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ORIGINAL ARTICLE

D-dimer increase: an unfavorable factor for patients with primary liver cancer treated with TACE

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Abstract

Purpose To explore the clinical significance of plasma D-dimer increase for transcatheter arterial chemoembolization (TACE) in patients with primary liver cancer (PLC).

Methods The clinical data of 80 PLC patients who underwent TACE in our hospital from January 2015 to January 2017 were collected, including the plasma D-dimer level 1 week before TACE (D0), D-dimer level 1 month after TACE (D1) and D-dimer level when the disease begins to progress (D2). 1 Month after TACE, these patients were divided into two groups according to the mRecist criteria: disease-controlled group (CR + PR + SD) and disease-progressing group (PD). In all subjects, progression-free survival (PFS) was recorded. D0 and D1 were compared between the two groups by the rank sum test; and the relation between D-dimer level and PFS was assessed by the Kaplan–Meier test and Breslow test.

Results In the disease-controlled group, there was no significant difference between D0 and D1 ($P > 0.05$); in the disease-progressing group, D1 was significantly higher than D0 ($P < 0.05$) and the D1 is higher than that in disease-controlled group. In the patients with a negative D1 or D2, PFS was longer than those with a positive level (both $P < 0.05$), but such difference was not statistically significant in D0 ($P > 0.05$). In the patients with a D-dimer level increase after TACE (group 3), PFS was shorter than that in those with a D-dimer level decrease after TACE (Group 1) and that in those with a relatively stable D-dimer level before and after TACE (Group 2) ($P < 0.05$); survival in Group 1 was slightly but not significantly longer than that in Group 2 ($P > 0.05$).

Conclusion The change in plasma D-dimer level can be used as a biological index to assess the efficacy of TACE and prognosis for PLC patients, and thus, a positive D-dimer level or D-dimer increase after TACE is an unfavorable factor.

Keywords Primary liver cancer · Transcatheter arterial chemoembolization · D-dimer · Efficacy · Prognosis

Introduction

As the No. 5 malignant tumor in the world, primary liver cancer (PLC) is severely malignant, with poor prognosis, and has a high incidence and mortality [1]. With a latent onset, liver cancer develops to a middle-advanced stage at definite diagnosis in most patients, thus losing the best opportunity for radical excision. However, transcatheter arterial chemoembolization (TACE) can induce tumor ischemia/necrosis and thus realizes the goal of chemotherapy by injecting the embolic and chemotherapeutic agents into the supplying vessels and the body of tumors in the liver. With such advantages as minimal invasion and fast recovery, TACE can delay disease progression and prolong the survival of patients. Therefore, TACE has gradually become an indispensable therapy for PLC, and it is applicable for older patients with liver cancer of middle-advanced stage and who cannot tolerate surgical resection.

In malignant tumor patients, the blood coagulation function is often abnormal: hypercoagulatory state, hyperfibrinolytic state, and plasma D-dimer increase [2]. In recent years, increased plasma D-dimer level in malignant tumor patients has attracted the concerns of many investigators: the plasma D-dimer level is considered relevant to the onset, progression and resulting complications of tumors [3], and increased plasma D-dimer level is regarded as unfavorable for the prognosis of malignant tumor patients. In clinical practice, we find that the plasma D-dimer level often increases in PLC patients (especially those with a serious illness). In

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this retrospective study, the clinical value of plasma D-dimer level for the efficacy and prognosis of TACE in PLC patients was assessed.

Patients and methods

Patients

The patients with definite diagnosis of PLC in our hospital from January 2015 to January 2017 were selected. They were followed up until June 31, 2017. Inclusion criteria: (1) TACE-naïve patients; (2) patients who did not receive relevant treatments in the past (e.g., surgery of liver/gallbladder system); (3) patients with good function of heart/lungs/liver/kidney; patients with BCLC Class A–C (BCLC staging); (4) patients who provided complete clinical data; and (5) patients who underwent successful embolization. Exclusion criteria: (1) patients with concomitant diseases in heart, lungs and peripheral blood vessels, acute/chronic inflammation, trauma, and other malignant tumors influencing blood coagulation function; and (2) patients who were pregnant. A total of 80 patients were enrolled, including 62 males and 28 females, with an age of 33–80 years (mean: 61 years).

Treatment and follow-up

In all subjects, TACE was performed using the embolic (iodized oil) and chemotherapeutic (epirubicin, platinums or their combination) agents. During the procedure, the dose of the above agents was determined according to some conditions (e.g., the size/number of tumors and staining conditions). Standards for successful embolization were as follows: the tumor was not stained at DSA examination after completion of TACE. At 4 weeks (almost 1 month) after TACE, liver-enhanced CT reexamination was performed, and every 3 months thereafter. If the tumor was enhanced in the arterial phase, a second TACE was performed. In all patients, progression-free survival (PFS) was recorded, i.e., the time from the first blood drawing to the progressive disease or death (Censored data were not included in this study).

Clinical data: the basic clinical data of subjects before TACE were collected. The plasma D-dimer level (normal range 0–252 μg/L) 1 week before TACE (D0), D-dimer level 1 month after TACE (D1) and D-dimer level when the disease begins to progress (D2) were measured. According to the modified Response Evaluation Criteria in Solid Tumor (mRECIST) [4], post-TACE efficacy was classified as follows: complete response (CR), partial response (PR), stable disease (SD), and progressive disease (PD). The patients with an efficacy of CR, PR and SD comprised the disease-controlled group, and those with PD were considered the disease-progressing group (Table 1).

Statistical analysis

The study data were processed using SPSS 25.0 statistical software. The measurement data were expressed as mean ± standard deviation (for data with normal distribution) or median (25th percentile, 75th percentile) (for data with skewed distribution), and compared with the *t* test or rank sum test (for data of skewed distribution). The counting data were compared with the χ^2 test. The correlation between the variables of non-normal distribution was discussed by Spearman correlation analysis, and survival was analyzed with the Kaplan–Meier test and Breslow test. $P < 0.05$ indicated that the difference was statistically significant (Table 2).

Results

General data

In this study, efficacy was evaluated as follows: CR (2 cases), PR (15 cases), SD (27 cases), and PD (36 cases). In the disease-controlled group and disease-progressing group, there were 44 and 36 cases, respectively. Only the prothrombin time (PT) in disease-controlled group was longer than that in disease-progressing group (12.81 ± 1.58 vs. 13.48 ± 1.33, $P < 0.05$), and there were no significant difference between other factors in the two groups (all $P > 0.05$).

Relation between the plasma D-dimer level and the efficacy of TACE

In all 80 patients, D1 was significantly higher than D0 ($P < 0.05$). In the disease-controlled group, the plasma D-dimer level did not change significantly ($P > 0.05$); but in the disease-progressing group, D1 was significantly higher than D0 ($P < 0.05$). In addition, D1 in disease-progressing group was significantly higher than D1 in disease-controlled group ($P < 0.05$).

Relation between plasma D-dimer level and PFS

In all patients, D0 level was not related to PFS significantly ($P = 0.509$) (Fig. 1), but D1 or D2 level was related to PFS with a high level of statistical significance ($P = 0.001$, 0.021, respectively) (Figs. 2, 3). In the patients with a negative D1 or negative D2, PFS was longer than that in those with a positive level.

Then, we divided patients into three groups according to D0 and D1 levels: patients with positive D0 and

Table 1 Relation of basic data between the disease-controlled group and disease-progressing group

Basic data	Disease-controlled group	Disease-progressing group	*P* value
Age (years)	61.93 ± 8.81	60.34 ± 8.70	0.423
WBC (10^9/L)	5.68 ± 2.16	5.48 ± 2.63	0.714
RBC (10^{12}/L)	5.92 ± 9.79	4.05 ± 0.68	0.261
PLT (10^9/L)	143.66 ± 75.51	124.09 ± 65.83	0.230
PT (s)	12.81 ± 1.58	13.48 ± 1.33	0.046
Liver function (Child–Pugh) (*n*)			0.088
Stage A	40	26	
Stage B	5	9	
Sex (*n*)			0.946
Male	35	27	
Female	10	8	
Ascites (*n*)			0.158
No	40	27	
Yes	5	8	
Liver cirrhosis (*n*)			0.677
No	11	10	
Yes	34	25	
Portal vein tumor thrombus (*n*)			0.434
No	32	22	
Yes	13	13	
Tumor size (cm)			0.440
Maximum diameter < 5 cm	16	8	
5 cm ≤ Maximum diameter < 10 cm	18	18	
Maximum diameter ≥ 10 cm	11	9	
Tumor stage (BCLC) (*n*)			0.129
Class A	13	7	
Class B	20	11	
Class C	12	17	

Table 2 Plasma D-dimer levels (μg/L) of 80 PLC patients before and after TACE

	n	D0	D1	*P* value
All patients	80	204.00 (99.00, 320.00)	262.00 (179.50, 486.25)	0.000
Disease-controlled group	45	165 (93.50, 298.50)	229.00 (103.00, 323.50)	0.382
Disease-progressing group	35	221.00 (122.00, 429.00)[1]	436.50 (252.00, 713.00)[2]	0.000

The plasma D-dimer levels were expressed as median (25th percentile, 75th percentile) because of the skewed distribution. Compared with the disease-controlled group: [1]$P = 0.134$, [2]$P = 0.000$

negative D1 as well as patients with positive D0 and much lower D1 were included into group 1 (D-dimer decreased); patients with negative D0 and negative D1 as well as patients with D1 much the same as D0 were included into group 2 (D-dimer changed unsignificantly); patients with negative D0 and positive D1 as well as patients with positive D0 and much higher D1 were included into group 3 (D-dimer increased). If D1 is 30 μg/L at least lower or higher than D0, we define the D1 as "much lower D1" or "much higher D1", and if the change amount is less than 30 μg/L we define it as "much the same as D0".

Patients in group 1 possessed longer PFS than patients in group 2, but not significantly ($P = 0.077$); However, patients in group 1 or group 2 possessed longer PFS than patients in group 3 significantly ($P = 0.005$, 0.002, respectively) (Fig. 4).

Discussion

In the nineteenth century, the relation between malignant tumors and hypercoagulation was first reported by Armand Trousseau. Subsequently, all clinical manifestations caused

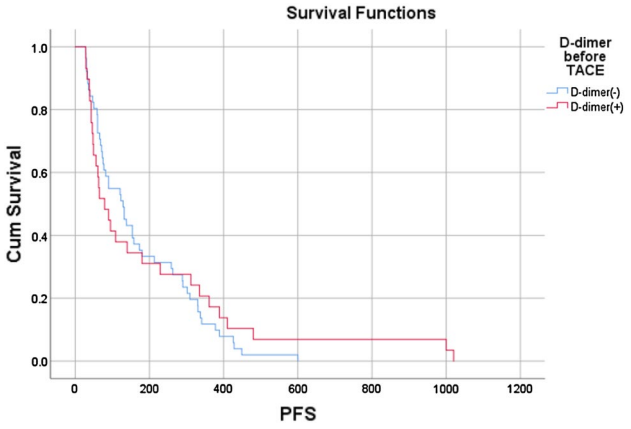

Fig. 1 Relation between D0 and PFS

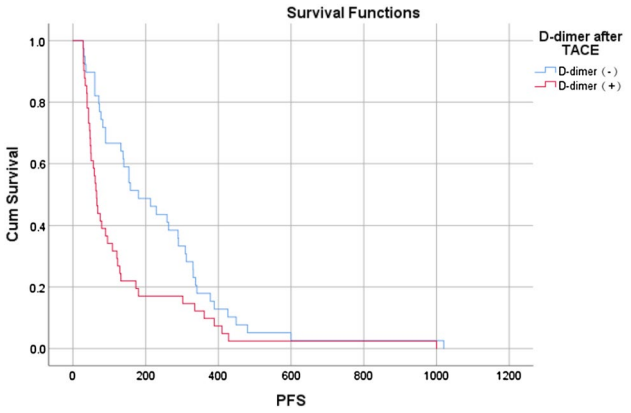

Fig. 2 Relation between D1 and PFS

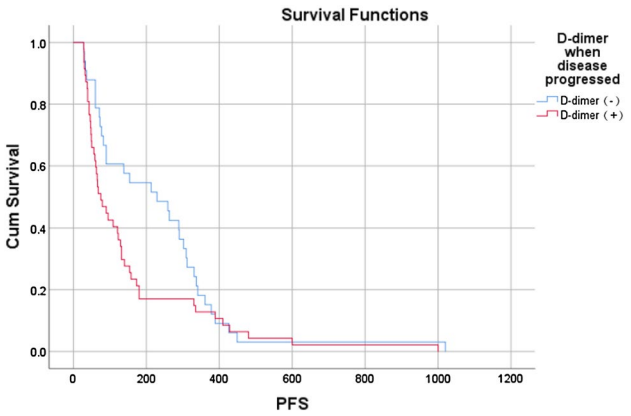

Fig. 3 Relation between D2 and PFS

by blood coagulation and fibrinolysis dysfunction during the pathogenesis of cancer are generally referred to as Trousseau syndrome [5]. In malignant tumor patients, blood is in a hypercoagulative state, and the possible mechanism is

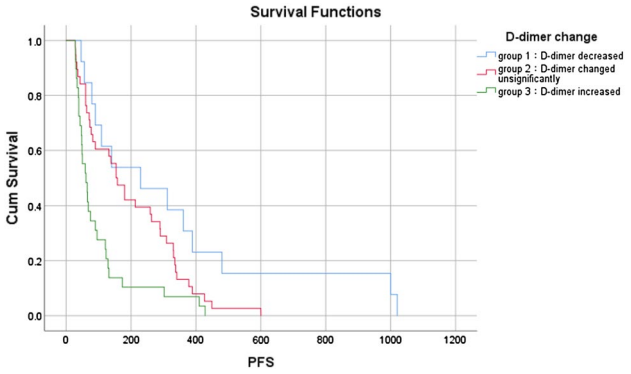

Fig. 4 Relation between PFS and the change of D0 and D1

as follows: tumor cells can directly release some cytokines (e.g., tissue factors, cancer procoagulants, IL-1 and TNF) and can activate the blood coagulation system, resulting in the activation of thrombin, increased production of fibrin, and the hypercoagulative state; meanwhile, they can activate platelets, leukocytes and macrophages, and promote thrombosis [6]. In liver cancer patients, blood coagulation function changes in a more complex way, and there is unbalanced synthesis of the above factors and blood coagulation dysfunction to different degrees, because most factors of coagulation, anticoagulation and fibrinolysis are synthesized in the liver. In liver cancer patients, TACE influences the state of blood coagulation. Chemotherapeutics can damage tumor cells and attenuate their effect of overactivating the blood coagulation system; in addition, they can release inflammatory factors and damage vascular endothelial cells, so as to increase the release of coagulation factors and reduce the activity of anticoagulants, and thus finally reverse the hypercoagulative state [7]. Moreover, due to some factors (e.g., operational procedures of TACE, embolic agents and contrast media), vascular endothelial cells and hepatic cells are damaged, influencing blood coagulation function. Therefore, blood in PLC patients is in a hypercoagulative state because of such multiple factors as the tumor itself and TACE. Interestingly, the hypercoagulative state reacts on the tumor meanwhile, so as to facilitate tumor progression, promote the proliferation, invasion and metastasis of tumor cells, and enhance the neovascularization of the tumor [8, 9].

The hypercoagulative state can induce secondary fibrinolytic hyperfunction and increase D-dimer level in the plasma. Therefore, the plasma D-dimer level is closely associated with tumors. As reported in numerous recent studies in the literature, the plasma D-dimer level has a certain correlation with the stage, clinical progression and prognosis of malignant tumors (e.g., lung cancer, gastric cancer, ovarian cancer and colon cancer) [10–15]. Furthermore, D-dimer is even regarded by some authors as a biomarker for chemotherapeutic effect on malignant tumors (e.g., advanced lung

cancer, gastric cancer, colorectal cancer, ovarian cancer and esophageal cancer) [16]. However, up to now, there are very few studies on the plasma D-dimer level and PLC, which mainly focus on the pre-TACE assessment; and there are rare studies that evaluate the efficacy and prognosis of TACE.

In this study, the relation of plasma D-dimer level with the efficacy and prognosis of TACE in PLC patients were assessed. As shown by statistical analysis, D1 is associated with the effacacy of TACE; plasma D-dimer after TACE in disease-progressing group increased compared to D0 and the D1 level is higher than D1 in disease-controlled group. This indicates that positive post-TACE D-dimer is unfavorable for the efficacy of TACE and the prognosis, which consists with the result of other studies [17, 18]. What is more, this study showed that PFS in patients with a positive D1 or D2 was shorter than the PFS in patients who possessed a negative D1 or D2. Besides, the relation between PFS and the change of D-dimer after TACE was analyzed. In the patients with a D-dimer increase after TACE (group 3), PFS was shorter than that in those with a D-dimer decrease (Group 1) and that in those with a relatively stable D-dimer level before and after TACE (Group 2) ($P < 0.05$); and survival in Group 1 was slightly but not significantly longer than that in Group 2 ($P > 0.05$). So to speak, in patients with a negative D1 level or a decreased D1 compared to D0, the prognosis was better, because a negative plasma D-dimer level indicates a milder illness and the decreased D-dimer means an excellent response to TACE. On the contrast, a positive D1 or increased D1 indicates poor efficacy of TACE and progression of disease. Therefore, a higher D1 or the D-dimer increase after TACE is unfavorable for the prognosis of malignant tumors [19, 20].

Due to the convenient and inexpensive measurement, the plasma D-dimer level can provide the certain reference information for the prognosis of tumor patients, and can be used to assess the efficacy of TACE. However, this study still has some shortcomings: (1) by excluding the patients with incomplete clinical data before TACE, incomplete images after TACE and incomplete embolization, this retrospective study had a obvious selection bias; (2) although PFS was determined according to the results of CT imaging, there was the possible disease progression before they underwent the examination which we just could not learn about; (3) there was no difference in liver/coagulation function between the two groups, but the reserve function of the liver and the physiological state of blood varied with individuals, which could not be ignored and thus might have influenced the results.

To sum up, in the malignant tumor patients, blood is at a hypercoagulative state, which is an important condition for promoting the growth and metastasis of tumors. As an important sign for the hypercoagulative and hyperfibrinolytic state in PLC patients, the plasma D-dimer level plays a certain role in assessing/predicting TACE efficacy and prognosis. Positive post-TACE D-dimer or increased D-dimer is an unfavorable factor for PLC patients.

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Compliance with ethical standards

Conflict of interest The authors have no conflict of interest to declare.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

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