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Postintervention Interleukin-6 (IL-6) Level, Rather than the Pretreatment or Dynamic Changes of IL-6, as an Early Practical Marker of Tumor Response in Hepatocellular Carcinoma Treated with Transarterial Chemoembolization

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Disclosures of potential conflicts of interest may be found at the end of this article.

Key Words. Hepatocellular carcinoma • Interleukin-6 • Transcatheter arterial chemoembolization • Tumor response

Abstract

Background. The aim of this study was to determine the potential prognostic roles of the perioperative interleukin-6 (IL-6) level and its dynamic changes in patients with hepatocellular carcinoma (HCC) undergoing transarterial chemoembolization (TACE).

Materials and Methods. Sixty patients with hepatitis B virus-associated HCC receiving TACE were enrolled in the study. Serum IL-6 levels were determined at baseline and 1 day after TACE by immunoassay. Response to TACE was evaluated after a 4–6-week interval. Factors associated with tumor response were analyzed by univariate and multivariate analysis in a Cox regression model. Receiver operating characteristic (ROC) curve analysis was performed to assess the predictive performance of the included variables on tumor response in patients with HCC undergoing TACE.

Results. The serum IL-6 level was significantly elevated 1 day after TACE. Patients in the low postintervention IL-6 level group had a high probability of achieving an objective response (OR) (66.7% vs. 18.8%, p = .021). Post-TACE IL-6 level (≤12.7 pg/mL) and post-/pre-TACE neutrophils ratio (>2.47) were independently correlated with OR after TACE. ROC curve analysis showed that a combined index based on those two factors exhibited optimal predictive power of tumor response among all the included variables (area under the curve = 0.740, 95% confidence interval: 0.601–0.879). Additionally, high post-TACE plasma IL-6 level was associated with maximum tumor size, vascular invasion, post-TACE aspartate aminotransferase, and Barcelona Clinic Liver Cancer stage.

Conclusion. Our study suggests that the post-treatment serum IL-6 level, rather than pretreatment or dynamic changes of IL-6, serves as a powerful predictor for tumor response. These findings provide evidence to help discriminate between patients who will particularly benefit from TACE and those who require more personalized therapeutic regimens and rigorous surveillance. ***The Oncologist*** 2019;24:e1489–e1495

Implications for Practice: Transarterial chemoembolization (TACE) is a major therapeutic regimen for advanced hepatocellular carcinoma. Thus, identification of early practical markers of tumor response to TACE is of high importance. This study indicated that the post-treatment serum interleukin-6 (IL-6) level, rather than the pretreatment or dynamic changes of IL-6, serves as a powerful predictor for tumor response. A combined index based on the post-TACE IL-6 level and post-/pre-TACE neutrophils ratio is optimal for predetermining an objective response after TACE, which may be helpful in guiding individualized treatments and surveillance.

Introduction

Transarterial chemoembolization (TACE) is an approved first-line therapy for advanced hepatocellular carcinoma (HCC) [1]. However, the response rates to TACE are heterogeneous, and it is not fully understood which patients will most likely benefit from TACE in terms of tumor response [1, 2]. Therefore, identification of new practical markers is important

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Table 1. Baseline characteristics of the hepatocellular carcinoma cohort

Characteristics	HCC (*n* = 60)
Sex, male/female	55/5
Age, mean ± SD, years	53.6 ± 10.4
Liver cirrhosis, absence/presence	54/6
Maximum tumor size, mean ± SD, cm	8.1 ± 3.8
Vascular invasion, absence/presence	24/36
ALT, median (range), U/L	37.0 (9.0–247.0)
AST, median (range), U/L	56.0 (17.0–412.0)
ALB, median (range), g/dL	35.4 (23.0–46.6)
TBiL, median (range), μmol/L	16.0 (6.0–188.4)
AFP, median (range), μg/mL	267.0 (1.6–1,506,466.0)
Child-Pugh classification, A/B	53/7
BCLC stage, A/B/C	2/15/43
ECOG PS, 0–1/2	54/6

Abbreviations: AFP, alpha-fetoprotein; ALB, albumin; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BCLC, Barcelona Clinic Liver Cancer; ECOG PS, Eastern Cooperative Oncology Group Performance Status; HCC, hepatocellular carcinoma; TBiL, total bilirubin.

to discriminate between patients who will benefit from TACE therapy and those requiring more individualized treatments and rigorous monitoring. Toward this end, great efforts have been made by a growing number of investigators in recent years, especially with regard to identification of serum markers, which can be more easily and noninvasively measured at different time points compared with tumor biopsy or imaging-based metrics. Nevertheless, few of these markers identified to date are satisfactory in terms of strong predictive power of a therapeutic response.

Interleukin-6 (IL-6) is a pivotal cytokine involved in many complex biological processes, including immunity, inflammation, metabolism, reproduction, hematopoiesis, angiogenesis, neural development, and bone remodeling [3]. In the tumor microenvironment, multiple cell types can produce IL-6, including tumor-infiltrating immune cells, fibroblast stromal cells, and the tumor cells themselves, which are induced by various factors, such as nuclear factor-kappa B, IL-β, prostaglandin E2, hypoxia, lack of signal transducer and activator of transcription 3-inhibitors, and microRNAs [4–9]. Previous studies have shown that baseline IL-6 level is a promising tumor marker for HCC [10]. High pretreatment plasma IL-6 levels were associated with a poor prognosis of patients with advanced HCC [11]. In patients with hepatitis B virus (HBV)-related early HCC who underwent hepatic resection or radiofrequency ablation with curative intention, a low serum IL-6 level was shown to be an independent prognostic factor for disease-free survival [12]. Moreover, elevated serum levels of IL-6 were significantly associated with an increased risk of HBV-associated HCC recurrence, suggesting that the preoperative IL-6 serum level is a potential biomarker for early prediction of HBV-associated HCC recurrence [13]. Several studies have also verified the prognostic role of IL-6 in patients who underwent TACE. For example, early-phase increases in IL-6 after TACE may have hepatoprotective effects and reflect acute-phase responses, and acute elevations in IL-6 are associated with post-treatment hepatitis [14].

Table 2. Univariate Cox regression analyses for tumor response in hepatocellular carcinoma

	Univariate analysis	
Characteristics	HR (95% CI)	*p* value
Sex (male vs. female)	1.778 (0.270–11.709)	.550
Age (>50 vs. ≤50 years)	1.728 (0.517–5.774)	.374
Maximum tumor size (>5 vs. ≤5 cm)	0.727 (0.206–2.565)	.620
Vascular invasion (presence vs. absence)	0.476 (0.152–1.489)	.202
Liver cirrhosis (presence vs. absence)	0.350 (0.063–1.939)	.229
Ascites (presence vs. absence)	1.015 (0.270–3.821)	.982
Baseline ALB, g/dL	0.882 (0.782–0.996)	**.043**
Baseline TBiL, μmol/L	1.084 (0.992–1.184)	.075
Baseline AFP (>400 vs. ≤400 μg/L)	0.880 (0.290–2.669)	.821
Pre-TACE serum IL-6 level (>8.1 vs. ≤8.1 pg/mL)	0.271 (0.084–0.876)	**.029**
Post-TACE serum IL-6 level (>12.7 vs. ≤12.7 pg/mL)	0.114 (0.021–0.614)	**.011**
Post-/pre-TACE IL-6 ratio (>1 vs. ≤1)	1.604 (0.387–6.655)	.515
Post-/pre-TACE ALT ratio (>2.0 vs. ≤2.0)	1.421 (0.461–4.384)	.541
Post-/pre-TACE AST ratio (>3.3 vs. ≤ 3.3)	1.179 (0.383–3.629)	.775
Post-/pre-TACE neutrophils ratio (>2.5 vs. ≤2.5)	5.538 (1.619–18.941)	**.006**

Bolded *p* values are statistically significant.
Abbreviations: AFP, alpha-fetoprotein; ALB, albumin; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CI, confidence interval; HR, hazard ratio; IL-6, interleukin-6; TACE, transarterial chemoembolization.

Furthermore, IL-6 serum levels could predict tumor response and overall survival (OS) after TACE for primary and secondary hepatic malignancies [15]. However, almost all of these studies focused on pretreatment levels, while ignoring the potential predictive value of the post-treatment circulating IL-6 level and its dynamic changes in the context of TACE treatment, which we consider will be more reflective of a biological reaction with inflammation and the immune system.

Therefore, we conducted a prospective observational study in a cohort of patients with HBV-associated HCC undergoing TACE, so as to shed light on the discriminating power of pre-and post-TACE IL-6 serum level and its dynamic changes in predicting tumor response.

Materials and Methods

Patients and Study Design

A total of 60 consecutive patients with HBV-associated HCC who underwent TACE between October 2017 and August 2018 at the First Affiliated Hospital of Sun Yat-sen University were enrolled in the final analysis (supplemental online Fig. 1). HCC was diagnosed according to the guideline of the European Association for the Study of the Liver and the

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Table 3. Multivariate Cox regression analyses for tumor response in hepatocellular carcinoma

Variables	Multivariate analysis		
	HR (95% CI)	*p* value	β
Pre-TACE serum IL-6 level (>8.1 vs. ≤8.1 pg/mL)	1.186 (0.134–10.502)	.878	0.171
Post-TACE serum IL-6 level (>12.7 vs. ≤12.7 pg/mL)	0.067 (0.005–0.872)	**.039**	−2.703
Baseline ALB, g/dL	0.868 (0.682–1.104)	.248	−1.420
Post-/pre-TACE neutrophils ratio (>2.47 vs. ≤2.47)	24.482 (1.722–348.092)	**.018**	3.198
Baseline AFP (>400 vs. ≤400 μg/L)	1.929 (0.204–18.191)	.566	0.657

Bolded *p* values are statistically significant.
Abbreviations: AFP, alpha-fetoprotein; ALB, albumin; CI, confidence interval; HR, hazard ratio; IL-6, interleukin-6; TACE, transarterial chemoembolization.

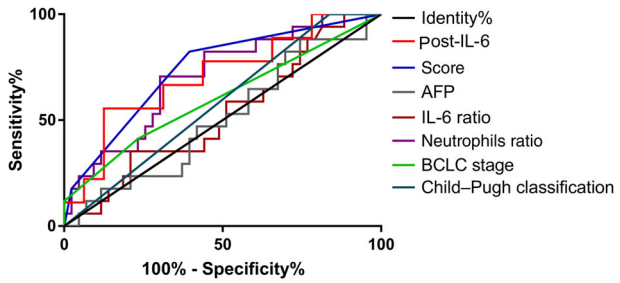

Figure 1. Receiver operating characteristic (ROC) curve analysis for the discrimination between objective response (OR) and non-OR patients: comparison of the ROC curves of baseline AFP, pre- and post-transarterial chemoembolization (TACE) IL-6 level, post-/pre-TACE IL-6 ratio, post-/pre-TACE neutrophils ratio, Child-Pugh classification, BCLC stage, and the new combined index.
Abbreviations: AFP, alpha-fetoprotein; BCLC, Barcelona Clinic Liver Cancer; IL-6, interleukin-6.

Table 4. Discriminant abilities of the variables examined

Variables	AUC	*p* value	HR (95% CI)
Baseline AFP	0.494	.649	0.346–0.666
Post-/pre-TACE IL-6 ratio	0.525	.768	0.366–0.684
Child-Pugh classification	0.581	.329	0.430–0.733
Pre-TACE serum IL-6 level	0.601	.225	0.447–0.755
BCLC stage	0.603	.216	0.435–0.771
Post-/pre-TACE neutrophils ratio	0.706	**.014**	0.564–0.847
Post-TACE serum IL-6 level	0.708	.059	0.513–0.903
Score	0.740	**.004**	0.601–0.879

Bolded *p* values are statistically significant.
Abbreviations: AFP, alpha-fetoprotein; AUC, area under the curve; BCLC, Barcelona Clinic Liver Cancer; CI, confidence interval; HR, hazard ratio; IL-6, interleukin-6; TACE, transarterial chemoembolization.

American Association for the Study of Liver [16]. Patients enrolled were required to meet the following criteria: (a) TACE was the first-line initial therapy; (b) Child-Pugh classification A or B; (c) Eastern Cooperative Oncology Group Performance Status (ECOG PS) of 0–2; (d) no serious infection before transarterial therapy. Vascular invasion was defined as branch portal vein or main portal vein invasion.

This study was approved by the ethics committee of the First Affiliated Hospital of Sun Yat-sen University. Informed consent was obtained from each patient.

Measurement of Serum IL-6 Levels

Serum samples were obtained from the patients at baseline and 1 day after TACE. Concentrations of IL-6 were analyzed by immunoassay using Human IL-6 Elecsys kits (Roche Diagnostics GmbH, Mannheim, Germany), according to the manufacture's instruction, and by automatic biochemical immunoassay system (Roche Cobas 6000's module e601). The sensitivity of the assay was 1.5 pg/mL.

TACE Procedure

All TACE procedures were conducted by our experienced radiologists using techniques previously described [17]. Briefly, the chemotherapeutic emulsion consisting of 10–20 mL lipiodol (Guerbet, Roissy, France) and 20–40 mg epirubicin (Pfizer, Wuxi, China) was slowly injected through a 5-Fr Yashrio catheter or 2.7-Fr micro-catheter (Progreat, Terumo, Tokyo, Japan). Subsequently, to reduce the residual blood flow, Gelfoam (Ailikang Medicine, Hangzhou, China) mixed with contrast medium was injected until there was no longer any tumor staining after repeated angiography. Depending on the features of the tumor, a superselective (subsegmental), selective (segmental), or nonselective (lobar) approach was performed whenever possible.

Evaluation of TACE Response

All patients were followed up with a physical examination; routine blood tests, including alpha-fetoprotein (AFP) measurements; liver and kidney function tests; and contrast-enhanced computed tomography (CT) or magnetic resonance imaging (MRI) scanning 4–6 weeks after TACE. Three experienced radiologists in imaging diagnosis interpreted all follow-up CT or MRI scans. Tumor response was assessed based on radiological evaluation according to the modified RECIST: complete response (CR), partial response (PR), stable disease, and progressive disease. CR and PR were further summarized into objective response (OR) [18].

Statistical Analyses

Statistical analyses were performed with SPSS version 24.0 (SPSS Inc., Chicago, IL) and GraphPad Prism version 7.0 software. The results are reported as means ± SDs. Continuous variables were compared using an independent sample *t* test. Categorical data were compared using the Pearson chi-squared test or Fisher's exact test. Significant cutoff value for IL-6 was determined via the receiver operating characteristic (ROC) curve. ROC curves were generated by plotting sensitivity

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Table 5. Associations between post-TACE plasma IL-6 levels and patients' characteristics

Characteristics	*n* (%)	Post-TACE plasma IL-6 level		*p* value
		Low level (*n* = 9)	High level (*n* = 51)	
Sex				
Male	55 (91.7)	11	44	
Female	5 (8.3)	1	4	1.000
Age, years				
≤50	23 (38.3)	4	19	
>50	37 (61.7)	8	29	.947
Liver cirrhosis				
Absent	6 (10.0)	1	5	
Present	54 (90.0)	11	43	1.000
Ascites				
Absent	46 (76.7)	10	36	
Present	14 (23.3)	2	12	.819
Maximum tumor size, cm				
≤5	15 (25.0)	7	8	
>5	45 (75.0)	5	40	**.009**
Vascular invasion				
Absent	24 (40.0)	9	15	
Present	36 (60.0)	3	33	**.015**
Extrahepatic metastasis				
Absent	42 (70.0)	10	32	
Present	18 (30.0)	2	16	.439
Serum AFP, μg/L				
≤400	28 (46.7)	8	20	
>400	32 (53.3)	4	28	.121
HBV-DNA, IU/mL				
≤100	35 (58.3)	8	27	
>100	25 (41.7)	4	21	.513
Post-TACE ALT, U/L				
≤40	18 (30)	6	12	
>40	42 (70)	6	36	.181
Post-TACE AST, U/L				
≤37	4 (6.7)	3	1	
>37	56 (93.3)	9	47	**.023**
Post-TACE leukocytes, U/L				
≤10	39 (65.0)	9	30	
>10	21 (35.0)	3	18	.636
Post-TACE neutrophils, U/L				
≤6.3	23 (38.3)	6	17	
>6.3	37 (61.7)	6	31	.550
Child-Pugh classification				
A	53 (88.3)	12	41	
B	7 (11.7)	0	7	.366
BCLC stage				
A	2 (3.3)	2	0	
B	15 (25.0)	6	9	
C	43 (71.7)	4	39	**.001**

Bolded *p* values are statistically significant.
Abbreviations: AFP, alpha-fetoprotein; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BCLC, Barcelona Clinic Liver Cancer; HBV, hepatitis B virus; IL-6, interleukin-6; TACE, transarterial chemoembolization.

against 1-specificity. The optimal cutoff values for ROC curves were established using the Youden index. Factors associated with tumor response were analyzed by univariate and multivariate analysis in the Cox regression model. A *p* value <.05 was considered statistically significant.

Results

Study Population and HCC Characteristics at Baseline

In total, 60 patients with HBV-associated HCC were included in the final analysis. The baseline characteristics of the study population are presented in Table 1. The mean patient age was 53.6 ± 10.4 years, and 91.7% of the patients were men. Most patients (90.0%) had cirrhosis, and 88.3% were determined to be Child-Pugh class A (based on Child-Pugh classification for severity of liver disease). The maximum tumor size of these patients was 8.1 ± 3.8 cm. According to the Barcelona Clinic Liver Cancer (BCLC) classification, 3.3%, 25.0%, and 71.7% of the patients had stage A, B, and C disease, respectively. Ninety percent of the participants had a good ECOG PS of 0–1.

Perioperative IL-6 Levels and Tumor Response to TACE Therapy

We first explored the dynamic changes of serum IL-6 levels in patients undergoing TACE. Compared with preintervention serum concentrations, the IL-6 levels dramatically increased 1 day after TACE (supplemental online Fig. 2).

To investigate the potential predictors of TACE therapy, we divided our cohort into patients with an OR or non-OR after TACE. In univariate logistic regression analysis, baseline albumin concentrations (p = .043), pre-TACE serum IL-6 levels (p = .029), post-TACE IL-6 levels (p = .011) and the post-/pre-TACE neutrophils ratio (p = .006) were found to be significantly associated with OR (Table 2). Subsequently, in the multivariate analysis, only the post-/pre-TACE neutrophils ratio (p = .018) and post-TACE IL-6 levels (p = .039) emerged as independent risk factors for OR (Table 3). To avoid the interference of collinearity factors, scoring systems, such as the Child-Pugh classification and BCLC stage, were excluded from the additional analyses, because such scores are derived from tumor size, vascular invasion, and

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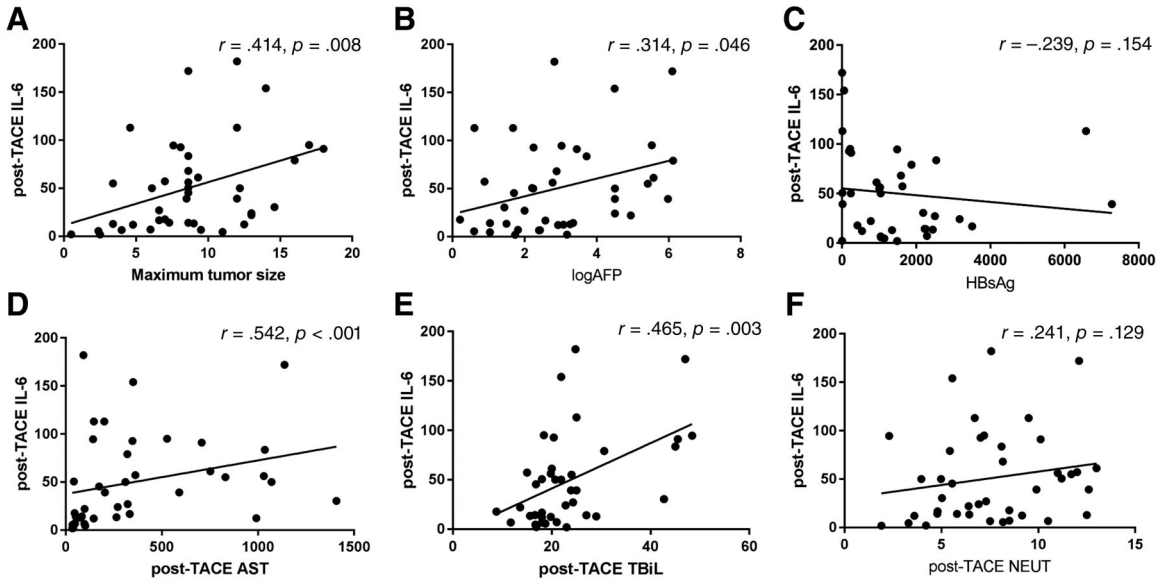

Figure 2. Correlations between post-TACE IL-6 levels and clinical parameters. **(A):** A positive correlation between post-TACE IL-6 levels and maximum tumor size (r = .414, p = .008). **(B):** A positive correlation between post-TACE IL-6 levels and log AFP (r = .314, p = .046). **(C):** Post-TACE serum IL-6 levels are not significantly associated with HBsAg amount (r = −.239, p = .154). **(D):** A positive correlation between post-TACE IL-6 levels and post-TACE AST (r = .542, p < .001). **(E):** A positive correlation between post-TACE IL-6 levels and post-TACE TBiL (r = .465, p = .003). **(F):** Post-TACE serum IL-6 levels are not significantly associated with post-TACE NEUT (r = .241, p = .129).
Abbreviations: AFP, alpha-fetoprotein; AST, aspartate aminotransferase; HBsAg, surface antigen of hepatitis B virus; IL-6, interleukin-6; NEUT, neutrophil; TACE, transarterial chemoembolization; TBiL, total bilirubin.

other variables. As illustrated in supplemental online Fig. 3, patients in the low level of post-TACE IL-6 group had a higher possibility of achieving an OR than the counterparts (66.7% vs. 18.8%, p = .021).

Based on the promising findings on the predictors for OR, a new combined index was established as follows: score = 3.2*(if post-/pre-TACE neutrophils >2.47) − 2.7*(if post-TACE IL-6 level > 12.7 pg/mL). We then performed ROC curves to identify the efficacy of those predictors. The area under the curve (AUC) of the new score was the largest (AUC = 0.740) among all the variables investigated, followed by post-TACE serum IL-6 level (AUC = 0.708). Other involved indicators for comparison include baseline AFP (AUC = 0.506), post/pre-TACE IL-6 ratio (AUC = 0.525), Child-Pugh classification (AUC = 0.581), the pre-TACE serum IL-6 level (AUC = 0.601), BCLC stage (AUC = 0.603), and post/pre-TACE neutrophils (AUC = 0.706; Fig. 1; Table 4).

Associations Between Post-TACE Plasma IL-6 Levels and Patient Characteristics

The association between post-TACE plasma IL-6 levels and clinicopathologic parameters was assessed by the chi-square test for proportion, as shown in Table 5. Low post-TACE plasma IL-6 level was found to correlate with maximum tumor size (p = .009), vascular invasion (p = .015), post-TACE liver aspartate aminotransferase (AST) levels (p = .023), and BCLC stage (p = .001).

To determine correlations between post-TACE plasma IL-6 levels with valuable clinical parameters, we subsequently performed Spearman's correlation analysis. IL-6 levels showed a statistically significant positive correlation with maximum tumor size (r = .414, p = .008), baseline AFP (r = .314, p = .046), post-TACE AST (r = .542, p < .001), and post-TACE total bilirubin (TBiL; r = .465, p = .003; Fig. 2). However, there were no significant correlations between post-TACE plasma IL-6 levels and baseline surface antigen of hepatitis B virus (HBsAg) levels (r = −.239, p = .154; Fig. 2), or post-TACE neutrophils (r = .241, p = .129; Fig. 2). Furthermore, patients with Child-Pugh class B HCC had a higher level of IL-6 than those in class A group (p < .001). Similarly, patients with higher Child-Pugh class HCC had a higher level of IL-6 (p = .001; supplemental online Fig. 4).

Discussion

Accumulated evidence indicates a key role of IL-6 in the process of liver damage and carcinogenesis and its predictive power in HCC. However, in contrast to the existing data demonstrating the predictive role of the pretreatment IL-6 level, our study is the first to investigate the prognostic value of the post-treatment IL-6 level as well as the dynamic changes of perioperative IL-6 levels in patients with HCC undergoing TACE.

We found that IL-6 increased substantially on 1 day after TACE, which is in accordance with a previous study including 41 patients with HCC that underwent TACE [19]. Remarkably, the post-TACE IL-6 level (≤12.7 pg/mL), but not the pretreatment IL-6 level or the alteration in IL-6, appears to be a better predictor of an OR in HCC. The explanation may be that the pretreatment IL-6 level simply reflects the chronic inflammatory response in carcinogenesis, whereas the post-TACE IL 6 level may represent acute immune and inflammatory response after treatment, given the strong necrosis and inflammation induced by chemoembolization. Moreover, persistent activation of the IL-6 signaling pathway is detrimental

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to the liver, which may lead to cell proliferation, protection from apoptosis, chemoresistance, and increased metastatic potential in HCC [20, 21]. Neutrophils, the most common white blood cells in the circulation, are the "first responders" to insult or injury and one of the first immune cells to come into contact with tumor cells [22]. Distinctly increased neutrophils, which was interpreted as the post-/pre-TACE neutrophils ratio (>2.47) in our analysis, was proved to be another significant predictor for OR. In particular, a new score based on the post-TACE IL-6 level and post-/pre-TACE neutrophils ratio was found to exhibit the optimal predictive power among all the variables examined.

As previously reported, high preoperative serum IL-6 levels were associated with large tumor sizes, advanced tumor stages, and recurrence or short survival after locoregional therapy for HCC [13, 23, 24]. In line with those results, we found that high post-TACE plasma IL-6 level was associated with maximum tumor size, vascular invasion, post-TACE AST, and BCLC stage. More specifically, the post-TACE plasma IL-6 level showed a significantly positive correlation with maximum tumor size, baseline AFP, post-TACE AST, and post-TACE TBiL. Patients with higher Child-Pugh class or BCLC stage were prone to having higher levels of post-TACE IL-6. It has been reported that preoperative serum IL-6 level has some association with the HBsAg amount in patients with HCC after curative resection [13]. Interestingly, there is no significant correlation between post-TACE plasma IL-6 levels and baseline HBsAg in our study. This discrepancy may be due to the difference in IL-6 detection time point and/or the varied treatments that the patients underwent between studies.

The present study has several limitations that should be mentioned. First, this study was conducted in a single center with a small sample size, and participants were treated with heterogeneous therapeutic strategies. Second, we detected only IL-6 circulating levels, without determining its corresponding expression in HCC tissues. Thus, it was difficult to interpret the precise pathophysiologic roles. In addition, postembolization fever is the most significant adverse effect after TACE and relevant to tumor response [25], but the relationship between the post-TACE IL-6 level and post-embolization fever is missed in our study. Finally, the follow-up period was limited, such that we could not evaluate OS in the present analysis. Our future work is expected to provide detailed information regarding the role of IL-6 levels in OS among patients with HCC treated with TACE.

Conclusion

Despite these limitations, collectively, these findings suggest that the post-TACE serum IL-6 level, but not the pretreatment level or its dynamic changes, serves as a potential candidate marker for predicting OR in TACE-treated patients with HBV-associated HCC. Remarkably, the diagnostic value of the new test significantly increased when combined with the post-/pre-TACE neutrophils ratio. A multicenter study incorporating a larger number of patients and with a prolonged observation period is required to confirm our findings. Moreover, further in-depth investigation is required to understand the exact biological role of this cytokine in patients with HCC undergoing TACE.

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Final approval of manuscript: Yanqin Wu, Wenzhe Fan, Miao Xue, Bihui Zhong, Shenghong Zhang, Yu Wang, Wang Yao, Yue Zhao, Jiaping Li

Disclosures

The authors indicated no financial relationships.

References

1. Sacco R, Tapete G, Simonetti N et al. Transarterial chemoembolization for the treatment of hepatocellular carcinoma: A review. J Hepatocell Carcinoma 2017;4:105–110.

2. Finn RS, Zhu AX, Farah W et al. Therapies for advanced stage hepatocellular carcinoma with macrovascular invasion or metastatic disease: A systematic review and meta-analysis. Hepatology 2018;67:422–435.

3. Garbers C, Heink S, Korn T et al. Interleukin-6: Designing specific therapeutics for a complex cytokine. Nat Rev Drug Discov 2018;17:395–412.

4. Johnson DE, O'Keefe RA, Grandis JR. Targeting the IL-6/JAK/STAT3 signalling axis in cancer. Nat Rev Clin Oncol 2018;15:234–248.

5. Rossi JF, Lu ZY, Jourdan M et al. Interleukin-6 as a therapeutic target. Clin Cancer Res 2015;21:1248–1257.

6. Guo Y, Xu F, Lu T et al. Interleukin-6 signaling pathway in targeted therapy for cancer. Cancer Treat Rev 2012;38:904–910.

7. Huynh PT, Beswick EJ, Coronado YA et al. CD90(+) stromal cells are the major source of IL-6, which supports cancer stem-like cells and inflammation in colorectal cancer. Int J Cancer 2016;138:1971–1981.

8. Lesina M, Wormann SM, Neuhofer P et al. Interleukin-6 in inflammatory and malignant diseases of the pancreas. Semin Immunol 2014;26:80–87.

9. Pop VV, Seicean A, Lupan I et al. IL-6 roles - Molecular pathway and clinical implication in pancreatic cancer - A systemic review. Immunol Lett 2017;181:45–50.

10. Porta C, De Amici M, Quaglini S et al. Circulating interleukin-6 as a tumor marker for hepatocellular carcinoma. Ann Oncol 2008;19:353–358.

11. Shao YY, Lin H, Li YS et al. High plasma interleukin-6 levels associated with poor prognosis of patients with advanced hepatocellular carcinoma. Jpn J Clin Oncol 2017;47:949–953.

12. Cho HJ, Kim SS, Ahn SJ et al. Low serum interleukin-6 levels as a predictive marker of recurrence in patients with hepatitis B virus related hepatocellular carcinoma who underwent curative treatment. Cytokine 2015;73:245–252.

13. Sheng T, Wang B, Wang SY et al. The relationship between serum interleukin-6 and the recurrence of hepatitis B virus related hepatocellular carcinoma after curative resection. Medicine (Baltimore) 2015;94:e941.

14. Kim MJ, Jang JW, Oh BS et al. Change in inflammatory cytokine profiles after transarterial chemotherapy in patients with hepatocellular carcinoma. Cytokine 2013;64:516–522.

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15. Loosen SH, Schulze-Hagen M, Leyh C et al. IL-6 and IL-8 serum levels predict tumor response and overall survival after TACE for primary and secondary hepatic malignancies. Int J Mol Sci 2018;19.

16. Bruix J, Sherman M. Management of hepatocellular carcinoma. Hepatology 2005;42:1208–1236.

17. Zhang Y, Huang G, Wang Y et al. Is salvage liver resection necessary for initially unresectable hepatocellular carcinoma patients downstaged by transarterial chemoembolization? Ten years of experience. ***The Oncologist*** 2016;21:1442–1449.

18. Lencioni R, Llovet JM. Modified RECIST (mRECIST) assessment for hepatocellular carcinoma. Semin Liver Dis 2010;30:52–60.

19. Chao Y, Wu CY, Kuo CY et al. Cytokines are associated with postembolization fever and survival in hepatocellular carcinoma patients receiving transcatheter arterial chemoembolization. Hepatol Int 2013;7:883–892.

20. Schmidt-Arras D, Rose-John S. IL-6 pathway in the liver: From physiopathology to therapy. J Hepatol 2016;64:1403–1415.

21. Johnson C, Han Y, Hughart N et al. Interleukin-6 and its receptor, key players in hepatobiliary inflammation and cancer. Transl Gastrointest Cancer 2012;1:58–70.

22. Margetts J, Ogle LF, Chan SL et al. Neutrophils: Driving progression and poor prognosis in hepatocellular carcinoma? Br J Cancer 2018;118:248–257.

23. Jang JW, Oh BS, Kwon JH et al. Serum interleukin-6 and C-reactive protein as a prognostic indicator in hepatocellular carcinoma. Cytokine 2012;60:686–693.

24. Pang XH, Zhang JP, Zhang YJ et al. Preoperative levels of serum interleukin-6 in patients with hepatocellular carcinoma. Hepatogastroenterology 2011;58:1687–1693.

25. Blackburn H, West S. Management of postembolization syndrome following hepatic transarterial chemoembolization for primary or metastatic liver cancer. Cancer Nurs 2016;39:E1–E18.

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