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ORIGINAL ARTICLE

Role of serum lactate dehydrogenase levels in evaluating efficacy of interventional therapy for hepatocellular carcinoma

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Abstract

Objective The aim of the study was to investigate the role of serum lactate dehydrogenase (LDH) levels in evaluating the efficacy of transcatheter arterial chemoembolization (TACE) for primary liver cancer.

Methods A total of 52 patients with liver cancer admitted in our hospital (Huangzhou District People's Hospital, Huanggang, China) from June 2015 to December 2017 were selected and divided into control group (LDH of ≤ 450 U/L, n = 26) and observation group (LDH of > 450 U/L, n = 26), based on the pretreatment level of LDH. Based on the changes in serum LDH levels before and after treatment, patients were classified into two groups: LDH increased group (22 cases) and LDH decreased group (30 cases). The relationship between LDH levels and efficacy of TACE treatment was analyzed in the four groups retrospectively.

Results No significant difference was seen in the clinical characteristics (gender, median age, performance status Eastern Cooperative Oncology Group, and staging system) between the control and observation groups. The efficacy rate in the control group was 57.7%, whereas that in the observation group was 42.3% (P > 0.05). The 1-year survival rate in the observation group was 53.8% and that in the control group was 84.6% (P < 0.05).

Conclusion Serum LDH levels may be of clinical value in evaluating the efficacy of TACE in patients with hepatocellular carcinoma.

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Key words: primary hepatocellular carcinoma (HCC); lactate dehydrogenase (LDH); interventional therapy; prognosis

Primary hepatocellular carcinoma (HCC) is one of the most common malignant tumors in the liver, and its incidence increases with age. HCC has become the fifth leading cause of malignant tumors worldwide, and is the leading cause of cancer-related deaths after lung and gastric cancers [1–2]. The 5-year survival rate following surgical resection and transplantation ranges from 60%-70%. Therefore, surgical treatment is the first choice in patients with HCC indications [3].

However, most patients are diagnosed with intermediate or late HCC at the time of treatment and cannot be treated with radical therapy. Therefore, these patients need to consider palliative treatment. Common palliative treatments include arterial chemoembolization (TACE), radiotherapy, radiofrequency ablation, targeted therapy, chemotherapy, and traditional Chinese medicine [4–5]. In recent years, TACE has become one of the common treatment methods, but its clinical effect is still not satisfactory, and only some patients experience positive effects. At present, studies on the molecular mechanisms underlying the poor efficacy of TACE are ongoing.

Studies have shown that the adaptive regulation of hypoxia in the tumor tissue may be a key factor for poor efficacy [6]. Hypoxia can induce neovascularization and lead to therapeutic tolerance in cancer cells. In addition, evidence that hypoxia may promote the development of cancer is also increasing. The energy metabolism of cancer cells is significantly different from that of the normal tissues. Cancer cells maintain high aerobic glycolysis rates and produce high levels of lactic acid and pyruvate, a phenomenon known as the Warburg effect [7]. Lactate dehydrogenase (LDH) is a glycolytic enzyme

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consisting of four polypeptide chains. Each chain is encoded by different genes (M and H) that exist in various human tissues and tumors. LDH is the key enzyme for converting pyruvic acid into lactic acid under anaerobic conditions. Five isoforms of LDH have been identified in five different combinations of peptide subunits. In animal experiments, upregulation of LDH can ensure effective glycolytic metabolism in hypoxic tumor cells and reduce the dependence of the tumor cells on oxygen and lead to tumor progression [8–9]. In patients with HCC receiving TACE treatment, the serum LDH level also fluctuated to varying degrees, suggesting that LDH might be related to the efficacy of TACE. Therefore, this study aimed to evaluate the efficacy of LDH measurements in patients with HCC treated by TACE.

Materials and methods

Research object

A total of 52 patients receiving TACE therapy (iodide oil or drug elution microspheres) and admitted in our hospital (Huangzhou District People's Hospital, Huanggang, China) from June 2015 to December 2017 were retrospectively analyzed. The cohort consisted of 12 female and 40 male patients, with an average age of 43 years. All patients were diagnosed with primary liver cancer, and the diagnostic criteria were "Diagnosis and Treatment of Primary Liver Cancer" (2017 Edition) [10]. Patients were diagnosed through liver imaging, alpha fetoprotein markers, and clinical history; among them, 29 patients were diagnosed through liver biopsy, and those with metastatic tumors and severe complications were excluded. The pretreatment assessment was performed based on the Eastern Cooperative Oncology Group physical status, and the Child-Pugh and BCLC staging system were used to identify the stages [10]. All patients were classified as BCLB B or C. Based on the serum LDH levels before TACE, all patients were divided into the observation group (LDH of > 450 U/L) and control group (LDH of ≤ 450 U/L). Based on the changes of serum LDH level after TACE treatment, all patients were divided into two groups: LDH increased group and LDH decreased group. No significant difference in age, sex, and liver function was observed between the two groups at baseline ($P > 0.05$).

Therapeutic method

The Seldinger method was used to place the 4-Fr catheter into the proper hepatic artery or its branches through the femoral artery. Digital angiography of the artery was performed to assess the anatomical structure of the hepatic artery, in order to determine the blood supply to the liver tumor and the size and number of tumors. A microcatheter was inserted into the blood supply artery, and patients were injected with different doses of doxorubicin, tegafur, and iodide suspension based on the patient's condition. Then, the gelatin sponge particles were injected into the arterial embolism until the tumor had no contrast. The amount of contrast medium and lipiodol in the suspension was adjusted according to the size of the tumor. Routine liver protection examination was performed before and after treatment. If chronic hepatitis B existed, antiviral therapy was added.

Determination of serum LDH level

Fasting venous blood was collected and serum LDH levels were recorded before (within 1 month) and after treatment (after 1 month). According to the method of International Federation of Clinical Chemistry and Laboratory Medicine, the serum LDH level was determined using the Backman DXC800 analyzer. Patients were divided into two groups according to the LDH serum concentration recorded before TACE: the control (LDH of ≤ 450 U/L) and observation group (LDH of > 450 U/L). The cut-off value of the LDH serum level was set to 450 U/L based on the upper limit of normal LDH values seen in blood samples at our hospital. Patients were classified according to the type of change (increase or decrease) in serum LDH level before and after treatment. The ethics committee of our hospital approved the analysis. The patients also agreed to the anonymous storage of their clinical information in the hospital database and its use for research.

Follow-up and evaluation criteria

Patients who received TACE treatment were followed up for 24 months. All patients received no less than 1 images of liver function test, liver MRI or CT after TACE to evaluate the efficacy, followed by telephone follow-up. The radiologist evaluated the film, and a senior professional doctor assessed the quality of treatment.

The curative effect of the modified solid tumor (mRECIST) is considered the standard of treatment efficacy. It is divided into complete remission (CR), partial remission (PR), stable state (SD), and disease progression (PD). In CR, the development of all target lesions disappeared during the arterial phase; in PR, the diameter of the target lesion is reduced to ≥ 30% during the enhancement phase of the arterial phase; in SD, tumor reduction does not satisfy PR or increase PD; and in PD, the total diameter of the target lesion increases by ≥ 20% when new lesions occur or when the arterial phase is enhanced. The overall effective rate (ORR) was defined as the ratio between the number of patients having CR and PR in different groups and the number of patients enrolled. The disease control rate (DCR) was defined as the ratio between the number of patients having CR, PR, and SD in different groups and the number of patients

enrolled.

Statistics

SPSS 17.0 analysis software (IBM, Chicago, IL, USA) was used to analyze the data. All data were expressed as mean ± standard deviation (mean ± SD) or median (range). Chi square test was used for statistical analysis of enumeration data, and the *t*-test was used for statistical analysis of measurement data. When a P value of < 0.05 was obtained, the difference between the two groups was considered to be statistically significant.

Results

General situation

All 52 patients included in the analysis were followed up. After treatment with TACE, serum LDH levels increased in 22 patients (LDH increased group) and decreased in 30 (LDH decreased group). No significant difference was observed in the baseline data between the two groups (Table 1).

The short-term effects of TACE treatment of patients

According to the LDH level before treatment, the effective rate of treatment in the groups with oberservation and control was 42.3% (n = 11) and 57.7% (n = 15), respectively; however, no statistical difference was observed between the two groups (χ^2 = 1.23, P = 0.27). The rate of disease control in the observation and control groups was 69.2% (n = 18) and 76.9% (n = 20), respectively. The statistical analysis showed that no statistical difference was observed between the two groups (χ^2 = 0.39, P = 0.53; Table 2).

According to the changes of LDH levels after treatment, the effective rate of treatments in LDH increased group was found to be 41% (n = 9), and ORR in the LDH decreased group was 50% (n = 14). Statistical analysis showed that no statistical difference was observed between the two groups (χ^2 = 0.42, P = 0.52). After treatment, the rate of disease control in the LDH increased group was 63.6% (n = 14), and the DCR in the LDH decreased group was 80% (n = 24). The statistical analysis showed that no statistical difference was observed between the two groups (χ^2 = 1.73, P = 0.19; Table 3).

The long-term effects of TACE treatment of patients

According to the pretreatment LDH level, the 1-year survival rate of the observation and control groups was 53.8% (n = 14) and 84.6% (n = 22), respectively. The statistical analysis showed that the two groups had significant statistical differences (χ^2 = 5.78, P = 0.016 < 0.05). The 2-year survival rate of the observation and control groups was 30.8% (n = 8) and 46.2% (n = 12). The statistical analysis showed that the two groups had no statistical difference (χ^2 = 1.3, P = 0.25).

Table 1 Patients' general information (*n*)

Class	Control group (*n* = 26)	Observation group (*n* = 26)
Age (year)	43 ± 6	43 ± 5
Sex (male/female)	19/7	21/5
ALT (U/L)	68.7 ± 7.3	67.4 ± 4.9
ALB (g/L)	39.1 ± 1.2	39.5 ± 1.1
Tbil (mg/dL)	1.1 ± 0.5	0.9 ± 0.6
PT (s)	71 ± 17	70 ± 19
AFP (ng/mL)	162	173
HbsAg (+)	19	21
The number of tumor bodies (≥ 3)	11	13
The tumor size (≥ 5 cm)	23	24
Vascular invasion	12	14

Note: variables are marked by *n*, mean ± standard deviation or median (range). ALT, alanine aminotransminase; ALB, serum albumin; Tbil, total bilirubin; AFP, alpha fetoprotein

Table 2 Short-term efficacy of TACE after treatment in the observation and control groups (*n*)

Group	CR	PR	SD	PD	ORR (%)	DCR (%)
Observation group	3	8	7	8	42.3	69.2
Control group	5	10	5	6	57.7	76.9

Note: CR, complete remission; PR, partial remission; SD; disease stability; PD, disease progression; ORR; treatment efficiency; DCR, disease control rate

Table 3 Short-term efficacy of TACE after treatment in the LDH increased and decreased groups (*n*)

Group	CR	PR	SD	PD	ORR (%)	DCR (%)
Increased group	2	7	5	6	41	63.6
Decreased group	5	9	10	6	50	80.0

Note: CR, complete remission; PR, partial remission; SD; disease stability; PD, disease progression; ORR; treatment efficiency; DCR, disease control rate

Discussion

TACE is one of the commonly used methods for the treatment of HCC. However, after TACE treatment, approximately 30%–50% of patients develop extensive tumor necrosis [11]. Methods for evaluating the curative effect of TACE early, adjusting the treatment in time, and ensuring that patients receive the benefit of treatment have become controversial research topics with respect to the use of TACE treatment for liver cancer.

LDH detection is economical and convenient and can be used as a metabolic marker in patients with cancer. Combined with the patients' imaging results, it can also help determine the tumor activity and disease changes [12]. The change in LDH activity has a suggestive effect on hypoxia and anaerobic glycolysis in the tissues. Hypoxia can activate hypoxia-inducible factor (HIF), whereas HIF can promote the expression of LDH. LDH is widely distributed in the body tissues, and its high activity may suggest tissue damage [13]. Abnormal anaerobic metabolism exists in the tumor tissues and cells. Serum LDH activity and level are often increased due to tissue and cell necrosis. Studies have reported that LDH levels in patients with tumors can reach up to six times the normal level [14–15]. In lymphoma, LDH has become an important factor in determining the efficacy and prognosis. Therefore, the predictive value of LDH should be investigated to determine the efficacy of TACE in hepatocellular carcinoma.

This article reviewed the clinical value of serum LDH measurements in evaluating the efficacy of transcatheter arterial chemoembolization for primary liver cancer. In this study, patients with advanced primary liver cancer, treated by transcatheter arterial chemoembolization, were placed in either the control group (serum LDH of ≤ 450 U/L before TACE) or the observation group (serum LDH of > 450 U/L before TACE). The related clinical data were collected and analyzed, and the short-term curative effect and survival rate between the two groups were compared. The results of this retrospective study showed that compared with the control group (with LDH of ≤ 450 U/L), the treatment efficacy, rate of disease control, and survival rate were lower in the observation group, and the 1-year survival rate was significantly lower than that in the control group. After the treatment with TACE, patients were divided into 2 groups based on the type of change in LDH levels. The efficacy rate and disease control rate of LDH increased group were lower than those of LDH decreased group. These findings are consistent with previously published studies on LDH evaluating the efficacy of TACE in the treatment of HCC.

This article has the following shortcomings. First, because TACE chemoembolic drugs do not establish a standard anticancer regimen, and the content and composition of anticancer drugs used in TACE are different. Second, this was a retrospective study and a certain selection bias may have occurred. Third, although free detection of LDH and other means to ensure that patients detect LDH in the same time, but there are still some differences in sampling and testing time. Despite these shortcomings, the results are reliable.

Based on the results of this analysis, serum LDH level can become a significant prognostic factor in patients with HCC. The best individualized treatment strategy is economic and effective for patients, who are better guided by stratification in the follow-up clinical trials. In the future, large-sample comparative studies are needed to further verify the results of this study.

Conflicts of interest

The authors indicated no potential conflicts of interest.

References

1. Gan L, Liu Z, Sun C. Obesity linking to hepatocellular carcinoma: A global view. Biochim Biophys Acta Rev Cancer, 2018, 1869: 97–102.
2. Alba de Jesús KA, Xu XM. Mechanisms of radioresistance in hepatocellular carcinoma. Oncol Transl Med, 2017, 3: 165–170.
3. Kawaguchi Y, Honda G, Endo I, *et al*. Current technical issues for surgery of primary liver cancer. Liver Cancer, 2016, 6: 51–58.
4. Chen XP, Zhang BH. Combined treatment is the hope to improve prognosis of liver cancer. Oncol Transl Med, 2015, 1: 241–242.
5. Galle PR. Treating hepatobiliary cancers: The oncology way. Dig Dis, 2017, 35: 384–386.
6. Ju C, Colgan SP, Eltzschig HK. Hypoxia-inducible factors as molecular targets for liver diseases. J Mol Med (Berl), 2016, 94: 613–627.
7. Hofmann P. Cancer and exercise: Warburg hypothesis, tumour metabolism and high-intensity anaerobic exercise. Sports (Basel), 2018, Jan 31; 6 (1). pii: E10. doi: 10.3390/sports6010010.
8. Shen J, Chen Z, Zhuang Q, *et al*. Prognostic value of serum lactate dehydrogenase in renal cell carcinoma: A systematic review and meta-analysis. PLoS One, 2016, 11: e0166482.
9. Obulikasimu A, Bawudun D, Ren WX. Transcatheter arterial chemoembolization for the treatment of Barcelona stage B hepatocellular carcinoma: analysis of the prognosis and survival. J Intervent Radiol, 2014, 23: 441–442.
10. Li Z, Zhu JY. An interpretation of diagnosis, management, and treatment of hepatocellular carcinoma (V2017). J Clin Hepatol (Chinese), 2017, 33: 1655–1657.
11. Yim HJ, Suh SJ, Um SH. Current management of hepatocellular carcinoma: an Eastern perspective. World J Gastroenterol, 2015, 21: 3826–3842.
12. Jurisic V, Radenkovic S, Konjevic G. The actual role of LDH as tumor marker, biochemical and clinical aspects. Adv Exp Med Biol, 2015, 867: 115–124.
13. Gallo M, Sapio L, Spina A, *et al*. Lactic dehydrogenase and cancer: an overview. Front Biosci (Landmark Ed), 2015, 20: 1234–1249.
14. Yang Z, Ye P, Xu Q, *et al*. Elevation of serum GGT and LDH levels, together with higher BCLC staging are associated with poor overall survival from hepatocellular carcinoma: a retrospective analysis. Discov Med, 2015, 19: 409–418.
15. Kohles N, Nagel D, Jüngst D, *et al*. Prognostic relevance of oncological serum biomarkers in liver cancer patients undergoing transarterial chemoembolization therapy. Tumour Biol, 2012, 33: 33–40.

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