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A real-world study of Chinese hepatocellular carcinoma patients treated with TACE

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Abstract. – OBJECTIVE: The aim of the study was to explore the real situation of transcatheter arterial chemoembolization (TACE) treatment mode and clinical benefits for hepatocellular carcinoma (HCC) patients, as well as to potentially provide data support and clinical basis for the decision-making of HCC patients.

PATIENTS AND METHODS: We collect the diagnosis and treatment information of patients who were clinically diagnosed with primary liver cancer (PLC) and received the first treatment in the medical center since January 1st, 2012 from the Chinese Liver Cancer Survey (CLCS) database. Then, we entered the formatted data into the real-world study (RWS) database. TACE-related data were collected prospectively. From December 2018 to January 2020, HCC patients who were eligible for CLCS and received TACE were treated at three time points (admission day/before TACE, before discharge/after TACE, follow-up/first follow-up after discharge) to collect and analyze the quality of life of patients and the use of medical resources. Patients with clinical diagnosis of HCC who received TACE treatment at least once were screened based on CLCS locking data. Demographic and TACE treatment related studies were conducted on the selected HCC patients.

RESULTS: The data of the whole group of 5436 HCC patients who received TACE treatment in 48 medical centers showed that the first department of patients was surgery (65.89%), followed by internal medicine (22.42%) ($p>0.05$). The proportion of patients treated with TACE was 51.85%; the proportion of patients treated with 2 TACE was 23.64%; the proportion of patients with more than 3 times was 20.60% ($p>0.05$). In the CLCS database, the TACE-first group, there were 1758 patients who received only one treatment in total, and 3069 patients who received ≥ 2 treatments ($p<0.05$). The common complications related to TACE treatment were nausea (25.77%), fever (31.53%), vomiting (20.99%), liver pain (40.67%) and other uncomfortable symptoms ($p<0.05$).

CONCLUSIONS: A more comprehensive understanding of the clinical impact and benefits of TACE in Chinese HCC patients is needed.

Key Words:
Hepatocellular carcinoma, Hepatic arterial infusion chemoembolization, Real-world study.

Introduction

The incidence of liver cancer is very high in China, and its patients account for about 50% of global patients. In recent years, the incidence of primary liver cancer (PLC) has been increasing year by year, of which up to 90% are hepatocellular carcinoma (HCC)[1,2]. Relevant research[3] found that the disease has become the fourth most common malignant tumor in China now and has been classified as the second cause of death from tumor, posing a serious threat to people's life. Clinical analysis found that there are many pathogenesis and risk factors, such as smoking, liver cirrhosis, virus, diabetes, overweight, etc. If we do not choose the appropriate treatment as soon as possible, with the continuous deterioration of the disease, it may directly endanger people's life[4,5]. According to statistics, 50% of the new cases of HCC in the world occur in China, and many patients have already entered an advanced stage when diagnosed, with the possibility to be treated with surgery for the 20% of them[6]. In recent years, with the continuous improvement of interventional radiology in China, transcatheter hepatic artery embolization has been clinically summarized as the first choice for non-surgical treatment of HCC[7]. Clinical studies[8] have found that there is no optimal chemotherapy method at this stage because liver cells are accompanied by different levels of multi-drug resistance genes. Therefore, some scholars have used hepatic arterial embolization to treat HCC, and many scholars believe that hepatic artery infusion chemotherapy can increase the concentration of chemotherapy drugs in the tumor area, and lipiodol carrying chemotherapy drugs can have a continuous killing effect on the

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tumor[9]. Therefore, the choice of transhepatic arterial chemoembolization (TACE) in the treatment of HCC can obtain significant value and can effectively improve the quality of life of patients and prolong the survival period[10,11]. So far, based on the single center data of front-line clinical practice experts, a large amount of data on the timing, frequency and even clinical benefits of TACE treatment in patients with liver cancer have been analyzed. However, because different medical centers have different TACE treatment modalities, there is still much unknown about the exact clinical benefit of TACE for HCC patients as a whole[12]. Therefore, this study conducted a real-world study (RWS) of TACE-treated HCC patients in China based on a large Chinese Liver Cancer Survey database (CLCS database). Through this study, we will find out the real situation of TACE treatment mode and clinical benefit used by HCC patients and will potentially provide data supports and clinical basis for the decision-making of HCC patients.

Patients and Methods

Based on the CLCS database, the main research questions of this study include: Which group of medical-insured HCC patients received TACE in real clinical practice in China? What are the characteristics of these TACE treatment? How effective is TACE in HCC patients? How safe is TACE in the treatment of HCC patients?

Research Purpose

The purposes of the research are to:

- Describe TACE treatment mode for HCC patients treated with TACE;
- Analyze the clinical outcomes of patients treated with TACE;
- Describe the demographics, health insurance distribution, and clinical characteristics of HCC patients treated with TACE;
- Examine TACE-related AE incidence and complications.

Moreover, the exploratory purpose of the research is to describe the use of healthcare resources related to TACE treatment and to describe health care costs associated with TACE treatment.

Research Methods

A real-world study was conducted on HCC patients previously treated with TACE in the CLCS database. CLCS is a multi-center, longitudinal real-world study, with Professor Qin Shukui and other more than 100 experts from 78 domestic medical centers. From January 1st, 2012, the diagnosis and treatment information of the patients who were clinically diagnosed with PLC and received the first treatment in the medical center were collected from the CLCS database and the RWS database.

This study is divided into two parts, the first is a cross-sectional study of TACE-related medical economics based on the CLCS project. This part of the study used cross-sectional enrolled HCC patients who received TACE, and prospectively collected TACE-related data. From December 2018 to January 2020, the quality of life and the use of medical resources in patients who were in line with CLCS and received TACE for HCC were treated at three time points (admission day/before TACE, before discharge/after TACE, follow-up/first follow-up after discharge) were collected and analyzed. The quality of life was evaluated and analyzed by the European five-dimensional health scale (EQ-5D-3L) and the liver and gallbladder scale (FACT-Hep). The second part of the study is focused on TACE-related RWS study based on the existing CLCS database. The data cut-off time for the enrolling patients is December 31, 2020. Based on CLCS lock-in data, patients with a clinical diagnosis of HCC and who received at least one TACE treatment were screened. Demographic and TACE treatment correlation analysis was performed on the screened HCC patient population.

Study Population

The data of the study population came from the CLCS database, and the patient's inclusion criteria were as follows: (1) whose age greater than 18 years old; (2) whose medical records are complete; (3) patients with clinical diagnosis or pathological diagnosis of HCC; (4) patients with at least one TACE treatment; (5) patients agree to participate in CLCS. The patient's exclusion criteria were: (1) patients with different degrees of cognitive impairment; (2) patients with other malignant tumors; (3) patients with hearing impairement or unable to communicate.

Data Analysis

After locking and downloading the data information of CLCS database on February 28, 2020, HCC patients were screened according

to the inclusion and exclusion criteria. General information, such as gender, age, occupation, educational background, type of medical insurance of the patients, the test results (laboratory examinations, imaging examinations, pathological examinations, etc.), treatment mode and efficacy, and clinical outcomes of each treatment were collected.

Statistical Analysis

The descriptive analysis is used in this study. Categorical variables are described using frequency and correlation percentages and 95% CI, including differences, median, 25th to 75th percentile, minimum and maximum number of patients. A significant difference was presumed at a p-value < 0.05.

Results

Screening and Stratification of TACE Patients

5436 patients with primary liver cancer who received TACE treatment were selected. Among them, the TACE group included 4827 people. The TACE group with non-first diagnosis and first treatment (TACE non first group) included the patients with local treatment history (including surgery, ablation, radiotherapy, etc.) after the first diagnosis of liver cancer and before TACE treatment. The first diagnosis and first treatment TACE group (TACE group I) included those whose preferred local treatment method is TACE after the first diagnosis of HCC and without any history of other local previous treatment or systemic treatment (except traditional Chinese medicine/immunomodulator, interferon, thymosin and other treatment history).

Patients' Basic Information

In this study, a total of 48 medical centers and 5436 HCC patients who received TACE treatment are included in the screening and group selection for analysis (Table I). The results of the data show that the department in which they were included was mainly that of surgery (65.89%), followed by internal medicine (22.42%), and other departments, including tumor and radiotherapy (Table II). In addition, the occupation and medical insurance of patients are also described in Table III and Table IV.

Conditions and Characteristics of TACE Treatment

In the TACE-first group, the proportion of patients who experienced once TACE treatment was 51.85%, the proportion of patients who experienced twice TACE treatment was 23.64%, and the proportion of patients who experienced more than 3 times was 20.60% (Table V).

Number of Patient Visits

In the TACE-first group, there were 1758 patients who received only one treatment in total, and 3069 patients who received ≥ 2 treatments, as shown in Table VI.

Distribution of Complications During TACE Treatment

Common complications during TACE treatment include nausea, fever, vomiting, and liver pain, as shown in Table VII.

Discussion

Related studies have found that hepatocellular carcinoma mainly originates from hepatocyte-rich malignant tumors, with 90% of the blood supply from the hepatic artery, while 80% of liver cancer patients in China are caused by hepatitis B virus infection[13]. As a matter of fact, the incidence of HCC in China is significantly higher than that in other developed countries[14]. The clinical symptoms of HCC were liver pain, accompanied by fatigue, weight loss, abdominal distention, loss of appetite, nausea and other symptoms. It can be seen through medical equipment that the patient's liver gradually increased, the edge of the liver is irregular and the surface was uneven[15,16]. At this stage, for patients with advanced liver cancer, surgical resection cannot be performed clinically, and the best surgical opportunity has been lost. Transcatheter arterial embolization has been clinically classified as the preferred treatment for HCC. Although it can stabilize the patient's condition and obtain certain therapeutic value, clinical studies have found that this therapy is easily inhibited by factors, such as portal vein tumor thrombus, which reduces the quality of clinical treatment, and thus, cannot achieve the optimal treatment efficiency[17,18]. At present, TACE has been recognized as one of the most commonly used non-surgical treatment options for liver cancer. Unlike Europe, America and Japan, HCC patients treated with TACE in China have larger tumors and are

Table I. Hospital distribution.

Hospital name	N	Percentage
Qingdao Central Hospital	46	0.85%
West China Hospital of Sichuan University	22	0.40%
Affiliated Hospital of Qinghai University	54	0.99%
Chinese Academy of Medical Sciences Peking Union Medical College Hospital	13	0.24%
The First Affiliated Hospital of Nanchang University	190	3.50%
Xinjiang Uygur Autonomous Region People's Hospital	171	3.15%
The First Affiliated Hospital of Guangzhou University of Traditional Chinese Medicine	6	0.11%
Tianjin Third Central Hospital	95	1.75%
Chinese People's Liberation Army General Hospital	40	0.74%
Sichuan Cancer Hospital	84	1.55%
Bethune First Hospital of Jilin University	23	0.42%
Army Oncology Center, Eastern Theater General Hospital	11	0.20%
Henan Cancer Hospital	214	3.94%
The First Affiliated Hospital of University of Science and Technology of China	135	2.48%
Peking University International Hospital	30	0.55%
The First Affiliated Hospital of China Medical University	39	0.72%
Union Hospital Affiliated to Fujian Medical University	107	1.97%
The First Affiliated Hospital of Guangxi Medical University	16	0.29%
Zhongda Hospital Affiliated to Southeast University	26	0.48%
Xijing Hospital of Air Force Military Medical University	661	12.16%
Xuzhou Central Hospital	26	0.48%
Fifth Medical Center of PLA General Hospital	244	4.49%
The Third Clinical Medical College of Xinjiang Medical University (Affiliated Cancer Hospital)	156	2.87%
The First Affiliated Hospital of Soochow University	380	6.99%
Jieyang People's Hospital	13	0.24%
Peking University Cancer Hospital	429	7.89%
The Second Affiliated Hospital of PLA Air Force Military Medical University	6	0.11%
Nantong Cancer Hospital	357	6.57%
The First Affiliated Hospital of Army Military Medical University	11	0.20%
The First Affiliated Hospital of Bengbu Medical College	45	0.83%
Second Affiliated Hospital of Army Military Medical University	162	2.98%
Sun Yat-Sen University Cancer Center	344	6.33%
The First Affiliated Hospital of Harbin Medical University	51	0.94%
The First Affiliated Hospital of Zhejiang University	32	0.59%
People's Hospital of Jiangyin City, Jiangsu Province	12	0.22%
The Second Affiliated Hospital of Chongqing Medical University	196	3.61%
Zhuhai People's Hospital	303	5.57%
Run Run Shaw Hospital Affiliated to Zhejiang University	99	1.82%
Hunan Cancer Hospital	151	2.78%
Shengjing Hospital Affiliated to China Medical University	42	0.77%
Guangxi Medical University Affiliated Cancer Hospital	142	2.61%
Jilin Cancer Hospital	49	0.90%
Liaoning Cancer Hospital	2	0.04%
Chinese Academy of Medical Sciences Cancer Hospital	57	1.05%
Xinjiang Uygur Autonomous Region Traditional Chinese Medicine Hospital	72	1.32%
Affiliated Hospital of Qingdao University	8	0.15%
Eastern Hepatobiliary Surgery Hospital of Naval Medical University	Twenty-two	0.40%
Beijing Tsinghua Chang Gung Memorial Hospital	42	0.77%
Total	5436	100.00%
p		> 0.05

accompanied by intrahepatic vascular invasion or distant metastasis[19,20]. TACE mainly injects lipiodol and chemotherapeutic drug emulsifier into tumor blood vessels, which can reasonably avoid the blood supply of tumor tissue. In addition, chemotherapeutic drugs are continuously released at the tumor site to further remove cancer cells and significantly reduce tumor volume, so as to achieve a satisfactory treatment outcome[21,22]. Relevant studies[23] have found that TACE can directly infuse chemotherapeutic drugs into the hepatic artery, so that the concentration of the drug in the cancerous site gradually increases, thereby effectively promoting the full effect of the drug.

Table II. Case distribution – department.

Department	N	Percentage
Radiotherapy	15	0.28%
Radiology	6	0.11%
Internal Medicine	1219	22.42%
other	403	7.41%
surgical	3582	65.89%
Oncology	211	3.88%
Total	5436	100.00%
t	0.000	
p	1.000 (> 0.05)	

Table III. Occupational distribution of patients.

Group	N	Percentage
Unknown	1172	21.56%
Self-employed persons	41	0.75%
Worker	372	6.84%
Civil Servants	49	0.90%
Teacher	22	0.40%
Soldier	2	0.04%
Retirees	563	10.36%
Lawyer	2	0.04%
Farmer	1179	21.69%
Other	1503	27.65%
Business managers	2	0.04%
merchant	9	0.17%
Unemployed	351	6.46%
student	3	0.06%
Doctor	2	0.04%
staff	143	2.63%
Professional skilled worker	14	0.26%
Freelancers	7	0.13%
total	5436	100.00%
t	0.000	
p	1.000 (> 0.05)	

Most of the current medical clinical practice guidelines are obtained from randomized controlled trials and lack the support of real-world data. The emergence of the evidence-based method of real-world research has greatly compensated for this shortcoming. This method refers to the random control trial method, which is based on the wishes of the guardian and the actual condition of the patient, adding a large sample size under the non-random selection treatment. RWS can verify the internal effectiveness and safety, track the short-term and long-term results of the research direction, and conduct long-term follow-up evaluation, so as to better evaluate the external effectiveness and safety of the intervention[24,25]. Real-world research methods have been used for more than 20 years. In the medical industry, real-world research has profoundly affected medical clinical practice and medical research. Real-world studies were first used in pharmacoepidemiology[26]. It refers to the nonrandom selection of treatment measures and a series of long-term evaluations based on large samples and the actual situation and wishes of patients in the process of medical diagnosis and treatment. It focuses on meaningful treatment of relevant outcomes, as well as in practical medicine.

Table IV. Types and distribution of patient insurance.

Type of reimbursement	TACE-First group (N = 4827)		TACE-non-First group (N = 609)	
	N	Percentage	N	Percentage
Basic medical insurance for urban workers in this city	802	16.61%	113	18.56%
Basic medical insurance for urban workers in others cities and town	165	3.42%	8	1.31%
Other social insurance	77	1.60%	4	0.66%
Social Basic Medical Insurance	9	0.19%	2	0.33%
Military medical	2	0.04%	0	0.00%
Basic medical insurance for urban residents in this city	503	10.42%	62	10.18%
Basic medical insurance for urban residents in other cities	119	2.47%	3	0.49%
The city's new rural cooperative medical care	476	9.86%	62	10.18%
New rural cooperative medical care in other cities	107	2.22%	4	0.66%
Poverty relief	4	0.08%	0	0.00%
Commercial medical insurance	32	0.66%	1	0.16%
public health care	11	0.23%	1	0.16%
All at own expense	822	17.03%	103	16.91%
Other	577	11.95%	30	4.93%
Unknown	1121	23.22%	216	35.47%
t	0.000			
p	1.000 (> 0.05)			

Table V. TACE treatment conditions and characteristics.

Group	TACE-First group (N = 4827)		TACE-non-First group (N = 609)	
	N	Percentage	N	Percentage
Number of TACE treatments				
1 time	2503	51.85%	281	46.14%
2 times	1141	23.64%	159	26.11%
3 times	559	11.58%	78	12.81%
4 times	273	5.66%	46	7.55%
5 times	162	3.36%	28	4.60%
6 times and above	189	3.92%	17	2.79%
t	0.001			
p	0.999 (> 0.05)			

Table VI. Number of patient visits.

Group	TACE-First group (N = 4827)		TACE-non-First group (N = 609)	
	N	Percentage	N	Percentage
1 time	1758	36.42	0	0.00
≥ 2 times	3069	63.58	609	100.00
χ^2	44.5287			
p	0.001 (< 0.05)			

Table VII. Distribution of complications during TACE treatment.

Group	TACE-First group (N = 4827)		TACE-non-First group (N = 609)	
	N	Percentage	N	Percentage
Liver damage	142	2.94%	6	0.99%
Liver failure	4	0.08%	1	0.16%
Tumor rupture	2	0.04%	0	0.00%
Liver abscess	3	0.06%	0	0.00%
Pulmonary embolism	0	0.00%	0	0.00%
Renal impairment	4	0.08%	0	0.00%
Contrast allergy	3	0.06%	0	0.00%
Femoral artery thrombosis	0	0.00%	0	0.00%
Femoral vein thrombosis	0	0.00%	0	0.00%
Pseudoaneurysm	0	0.00%	0	0.00%
Femoral arteriovenous fistula	0	0.00%	0	0.00%
Ectopic embolism	0	0.00%	0	0.00%
Necrotizing cholecystitis	0	0.00%	0	0.00%
Myelosuppression	36	0.75%	2	0.33%
Post-embolic syndrome	241	4.99%	11	1.81%
Fever	1522	31.53%	109	17.90%
Nausea	1244	25.77%	63	10.34%
Vomit	1013	20.99%	42	6.90%
Pain in the liver area \ pain in the liver area \ abdominal pain	1963	40.67%	122	20.03%
Bloating	685	14.19%	72	11.82%
Anorexia	419	8.68%	twenty-four	3.94%
Intraoperative allergy	3	0.06%	0	0.00%
Intraoperative bleeding	1	0.02%	0	0.00%
Intraoperative gallbladder reflex	0	0.00%	0	0.00%
Other	963	19.95%	78	12.81%
t	2.800			
p	0.010 (<0.05)			

The external efficacy and safety of interventions were evaluated during the process[27,28]. The efficacy index includes the following data. (1) Endpoint index, which is the main index for evaluating clinical trials. It generally refers to the events that patients are most concerned about, have the greatest impact on, and have the most vital interests, and usually require long-term follow-up. This indicator mainly includes important clinical events, such as the level of disability, relapse, survival or death and so on. Endpoint outcome indicators are usually expressed in terms of rates, such as survival rate, case fatality rate, cure rate, remission rate, recurrence rate and so on[29]. (2) Surrogate indicators. The surrogate indicators are used to evaluate the effect of intervention measures when the measurement feasibility of the endpoint indicators is not high. Commonly used are simple biological indicators, including physical signs, clinical experimental data, such as body weight, blood sugar, blood pressure and so on. (3) Symptoms and signs. Some symptoms and reactions of the patient and signs found in the physical examination, such as breathing, heart rate, nature and degree of pain and so on. These subjective symptoms are clinically less reliable and vary from person to person. To improve the accuracy, some scientific questionnaires and scales can be used[30]. (4) Quality of life, which is generally assessed by scales. The appropriate scale is selected according to the purpose and object. It usually includes two aspects: one is a general scale applicable to the general population, and the other is a specific scale for specific disease groups. (5) Sex scale[31]. On the other hand, safety indicators refer to the impact of intervention measures on the disease after the implementation of the intervention, which may cause adverse effects or harm to the patient. In the process of clinical diagnosis and treatment, adverse reactions are often recorded and reported. Safety was assessed[32,33]. The measurement of outcome indicators is mainly determined by the data type and clinical significance of the outcome indicators. Variables are usually dichotomous variables and continuous variables. The outcomes of dichotomous variables are relative, that is, either A or B, such as effective and ineffective treatment effects, positive and negative test results, and presence or absence of side effects[34]. In addition, the outcome indicators can also be quantitatively divided, and the clinical outcomes are often represented by continuous variables, so that the degree of outcome will be more accurate[35].

5,436 patients who received at least one TACE treatment are selected from the CLCS database to enter into the study. The results show that 65.89% of the patients were first treated in surgery, followed by internal medicine (22.42%), and other departments involved oncology, radiotherapy, etc. (p>0.05). Medical insurance for patients is widely distributed, mainly in the following types: basic medical insurance for urban employees (16.61%), basic medical insurance for urban residents (10.42%), new rural cooperative medical care (9.86%), At the same time, the proportion of patients at their own expense was relatively high (17.03%) (p>0.05). In addition, the proportion of social basic medical care, public medical care, and commercial medical insurance is very low, ranging from 0.1% to 0.6%. The data of patients with insurance records in the whole group of patients showed that 74.4% of the patients had basic medical insurance, and 26.6% of them are self-paid. Because 23.22% of the overall population were missing in insurance records, and some medical insurance data were not classified and displayed, the category of medical insurance needs further research combined with the actual situation. The whole group of patients was divided into 2 groups according to the condition of receiving TACE for the first time. The first diagnosis and first treatment TACE group (TACE-first Group, N= 4827) and the non-first diagnosis and first treatment TACE group (TACE-non-first Group, N=609). Based on the significance of the data, the results of this study will mainly be described by the TACE-first Group. According to the demographic information data of the TACE-first group, as of the lock-up time, the results of the TACE treatment mode data show that the proportion of patients with one TACE was 51.85%, the proportion of patients with two TACE was 23.64%, and the proportion of patients with more than three times was 20.60%. The common complications related to TACE treatment were nausea (25.77%), fever (31.53%), vomiting (20.99%), and liver pain (40.67%).

Conclusions

So far, in common single-center real-sample studies, due to few and missing data from a single center, selective metastasis often occurs when analyzing the demographic characteristics, clinical diagnosis and treatment characteristics, and embolization pattern characteristics of overall liver cancer patients. Based on the CLCS database, this study provides a more comprehensive

understanding of the clinical impact and benefits of TACE in Chinese HCC patients through a multicenter longitudinal and cross-sectional study. However, the lack of patient data is often an unavoidable problem in the real world, and this study is no exception. The inadequacy of data needs to be improved through further prospective data collection settings, and more comprehensive data and more reliable conclusions can be obtained through scientific statistical methods, such as data trend scoring.

Conflict of Interest

The Authors declare that they have no conflict of interests.

Informed Consent

This study involves obtaining informed consent from all patients and filing by Beijing Xisco Clinical Oncology Research Foundation (Public Welfare).

Ethical Approval

This study was approved by the Ethics Committee of Hunan Environmental Biology Vocational and Technical College.

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