ap-
proximately 12 h of bed rest in hospital. During the first
6 h, a clinical examination (abdominal evaluation and
measurements of pulse rate, arterial blood pressure and
body temperature) was performed every two hours. All
patients underwent routine laboratory tests (liver enzyme
biochemistry, AFP, routine blood) to assess peri-proce-
dural complications and impact on liver function 7 d later
after TACE.

One month after each cTACE procedure, a CT scan
was performed in order to evaluate the tumor radiologi-
ical response and then in all cases with complete response,
scans were performed every three months in order to
monitor the appearance of recurrence. Tumor response
was assessed at CT by two expert abdominal radiologists
according to the amended RECIST criteria[19,20]. Com-
plete response (CR) was defined as the disappearance of
any intratumoral arterial enhancement in all target lesions.
All the other radiological responses were considered non-
complete (non-CR) and categorized as partial response
(PR), progressive disease (PD) and stable disease (SD) ac-
cording to mRECIST criteria.

Viable tumor was defined as contrast uptake in the
arterial phase and wash-out in portal venous and/or late
venous phases. Contrast enhancement was visually as-
sessed in the majority of cases. However, in doubtful
cases at CT, quantitative measurements were obtained by
placing a region-of-interest in specific areas in all phase
images, according to Kim et al[21]. Repeated cTACE cycles
were performed “on demand” upon the demonstration of
viable tumour (non-CR) or intrahepatic recurrences in
patients of Child-Pugh A and B.

Study endpoints
The primary endpoint of our study was overall survival.
Secondary endpoints were: (1) safety and liver toxicity;
(2) tumor response at one month; and (3) time to local
tumor recurrence (within target lesion) and intrahepatic
tumor recurrence (new lesions).

Statistical analysis
Continuous variables were reported as median and range.
Comparisons among groups were calculated using non-
parametric tests (Mann-Whitney and Wilcoxon). Cate-
gorical variables were compared with the $\chi^2$ test. Survival
analysis was performed with Kaplan-Meier statistics for
all the patients as well as for the different Child-Pugh,
MELD, CLIP, and BCLC stages. Median survival and
CI were calculated. Differences in survival between the
groups were assessed for statistical significance with the
log-rank test. SPSS-software (version 15.0, SPSS Inc.,
Chicago, United States) was used for data evaluation and
statistical analysis. A two-sided $P$ value of less than 0.05
was considered statistically significant.

RESULTS
Baseline patient characteristics are shown in Table 1. The
primary tumor was verified histopathologically in 17/107
of patients. In 90 patients, HCC was diagnosed based on
radiological imaging procedures and AFP levels accord-
ing to EASL criteria. A total of 53 patients were AFP-
positive with levels greater than 400 ng/mL. Cirrhosis of
the liver was present in 62 patients (58%) and thrombosis
of a portal vein branch was present in 33 patients (31%).
The mean tumor maximal diameter was 7.8 ± 4.1 cm. A
mean of 2.0 ± 2.0 selective chemoembolization sessions
were performed in each patient and the total number for
all patients was 264.

Treatment response
Treatment response was evaluated one month after the
first TACE session. In the CPT-11 group, 4 (16.7%) and
16 (66.7%) patients showed a CR and PR respectively,
two patients (8.3%) progressed and two (8.3%) had SD.
In the GEM group, 3 (12.5%) and 16 (66.7%) patients
showed a CR and PR respectively, 2 (8.3%) progressed
and 3 (12.5%) had SD. In the doxorubicin group, 3
(12.5%) and 16 (66.7%) patients showed a CR and PR
respectively, 2 (8.3%) progressed and 3 (12.5%) had SD.
There was no significant difference in treatment respons-
es among the three groups.

Time to progression
During follow-up, the median time to progression in the
CPT-11, GEM and doxorubicin groups was 11.41,
8.25 and 9.46 mo respectively. The time to progression
was significantly longer in the CPT-11 group than the
other two groups ($P = 0.02$, Figure 1A). Furthermore,
subgroup analysis according to BCLC stage showed that
A lower rate of death in the CPT-11 group compared with the GEM or doxorubicin group ($P = 0.02$) due to less tumor progression. The median overall survival times in the CPT-11, GEM and doxorubicin groups were 21.68, 12.72 and 14.46 mo respectively. The cumulative survival rates at 12 and 24 months were 87.5% and 45.8% in the CPT-11 group, 66.7% and 0% in the GEM group and 69.5% and 22.0% in the doxorubicin group (Figure 2A). The overall survival was significantly higher in the CPT-11 group compared with the GEM or doxorubicin groups ($P = 0.004$). Subgroup analysis showed that the difference between the three groups was also significant in patients with intermediate-stage HCC ($P = 0.003$, BCLC B stage, Figure 2B). Univariate analysis revealed eight prognostic factors affecting overall survival: cirrhosis of the liver, BCLC stage, CLIP stage, pathological stage, number of tumors (single/multiple), TACE sessions ($\leq 2/> 2$), ALB and chemotherapy agent used. In multivariate analysis, the chemotherapy agent used was significant in patients with intermediate-stage HCC, time to progression was significantly longer in the CPT-11 group compared with the GEM or doxorubicin groups ($P = 0.022$, Figure 1B). Univariate analysis revealed eight prognostic factors affecting tumor progression were recognized: cirrhosis of the liver, BCLC stage, CLIP stage, pathological stage, number of tumors (single/multiple), TACE sessions ($\leq 2/> 2$), PS score and chemotherapy agent used. In multivariate analysis, pathological stage ($P = 0.021$) and PS score ($P = 0.032$) were significant independent factors for tumor progression (Table 2).

### Overall survival

Overall survival was evaluated from the time of first TACE session to the endpoint of death or the last follow-up time (31st December, 2012). In patients who died, the cause of death was progression of liver disease (74.8%), rupture of esophageal varices (18.7%) and others (6.5%). There were no treatment related deaths. There was a lower rate of death in the CPT-11 group compared with the GEM or doxorubicin group ($P = 0.02$) due to less tumor progression. The median overall survival times in the CPT-11, GEM and doxorubicin groups were 21.68, 12.72 and 14.46 mo respectively. The cumulative survival rates at 12 and 24 months were 87.5% and 45.8% in the CPT-11 group, 66.7% and 0% in the GEM group and 69.5% and 22.0% in the doxorubicin group (Figure 2A). The overall survival was significantly higher in the CPT-11 group compared with the GEM or doxorubicin groups ($P = 0.004$). Subgroup analysis showed that the difference between the three groups was also significant in patients with intermediate-stage HCC ($P = 0.003$, BCLC B stage, Figure 2B). Univariate analysis revealed eight prognostic factors affecting overall survival: cirrhosis of the liver, BCLC stage, CLIP stage, pathological stage, number of tumors (Single/Multiple), TACE sessions ($\leq 2/> 2$), ALB and chemotherapy agent used. In multivariate analysis, the chemotherapy agent used was significant in patients with intermediate-stage HCC, time to progression was significantly longer in the CPT-11 group compared with the GEM or doxorubicin groups ($P = 0.022$, Figure 1B). Univariate analysis revealed eight prognostic factors affecting tumor progression were recognized: cirrhosis of the liver, BCLC stage, CLIP stage, pathological stage, number of tumors (single/multiple), TACE sessions ($\leq 2/> 2$), PS score and chemotherapy agent used. In multivariate analysis, pathological stage ($P = 0.021$) and PS score ($P = 0.032$) were significant independent factors for tumor progression (Table 2).

## Table 1 Baseline characteristics

|                     | Total ($n = 107$) | CPT-11 ($n = 24$) | GEM ($n = 24$) | DDP+5-FU ($n = 59$) | $P$ value |
|---------------------|------------------|------------------|---------------|-------------------|-----------|
| Mean age ± SD (yr)  | 57.0 ± 11.0      | 61.0 ± 8.7       | 57.5 ± 12.4   | 56.0 ± 11.4       |           |
| Sex (M:F)           | 95:12            | 22:2             | 24:0          | 49:10             |           |
| HBV Absent/Present  | 26/81            | 7/17             | 6/18          | 13/46             | 0.583     |
| Cirrhosis of the liver Absent/Present | 45/62 | 13/11 | 6/18 | 26/33 | 0.003 |
| Tumor maximal diameter (cm) $\leq 5/5$ | 7.8 ± 4.1 | 8.0 ± 3.9 | 7.7 ± 4.1 | 7.4 ± 4.2 | 0.361 |
| Pathological $T$ $\leq 5/T2/T3/T4$ | 8/32/50/17 | 3/8/10/3 | 0/9/10/5 | 5/15/30/9 | 0.070 |
| Pathological Stage $I/II/III/IV$ | 7/26/57/17 | 3/6/10/5 | 0/6/13/5 | 4/14/34/7 | 0.013 |
| TACE Sessions $\leq 2/> 2$ | 73/34 | 8/16 | 18/6 | 47/12 | 0.001 |
| Initial AFP (ng/dL) $\leq 400/> 400$ | 59/48 | 18/6 | 11/13 | 16/43 | 0.005 |
| Number of Tumor Single/Multiple | 57/50 | 12/12 | 13/11 | 32/27 | 0.017 |
| Vascular invasion Absent/Present | 74/33 | 18/6 | 15/9 | 41/18 | 0.014 |
| Child-Pugh A/B | 98/9 | 20/4 | 23/1 | 55/4 | 0.746 |
| BCLC Stage A/B/C | 15/59/33 | 2/16/6 | 1/14/9 | 12/29/18 | 0.005 |
| CLIP Score $\leq 2/> 2$ | 77/20 | 20/4 | 18/6 | 39/20 | 0.013 |
| MELD Score $\leq 6/> 6$ | 74/33 | 17/7 | 16/8 | 41/18 | 0.914 |
| ALB (g/L) $\leq 40/> 40$ | 49/58 | 9/15 | 7/17 | 33/26 | 0.033 |
| TB (µmol/L) $\leq 17/> 17$ | 55/52 | 14/10 | 12/12 | 29/30 | 0.440 |
| AST (U/L) $\leq 40/> 40$ | 23/84 | 8/16 | 8/16 | 7/52 | 0.947 |
| ALT (U/L) $\leq 40/> 40$ | 32/75 | 11/13 | 8/16 | 13/46 | 0.456 |
| Lipiodol (mL) $\leq 10/> 10$ | 62/45 | 11/13 | 15/9 | 36/32 | 0.997 |

Exp(B) stands for relative risk (RR). M: Male; F: Female; MELD: Model for End-stage Liver Disease; BCLC: Barcelona Clinic Liver Cancer Group; CLIP: Cancer of the Liver Italian Program; ALB: Albumin; TACE: Transarterial chemoembolization; CPT-11: Chemotherapeutic agent irinotecan; GEM: Gemcitabine; 5-FU: 5-fluorouracil oxalate; HBV: Hepatitis B virus; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; BCLC: Barcelona Clinic Liver Cancer; OS: Oxidative stress.
a significant independent factor for overall survival \( P = 0.016, \) Table 3). In addition, ALB \( (P = 0.030) \), pathological stage \( (P = 0.012) \) and number of TACE sessions \( (P = 0.001) \) were related to survival. These results suggest that the use of CPT-11 may be associated with a better prognosis in patients with HCC.

**Treatment-related toxicity**

Overall, adverse events were transient and tolerable and successfully managed with conservative treatment. Post-embolization symptoms, such as fever or pain, occurred in 23 patients and were reported as mild. There were no major complications or grade 4 liver toxicity\(^{23}\) in either group within one week after cTACE. The most common adverse event was bone marrow suppression (37 patients) in the CPT-11, GEM and doxorubicin groups. Grade IV of bone marrow suppression was experienced in 1, 2 and 0 patients; 2, 3 and 4 patients had grade III; and mild elevation was seen in 3, 9 and 13 patients (grade I and II), respectively. Elevation of bilirubin was documented in three patients. Four patients experienced mild gastrointestinal symptoms (nausea or vomiting). Diarrhea occurred in only two patients treated with CPT-11 (Table 4).

**DISCUSSION**

Conventional transarterial chemoembolization is widely accepted as a predominantly palliative approach for
patients with HCC when surgical intervention is not appropriate. The rationale for TACE is that a powerful cytotoxic effect combined with ischemia followed by chemomobolization of the hepatic artery will result in therapeutic efficacy and survival benefit compared with supportive care.[23] If performed in a selective and sequential way, high concentrations of embolic and chemotherapeutic agents may offer effective local tumor control, whilst maintaining tolerable systemic concentrations reducing the risk of significant adverse events, such as liver failure and other clinical adverse events. This study demonstrated that local tumor control translates into long survival times for patients treated with more sessions of cTACE.[23,24] However, there is insufficient evidence of chemotherapeutic agents used with cTACE to allow informed comparisons. Doxorubicin has been widely used as the chemotherapeutic agent of choice in cTACE, but with the development of new chemotherapeutic agents, such as CPT-11, GEM and oxaliplatin, comparative studies are needed to find the optimum agent for use in cTACE for the treatment of HCC.

This study is based on previous research on the application of the adenosine triphosphate tumor chemosensitive assay system as sole chemotherapy for HCC.[9] A comparison of CPT-11, GEM and doxorubicin agents used in cTACE for the treatment of HCC was performed. The time to progression and overall survival were significantly longer in patients treated with CPT-11.

**Figure 2** Overall survival rates in the chemotherapeutic agent irinotecan, gemcitabine and doxorubicin groups. A: Significantly better overall survival rates were observed in the chemotherapeutic agent irinotecan (CPT-11) group than in the GEM and doxorubicin group (P = 0.004). B: Overall survival rates in intermediate-stage HCC among the three groups (P = 0.003). GEM: Gemcitabine; HCC: Hepatocellular carcinoma.

**Table 3** Univariate and multivariate analysis for the factors influencing survival rate

| Factors                                      | Univariate (P value) | Multivariate (P value) | Exp(B)  | 95%CI         |
|----------------------------------------------|----------------------|------------------------|---------|--------------|
| Cirrhosis of the liver                       | Absent/ Present      |                         | 0.003   | 0.083        |
| Pathological Stage                           | I / II / III / IV    |                         | 0.013   | 0.012        |
| TACE Sessions                                | ≤ 2/> 2              |                         | 0.001   | 0.001        |
| BCLC Stage                                   | A/B/C                |                         | 0.017   | 0.061        |
| Number of Tumor                              | Single/Multiple      |                         | 0.017   | 0.460        |
| CLIP Score                                   | ≤ 2/> 2              |                         | 0.013   | 0.982        |
| Chemotherapy agent                           | CPT-11/GEM/Doxorubicin |                     | 0.004   | 0.019        |
| ALB (g/L)                                    | ≤ 40/> 40            |                         | 0.033   | 0.030        |

TACE: Transarterial chemoembolization; BCLC: Barcelona Clinic Liver Cancer Group; CLIP: Cancer of the Liver Italian Program; GEM: Gemcitabine; CLIP: Cancer Liver Italian Program; ALB: Albumin; CPT-11: Chemotherapeutic agent irinotecan; GEM: Gemcitabine.
sessions of cTACE regarding overall survival. This result is accurate, and more research should be performed to confirm it.

In the future, the combination of CPT-11-cTACE with drug-eluting beads or sorafenib is interesting with a view to performing more research. Sorafenib, a new multi-targeting drug, inhibits components of the Raf signaling pathway, VEGF, PDGF and RTKs, resulting in inhibition of tumor angiogenesis and proliferation. The efficacy and safety of sorafenib in the treatment of advanced HCC has been demonstrated in clinical practice\(^{29}\) and in a phase III trial. Furthermore, it has been found to prolong survival times in patients with advanced HCC\(^{30,31}\). Studies are needed to compare the tumor response, time to progression and overall survival of patients treated with cTACE using sorafenib.

**Conclusion**

This study demonstrated that cTACE with CPT-11 could prolong the time to progression and overall survival in patients with HCC compared with GEM or doxorubicin. There were no significant differences in hepatic treat-related toxicities and clinic adverse events. CPT-11 with drug-eluting beads or sorafenib is interesting with a view to performing more research. Sorafenib, a new multi-targeting drug, inhibits components of the Raf signaling pathway, VEGF, PDGF and RTKs, resulting in inhibition of tumor angiogenesis and proliferation. The efficacy and safety of sorafenib in the treatment of advanced HCC has been demonstrated in clinical practice\(^{29}\) and in a phase III trial. Furthermore, it has been found to prolong survival times in patients with advanced HCC\(^{30,31}\). Studies are needed to compare the tumor response, time to progression and overall survival of patients treated with cTACE using sorafenib.

**COMMENTS**

**Background**

Hepatocellular carcinoma (HCC) is one of the most common malignant tumors worldwide. Over 60% to 70% of patients with HCC are diagnosed at a late stage and therefore curative therapies are not appropriate. Transarterial chemoembolization (TACE) is the primary treatment used most frequently for unresectable HCC. However, there is a lack of data to support the use of one chemotherapeutic agent or combination of agents over another. Chemotherapeutic agent irinotecan (CPT-11) (irinotecan), a drug used for the treatment of
cancer, prevents DNA unwinding by inhibition of topoisomerase 1. Many studies reported that CPT-11 might be a potential drug for the treatment of HCC and prolong survival time of HCC patients, but the effect has not been evaluated in TACE.

Research frontiers:

Conventional transarterial chemoembolization (cTACE) is widely accepted as a predominantly palliative approach for patients with HCC when surgical intervention is not appropriate. The rationale for TACE is that a powerful cytotoxic effect combined with ischemia followed by chemoembolization of the hepatic artery will result in therapeutic efficacy and survival benefit compared with supportive care.

Innovations and breakthroughs:

Doxorubicin has been widely used as the chemotherapeutic agent of choice in cTACE, but with the development of new chemotherapeutic agents, such as CPT-11, gemcitabine (GEM) and oxaliplatin, comparative studies are needed to find the optimal agent for use in cTACE for the treatment of HCC. Currently, there are limited data available regarding the use of chemotherapeutic agents administered via cTACE in patients with HCC. This study evaluated the efficacy, tumor response, clinical adverse events, time to progression and overall survival benefit of three chemotherapy agents: CPT-11, GEM and doxorubicin.

Applications:

The study results suggest that the chemotherapeutic agent CPT-11 is significantly associated with improved overall survival and delayed tumor progression compared with GEM or doxorubicin. CPT-11 thus appears to be a promising agent when combined with cTACE for the treatment of HCC.

Terminology:

CPT-11: a semi-synthetic analogue of the natural alkaloid camptothecin and activated by hydrolysis to SN-38, an inhibitor of topoisomerase-1. Inactivation follows by uridine diphosphate glucuronosyltransferase 1A1 glucuronidation. The inhibition of topoisomerase 1 by the active metabolite SN-38 eventually leads to inhibition of topoisomerase eventually leads to the cell cycle arrest and apoptosis.

Peer review:

The authors present the scope and limitations of the study and pointed out that the most important items are the small number of cases and the retrospective character of the study.

REFERENCES:

1. El-Seraf HB, Mason AC. Rising incidence of hepatocellular carcinoma in the United States. N Engl J Med 1999; 340: 745-750 [PMID: 10072408 DOI: 10.1056/NEJM199909133401101]
2. El-Seraf HB. Hepatocellular carcinoma: recent trends in the United States. Gastroenterology 2004; 127: S27-S34 [PMID: 15588904 DOI: 10.1053/j.gastro.2004.09.013]
3. Forner A, Reig ME, de Lope CR, Bruix J. Current strategy for staging and treatment: the BCLC update and future prospects. Semin Liver Dis 2010; 30: 61-74 [PMID: 20175034 DOI: 10.1055/s-0030-1247133]
4. Llovet JM, Brui J. Novel advancements in the management of hepatocellular carcinoma in 2008. J Hepatol 2008; 48 suppl 1: S20-S37 [PMID: 18304676 DOI: 10.1016/j.jhep.2008.01.022]
5. Lo CM, Ngan H, Tso WK, Liu CL, Lam CM, Poon RT, Fan ST, Wong J. Randomized controlled trial of transarterial lipiodol chemoembolization for inoperable hepatocellular carcinoma. Hepatology 2002; 35: 1164-1171 [PMID: 11981766 DOI: 10.1053/jhep.2002.33156]
6. Llovet JM, Brui J. Systematic review of randomized trials for unresectable hepatocellular carcinoma: Chemoembolization improves survival. Hepatology 2003; 37: 429-442 [PMID: 12540544 DOI: 10.1053/jhep.2003.50047]
7. Brui J, Sala M, Llovet JM. Chemoembolization for hepatocellular carcinoma. Gastroenterology 2004; 127: S179-S188 [PMID: 15508083 DOI: 10.1053/j.gastro.2004.09.032]
8. Lencioni R. Loco-regional treatment of hepatocellular carcinoma. Hepatology 2010; 52: 762-773 [PMID: 20564355 DOI: 10.1002/hep.23725]
9. Chen T, Chu ZH, Liu JP, Wang J, Zhao HY, Ou QJ. Application of adenovirus triphosphate tumor chemosensitive assay system to individual chemotherapy for hepatocellular carcinoma: Aizheng 2005; 24: 1018-1022 [PMID: 16068886]
10. Takeba Y, Kumat T, Matsumoto N, Nakaya S, Tsuzuki Y, Yanagida Y, Kobayashi S. Irinotecan activates p53 with its active metabolite, resulting in human hepatocellular carcinoma apoptosis. J Pharmacol Sci 2007; 104: 232-242 [PMID: 17690585 DOI: 10.1254/jphs.FP0070442]
11. Bruix J, Sherman M, Llovet JM, Beaugrand M, Lencioni R, Burroughs AK, Christensen E, Pagliari L, Colombo M, Rodés J. Clinical management of hepatocellular carcinoma. Conclusions of the Barcelona-2000 EASL conference. European Association for the Study of the Liver. J Hepatol 2001; 35: 421-430 [PMID: 1150267 DOI: 10.1016/s0168-8278(01)00136-1]
12. Brown DB, Gould JE, Gervais DA, Goldberg SN, Murthy R, Millward SF, Rilling WS, Geschwind JF, Salem R, Vedantham S, Cardella JF, Soulen MC. Transcatheter therapy for hepatic malignancy: standardization of terminology and reporting criteria. J Vasc Interv Radiol 2007; 18: 1469-1478 [PMID: 18057279 DOI: 10.1016/j.jvir.2007.08.027]
13. Pugh RN, Murray-Lyon IM, Dawson JL, Pietroni MC, Williams R. Transection of the oesophagus for bleeding oesophageal varices. Br J Surg 1973; 60: 646-649 [PMID: 4541913 DOI: 10.1002/bjs.1806060817]
14. Child CG, Turcotte JG. Surgery and portal hypertension. Modern Clin Surg 1964; 1: 1-85 [PMID: 4950264]
15. Testa R, Testa E, Giannini E, Botta F, Malfatti F, Chiarbonnel B, Fumagalli A, Polegata S, Pedesta E, Romagnoli P, Risso D, Cittadini G, De Caro G. Trans-catheter arterial chemoembolization for hepatocellular carcinoma in patients with viral cirrhosis: role of combined staging systems, Cancer Liver Italian Program (CLIP) and Model for End-stage Liver Disease (MELD), in predicting outcome after treatment. Aliment Pharmacol Ther 2003; 17: 1563-1569 [PMID: 12823161 DOI: 10.1046/j.1365-2036.2003.01647.x]
16. Prospective validation of the CLIP score: a new prognostic system for patients with cirrhosis and hepatocellular carcinoma. The Cancer of the Liver Italian Program (CLIP) Investigators. Hepatology 2000; 31: 840-845 [PMID: 10735537 DOI: 10.1053/hep.2000.5628]
17. Llovet JM, Bru C, Brui J. Prognosis of hepatocellular carcinoma: the BCLC staging classification. Semin Liver Dis 1999; 19: 329-338 [PMID: 10518312 DOI: 10.1053/s-l-2007.017122]
18. Brown DB, Cardella JF, Sacks D, Goldberg SN, Gervais DA, Rajan DK, Vedantham S, Miller DL, Browntown EN, Grassi CJ, Towbin RB, Angle JF, Balter S, Clark TW, Cole PE, Drescher P, Freiman MJ, Georgi D, Haskal Z, Hovsepian DM, Kilnani NM, Kundu S, Malloy PC, Martin LG, Murphy K, Neithamer CD, Omary RA, Patel NH, Roberts AC, Schwartzberg MS, Siskin GP, Smouse HR, Swan TL, Thorpe PE, Vesely TM, Wagner LK, Wiechmann BN, Bakal CW, Lewis CA, Nemcek AA, Rholl KS. Quality improvement guidelines for transhepatic arterial chemoembolization, embolization, and chemotherapeutic infusion for hepatic malignancy. J Vasc Interv Radiol 2009; 20: S219-S226, S226.e1-10 [PMID: 19560002 DOI: 10.1016/j.jvir.2009.04.033]
19. Llovet JM, Di Bisceglie AM, Brui J, Kramer BS, Lencioni R, Zhu AX, Sherman M, Schwartz M, Lotze M, Talwalkar J, Gores GJ. Design and endpoints of clinical trials in hepato-cellular carcinoma. J Natl Cancer Inst 2008; 100: 698-711 [PMID: 18477802 DOI: 10.1093/jnci/djn134]
20. Lencioni R, Llovet JM. Modified RECIST (mRECIST) assessment for hepatocellular carcinoma. Semin Liver Dis 2010; 30: 52-60 [PMID: 20175033 DOI: 10.1055/s-0030-1247132]
21. Kim SH, Lee WJ, Lim HK, Lim JH. Prediction of viable tumor in hepatocellular carcinoma treated with transcatheter arterial chemoembolization: usefulness of attenuation value measurement at quadruple-phase helical computed tomography. J Comput Assist Tomogr 2007; 31: 198-203 [PMID: 17414753 DOI: 10.1097/01.rct.0000296424.20514.2e]
Wu J et al. CPT-11 in TACE for hepatocellular carcinoma

22 King PD, Perry MC. Hepatotoxicity of chemotherapy. Oncologist 2001; 6: 162-176 [PMID: 11306728 DOI: 10.1634/the-oncologist.6-2-162]

23 Llovet JM, Real MI, Montaña X, Planas R, Coll S, Aponte J, Ayuso C, Sala M, Muchart J, Solà R, Rodés J, Bruix J. Arterial embolisation or chemoembolisation versus symptomatic treatment in patients with unresectable hepatocellular carcinoma: a randomised controlled trial. Lancet 2002; 359: 1734-1739 [PMID: 12049862 DOI: 10.1016/S0140-6736(02)06736-X]

24 Kawai S, Okamura J, Ogawa M, Ohashi Y, Tani M, Inoue J, Kawarada Y, Kusano M, Kubo Y, Kuroda C. Prospective randomized clinical trial for the treatment of hepatocellular carcinoma--a comparison of lipiodol-transcatheter arterial embolization with and without adriamycin (first cooperative study). The Cooperative Study Group for Liver Cancer Treatment of Japan. Cancer Chemother Pharmacol 1992; 31 Suppl: S1-S6 [PMID: 1281041 DOI: 10.1007/BF00687096]

25 Hiraoka A, Horiike N, Yamashita Y, Koizumi Y, Doi H, Yamamoto Y, Ichikawa S, Hasebe A, Yano M, Miyamoto Y, Ninomiya T, Ootani H, Kamura K, Kawasaki H, Otomi Y, Kogame M, Sogabe I, Ishimaru Y, Kashiwara K, Miyagawa M, Hirooka M, Hiasa Y, Matsura B, Michitaka K, Onji M. Risk factors for death in 224 cases of hepatocellular carcinoma after transcatheter arterial chemoembolization. Hepatogastroenterology 2009; 56: 213-217 [PMID: 19453060]

26 Wigmore SJ, Redhead DN, Thomson BN, Parks RW, Garden OJ. Predicting survival in patients with liver cancer considered for transarterial chemoembolization. Eur J Surg Oncol 2004; 30: 41-45 [PMID: 14736521 DOI: 10.1016/j.ejso.2003.10.007]

27 O’Suilleabhain CB, Poon RT, Yong JL, Ooi GC, Tso WK, Fan ST. Factors predictive of 5-year survival after transarterial chemoembolization for inoperable hepatocellular carcinoma. Br J Surg 2003; 90: 325-331 [PMID: 12594668 DOI: 10.1002/bjs.4045]

28 Farinati F, De Maria N, Marafin C, Herszényi L, Del Prato S, Rinaldi M, Perini L, Cardin R, Naccarato R. Unresectable hepatocellular carcinoma in cirrhosis: survival, prognostic factors, and unexpected side effects after transcatheter arterial chemoembolization. Dig Dis Sci 1996; 41: 2332-2339 [PMID: 9011438 DOI: 10.1017/BF02180123]

29 Di Costanzo GG, Tortora R, Iodice L, Lanza AG, Lampasi F, Tartaglione MT, Picciotto FP, Mattera S, De Luca M. Safety and effectiveness of sorafenib in patients with hepatocellular carcinoma in clinical practice. Dig Liver Dis 2012; 44: 788-792 [PMID: 22579445 DOI: 10.1016/j.dld.2012.04.001]

30 Cheng AL, Kang YK, Chen Z, Tsao CJ, Qin S, Kim JS, Luo R, Feng J, Ye S, Yang TS, Xu J, Sun Y, Liang H, Liu J, Wang J, Tak WY, Pan H, Barock K, Zou J, Vologiots D, Guan Z. Efficacy and safety of sorafenib in patients in the Asia-Pacific region with advanced hepatocellular carcinoma: a phase III randomised, double-blind, placebo-controlled trial. Lancet Oncol 2009; 10: 25-34 [PMID: 19095497 DOI: 10.1016/S1470-2045(08)70285-7]

31 Zhang T, Ding X, Wei D, Cheng P, Su X, Liu H, Wang D, Gao H. Sorafenib improves the survival of patients with advanced hepatocellular carcinoma: a meta-analysis of randomised trials. Anticancer Drugs 2010; 21: 326-332 [PMID: 20016366 DOI: 10.1097/CAD.0b013e3283530c26]

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