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ORIGINAL RESEARCH

Predictive value of LDH kinetics in bevacizumab treatment and survival of patients with advanced NSCLC

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Background: The combination of bevacizumab and chemotherapy is still one of the standard treatments for advanced non-small-cell lung cancer (NSCLC) patients in the new era of targeted therapy. Although a high level of baseline lactate dehydrogenase (LDH) was found to predict survival benefit from bevacizumab in patients with metastatic colorectal cancer, the predictive value of serum level of LDH in NSCLC patients treated with bevacizumab has not been investigated yet. Moreover, dynamic evaluation of serum level of LDH changes may be more informative and promising in predicting patients' prognosis. We thus sought to analyze LDH kinetics and evaluate its predictive role in the response and survival of advanced NSCLC patients treated with bevacizumab.

Method: We retrospectively collected and analyzed a total of 161 advanced NSCLC patients who had undergone treatment with bevacizumab. Univariate and multivariate logistic regression analyses of serum level of LDH were used for response analyses, and Cox models for both overall survival (OS) and progression-free survival analyses (PFS). Longitudinal analysis of LDH was performed using a mixed-effect regression model.

Results: On multivariate Cox models, increase of serum level of LDH after 4 cycles with bevacizumab (INC4) treatment was shown to be the independent risk factor for OS (hazard ratio =2.17, 95% CI: 1.21–3.90, P=0.009), and the serum level of LDH after 2 cycles (LDH2) and the increase of LDH after 6 cycles with bevacizumab (INC6) treatment were the predictive factors for PFS (hazard ratio =2.33, 95% CI: 1.38–3.93, P=0.001; hazard ratio =1.96, 95% CI: 1.27–3.03, P=0.002, respectively). Patients with increase of serum level of LDH after 2 cycles of treatment with bevacizumab (INC2) (odds ratio =3.75, 95% CI: 1.83–7.68, P<0.001) were more likely to attain stable disease/progressive disease on multivariate logistic regression analyses, while patients with complete response (CR)/partial response (PR) experienced a reduction of serum level of LDH every 2 cycles (Coef =–0.076, std error =0.017, P<0.001) over time.

Conclusion: Dynamic changes of LDH were superior to baseline LDH in predicting prognosis of NSCLC patients treated with bevacizumab. Serum level of LDH reducing over time was a potential biomarker for patients to achieve good clinical response (CR/PR) to bevacizumab.

Keywords: lactate dehydrogenase, bevacizumab, non-small-cell lung cancer, mixed-effect model, predictive factor

Introduction

Non-small-cell lung cancer (NSCLC) accounts for almost 85% of all newly diagnosed cancers every year.[1] Although the efficacy has been improved by the clinical use of EGFR-TKIs,[2,3] ALK-TKIs,[4] checkpoint inhibitors,[5–7] and other drugs in the new era of targeted therapy, bevacizumab combined with chemotherapy is still the recommended option for nonsquamous NSCLC patients without driver genes.[8–10] Moreover,

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bevacizumab was also combined with other target agents such as erlotinib, alectinib, osimertinib, and pembrolizumab for improving outcomes of NSCLC patients.[11,12] Unfortunately, it remains difficult to identify suitable patients who can obtain benefits from using bevacizumab, and the prognosis of advanced NSCLC patients treated with bevacizumab is still extremely poor, with the median overall survival (OS) ranging from 12.3 to 24.3 months. Thus, sensitive and specific factors for predicting the response and prognosis of NSCLC patients treated with bevacizumab are urgently needed.

It is widely recognized that the growth and proliferation of tumor cells rely on anaerobic respiration, converting glucose to lactate, even under aerobic conditions. Lactate dehydrogenase (LDH) plays a pivotal role in glycolysis by catalyzing the interconversion between pyruvate and lactate, and it is considered to be a poor prognosis marker in several cancers, including NSCLC.[13,14] Interestingly, the enrichment of LDH in tumor tissue has been demonstrated to be significantly associated with angiogenic factors including VEGF, bFGF, and TP,[15] demonstrating the close relationship between LDH and tumor angiogenesis. Besides, a high baseline level of LDH was found to be promising in predicting the survival benefit from bevacizumab, a VEGF-signaling inhibitor, in patients with metastatic colorectal cancer.[16–18] Nevertheless, the predictive value of serum level of LDH in NSCLC patients treated with bevacizumab has not been investigated yet.

Emerging evidence has shown that the microenvironment of cancer undergoes dynamic changes during treatment.[19] The hypoxic nature of the tumor microenvironment, commonly induced by insufficient tumor angiogenesis, could be shifted during treatment, especially when including agents targeting tumor vasculature.[20,21] However, information regarding baseline LDH level is extremely limited. Dynamic evaluation of serum level of LDH changes might be more accurate and informative for predicting the response and survival of patients with NSCLC after administration of bevacizumab, and it would be valuable information for therapeutic decision-making in clinical practice.

Therefore, the aim of our study was to evaluate the prognostic value of dynamic changes of serum level of LDH in advanced nonsquamous NSCLC patients treated with bevacizumab, and for the first time to explore the role of LDH longitudinal kinetics in predicting the early response of bevacizumab in these patients.

Materials and methods

Patient population

This study was approved by the Institutional Review Board of Shandong Cancer Hospital Affiliated to Shandong University (no SDTHEC20171206). All procedures were in accordance with the principles of the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards. For this retrospective study, formal written informed consent from all patients was not required, and all data were kept confidential. A total of 161 patients with advanced or recurrent NSCLC treated with bevacizumab plus standard chemotherapy between June 2011 and February 2018 were included in this study. Patient inclusion criteria comprised a diagnosis of stage IIIB or IV or recurrent nonsquamous NSCLC with no prior anti-VEGF therapy. Eligible patients were ≥18 years old, with an Eastern Cooperative Oncology Group performance status of 0 or 1, and histologically confirmed nonsquamous NSCLC, with adequate hepatic, renal, and bone marrow functions. Main exclusion criteria included gross hemoptysis, therapeutic anticoagulation, history of documented hemorrhagic or coagulated disease, the use of drugs inhibiting platelet function, clinically significant cardiovascular disease, and uncontrolled hypertension.

Detailed data on the serum levels of biological markers and other clinical factors, including gender, age, smoking status, EGFR status, and the presence of liver metastases, brain metastases, bone metastases, were collected retrospectively for all patients using uniform database templates to ensure consistent data collection. The response, defined as disease status after 6 cycles of bevacizumab, was assessed according to Response Evaluation Criteria in Solid Tumors version 1.1.

Statistical analysis

High level of baseline LDH was defined as baseline LDH exceeding 245 U/L, which was the upper limit of normal of LDH. Changes of LDH (CHG) during bevacizumab treatment were defined as decrease or increase compared with baseline LDH after 2, 4, or 6 cycles of bevacizumab treatment, respectively.

Associations of baseline LDH status with patient characteristic were analyzed by χ^2 test as appropriate. Univariate and multivariate logistic regression analyses were used to describe the association between variables and response including LDH levels and CHG during bevacizumab treatment. Kaplan–Meier plots were used to assess and present the OS and progression-free survival (PFS) based on baseline LDH status. The proportional hazards assumption for Cox models was checked and validated first; then univariate and multivariate proportional hazards Cox models were used in both OS and PFS analyses to assess the independent prognostic values. If the proportional hazards assumption did not hold, time × covariates interaction Cox model was used. Variables with $P<0.1$ in univariate analyses were included

in multivariate Cox models.[22,23] Results were presented as hazard ratios (HR) with 95% confidence intervals (95% CIs). Survival and logistic analyses were conducted using SPSS 24 (IBM Corporation, Armonk, NY, USA).

A mixed-effect regression model with per-patient random intercept and slope were performed for the longitudinal analyses for LDH using R v3.4.4 (The R Foundation, Vienna, Austria). The value of LDH was transformed to be normally distributed to better perform regression analysis. Transformed LDH was defined as ln (LDH-105.8) using a zero-skewness log transformation in Stata v12.0 (StataCorp LLC, College Station, TX, USA).

Results

Patient characteristics

After a median follow-up of 17.1 months (2.3–86.3 months), a total of 161 advanced nonsquamous NSCLC patients treated with bevacizumab were enrolled in our study, and 87 patients were still alive at the end of follow-up. Baseline characteristics were well balanced in groups divided by high and low baseline serum level of LDH (Table 1).

Table 1 Baseline characteristics

Variable	Baseline LDH <245		Baseline LDH ≥245		*P*-value
	N	%	N	%	
Total	118		43		
Age, years					0.544
≤57	64	54.2	21	48.8	
>57	54	45.8	22	51.2	
Sex					0.730
Male	66	55.9	24	55.8	
Female	52	44.1	19	44.2	
Smoking history					0.237
No	88	74.6	28	65.1	
Yes	30	25.4	15	34.9	
Anatomical classification					0.130
Peripheral	81	68.6	24	55.8	
Central	37	31.4	19	44.2	
EGFR					0.424
Sensitive mutations	35	29.7	12	27.9	
Negative	54	45.8	25	58.1	
Resistant mutations	3	2.5	1	2.3	
Not available	26	22.0	5	11.7	
Bone metastasis					0.915
No	72	61.0	28	65.2	
Yes	46	39.0	15	34.8	
Brain metastasis					0.077
No	76	64.4	34	79.1	
Yes	42	35.6	9	20.9	
Liver metastasis					0.06
No	103	87.3	33	74.4	
Yes	15	112.7	10	25.6	

Abbreviation: LDH, lactate dehydrogenase.

Survival analysis

The median PFS and OS for all patients was 8.7 months (95% CI: 6.5–10.9) and 27.9 months (95% CI: 21.2–34.5), respectively. In low baseline LDH group, the PFS of patients was much better than that in high LDH group (10.6 vs 6.7 months, 95% CI: 5.2–8.2 vs 9.2–11.9, *P*=0.014, Figure 1A), and OS benefit was also found in the low LDH group with statistical significance (32.5 vs 21.9 months, 95% CI: 20.5–44.5 vs 10.6–33.1, *P*=0.01, Figure 1B).

Univariate Cox models were then performed for analyzing the variables related with OS and PFS in all patients (Tables 2 and 3). Smoking history, central tumor, bone metastasis, and liver metastasis were found to be associated with inferior OS and PFS. In terms of the serum level of LDH, high level of LDH at baseline and cycle 2, 4, 6 and increase of CHG2, CHG4, CHG6 (INC2, INC4, and INC6, respectively) were significantly correlated with worse PFS and OS.

On multivariate analyses, central tumor remained the independent risk factor for both progression and death, and liver metastasis and bone metastasis were the independent risk factors for PFS and OS, respectively. High LDH level at cycle 2 (LDH2) and increase of CHG6 (INC6) were associated with inferior PFS (HR =2.33, 95% CI: 1.38–3.93, *P*=0.001; HR =1.96, 95% CI: 1.27–3.03, *P*=0.002), while CHG4 of increased serum level of LDH (INC4) was shown to be an independent risk factor for OS (HR =2.17, 95% CI: 1.21–3.90, *P*=0.009) (Tables 2 and 3).

Response analysis

Overall, 68/161 patients achieved complete response (CR)/partial response (PR) after 6 cycles of bevacizumab treatment. As shown in Table 4, central tumor, bone metastasis, high LDH level at cycle 2 and 4, and increase of CHG2, CHG4, and CHG6 (INC2, INC4, and INC6, respectively) were associated with lower odds of CR/PR by univariate logistic regression analysis. On multivariate analyses, increase of CHG2 (INC2, odds ratio=3.75, 95% CI: 1.83–7.68, *P*<0.001) was shown to be independent in predicting worse response to bevacizumab (Table 4).

Mixed-effects regression analysis of LDH during treatment

We subsequently analyzed LDH over time. A mixed-effect regression analysis with per-patient random intercept was used to analyze changes in LDH during 6 cycles of treatment. A spaghetti plot of transformed LDH is shown in Figure 2. Patients with CR/PR and stable disease (SD) had a lower log-transformed baseline LDH compared with patients with progressive disease (PD) (Coef =–0.28, std error =0.11, *P*=0.009

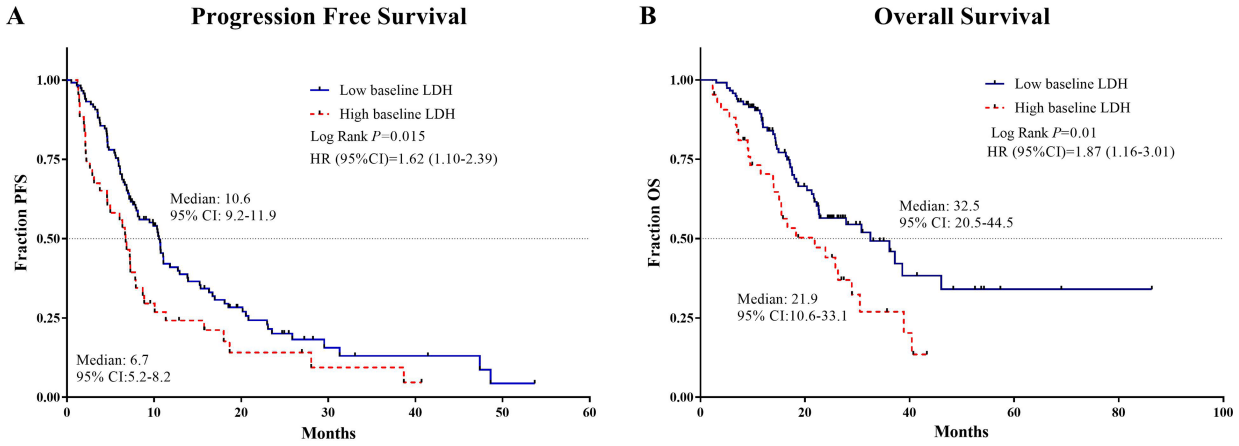


Figure 1 Kaplan–Meier survival plots of baseline LDH for PFS and OS.
Note: Plots of Kaplan–Meier estimates for PFS (**A**) and OS (**B**) in high and low baseline LDH group of advanced NSCLC patients with bevacizumab.
Abbreviations: NSCLC, non-small-cell lung cancer; OS, overall survival; PFS, progression-free survival.

and Coef =–0.39, std error =0.11, P=0.001, respectively). Besides, patients with a response of CR/PR had a −0.076 change in transformed LDH every 2 cycles of bevacizumab treatment (std error =0.017, $P<0.001$) compared with patients with PD, while there was no statistical significance when compared patients with SD (Coef =–0.023, std error =0.017, P=0.18). When combining patients with SD and PD, patients with CR/PR experienced a −0.062 changes in transformed LDH every 2 cycles (std error =0.013, $P<0.001$).

We further applied the mixed-effects regression model to predict LDH by response category (Figure 3), which showed that patients with CR/PR on bevacizumab experienced a reduction in LDH over time compared with SD and PD patients.

Discussion

LDH has been demonstrated to be an indirect marker of tumor hypoxia, neoangiogenesis, and metastasis and is associated with poor prognosis in several cancers,[13,14] including NSCLC.[15,24–28] Besides, high level of baseline LDH was found to predict a worse outcome in metastatic colorectal cancer patients with bevacizumab or receiving beyond-progression administration of bevacizumab in combination with chemotherapy.[16–18] However, the potential role of serum level of LDH in advanced nonsquamous NSCLC treated with bevacizumab was still unknown. Here, we studied for the first time the kinetics of serum level of LDH during bevacizumab treatment and evaluated its predictive role in the response and survival of NSCLC patients.

Table 2 Univariate and multivariate Cox models for PFS

Variables	Univariate HR	95% CI	*P*-value	Multivariate HR	95% CI	*P*-value
Age	1.04	0.73–1.48	0.83			
Sex	0.30	0.84–1.73	0.30			
Smoking history	1.52	1.03–2.25	0.035			
Anatomical classification	1.88	1.30–2.71	0.001	1.87	1.20–2.94	0.006
EGFR						
Negative	1.01	0.67–1.51	0.98			
Resistant mutations	2.74	0.66–11.5	0.17			
Bone metastasis	1.62	1.12–2.34	0.011			
Brain metastasis	1.57	0.74–1.62	0.64			
Liver metastasis	2.32	1.48–3.64	<0.001	2.21	1.25–3.92	0.007
Baseline LDH	1.62	1.1–2.39	0.015			
LDH2	2.74	1.84–4.09	<0.001	2.33	1.38–3.93	0.001
LDH4	2.25	1.49–3.39	<0.001			
LDH6	1.96	1.24–3.08	0.004			
CHG2	2.05	1.43–2.96	<0.001			
CHG4	1.73	1.19–2.52	0.004			
CHG6	2.25	1.49–3.40	<0.001	1.96	1.27–3.03	0.002

Abbreviations: CHG2, change after 2 cycles of bevacizumab; CHG4, change after 4 cycles of bevacizumab; CHG6, change after 6 cycles of bevacizumab; HR, hazard ratio; LDH, lactate dehydrogenase; LDH2, LDH after 2 cycles of bevacizumab; LDH4, LDH after 4 cycles of bevacizumab; LDH6, LDH after 6 cycles of bevacizumab; PFS, progression-free survival.

Table 3 Univariate and multivariate Cox models for OS

Variables	Univariate HR	95% CI	*P*-value	Multivariate HR	95% CI	*P*-value
Age	1.23	0.78–1.94	0.38			
Sex	1.32	0.83–2.09	0.24			
Smoking history	1.70	1.04–2.74	0.036			
Anatomical classification	2.03	1.28–3.20	0.003	2.10	1.18–3.73	0.011
EGFR						
Negative	1.27	0.74–2.18	0.40			
Resistant mutations	2.62	0.35–19.6	0.35			
Bone metastasis	1.79	1.13–2.84	0.014	2.12	1.19–3.80	0.012
Brain metastasis	1.15	0.71–1.87	0.58			
Liver metastasis	2.18	1.26–3.76	0.005			
Baseline LDH	1.87	1.16–3.01	0.01			
LDH2	2.23	1.37–3.62	0.001			
LDH4	2.05	1.21–3.46	0.007			
LDH6	1.92	1.06–3.46	0.031			
CHG2	1.93	1.21–3.09	0.006			
CHG4	1.99	1.21–3.27	0.007	2.17	1.21–3.90	0.009
CHG6	208	1.22–3.54	0.007			

Abbreviations: CHG2, change after 2 cycles of bevacizumab; CHG4, change after 4 cycles of bevacizumab; CHG6, change after 6 cycles of bevacizumab; HR, hazard ratio; LDH, lactate dehydrogenase; LDH2, LDH after 2 cycles of bevacizumab; LDH4, LDH after 4 cycles of bevacizumab; LDH6, LDH after 6 cycles of bevacizumab; OS, overall survival.

Bevacizumab, a humanized anti-VEGF antibody, is widely used in NSCLC and metastatic colorectal cancers and could induce transient "normalization" of vasculature and thus improve oxygen distribution in tumors.[29,30] Since serum level of LDH was shown to be an indirect factor indicative for hypoxia in tumor tissues with large tumor burden,[13,14] it seems plausible that the improvement of hypoxia in the tumor microenvironment by bevacizumab could be reflected by the decrease of serum level of LDH. Therefore, dynamic changes of serum level of LDH may more exactly and in a more sensitive manner reveal the real hypoxia status during treatment. In our present study, baseline LDH was found to be associated with worse PFS and OS in advanced nonsquamous NSCLC patients treated with bevacizumab, which is in agreement with previous results seen in NSCLC patients without bevacizumab.[15,28] However, the baseline level of LDH loses its significance in multivariate Cox models, and only CHG during bevacizumab treatment are shown to be independently predictive in progression and death, demonstrating that the dynamic changes in serum level of LDH are superior to baseline evaluation in predicting the prognosis of NSCLC patients treated with bevacizumab.

Table 4 Univariate and multivariate regression analysis for response (CR + PR)

Variables	Univariate OR	95% CI	*P*-value	Multivariate OR	95% CI	*P*-value
Age	1.01	0.54–1.89	0.98			
Sex	1.68	0.89–3.16	0.11			
Smoking history	1.68	0.82–3.46	0.16			
Anatomical classification	1.92	0.97–3.79	0.06			
EGFR						
Negative	1.62	0.78–3.35	0.20			
Resistant mutations	1.04	0.14–8.04	0.97			
Bone metastasis	1.35	0.71–2.60	0.36			
Brain metastasis	1.35	0.68–2.67	0.38			
Liver metastasis	1.47	0.61–3.52	0.39			
Baseline LDH	1.52	0.74–3.14	0.26			
LDH2	2.99	1.38–6.46	0.005			
LDH4	2.70	1.27–5.77	0.01			
LDH6	1.36	0.63–2.96	0.43			
CHG2	4.8	2.44–9.44	<0.001	3.75	1.83–7.68	<0.001
CHG4	3.95	2.00–7.80	<0.001			
CHG6	2.90	1.45–5.80	0.003			

Abbreviations: CHG2, change after 2 cycles of bevacizumab; CHG4, change after 4 cycles of bevacizumab; CHG6, change after 6 cycles of bevacizumab; LDH, lactate dehydrogenase; LDH2, LDH after 2 cycles of bevacizumab; LDH4, LDH after 4 cycles of bevacizumab; LDH6, LDH after 6 cycles of bevacizumab; OR, odds ratio.

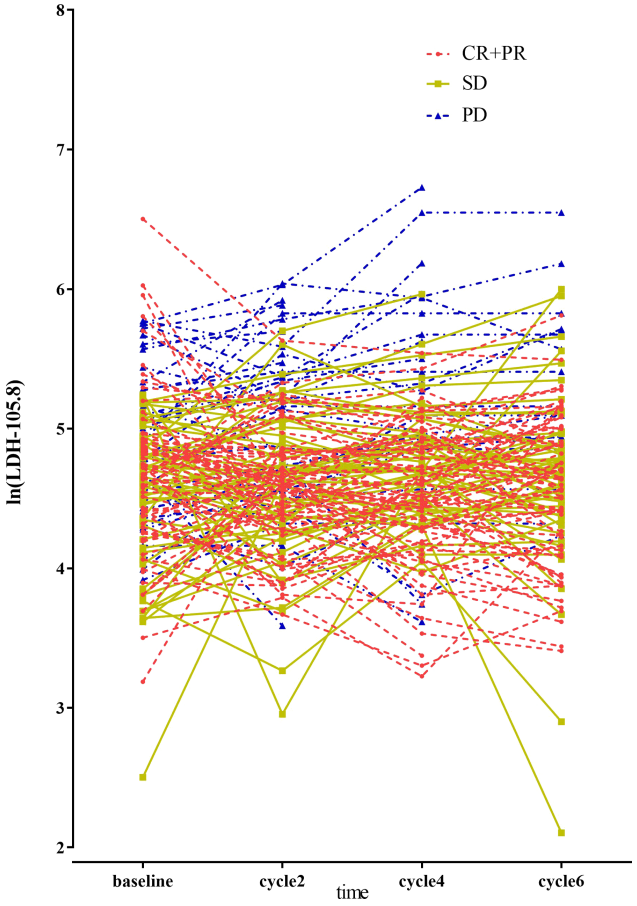


Figure 2 Longitudinal plot of natural log of LDH over time by response status.
Notes: The spaghetti plot of transformed LDH from each patient over time. All patients were divided into CR/PR, SD, or PD group according to response status.
Abbreviations: CR, complete response; PR, partial response; LDH, lactate dehydrogenase; SD, stable disease; PD, progression disease.

Moreover, we found that the level of baseline LDH was not correlated with response to bevacizumab in NSCLC patients. Instead, increase of serum level of LDH after 2 cycles of bevacizumab was an independent factor for poor response to bevacizumab in multivariate regression analysis. Mixed-effects regression analysis also indicated that serum level of LDH in patients with CR/PR showed a consistent decrease over time, with an increase seen in patients with PD and SD. Thus, dynamically monitoring serum level of LDH before and during bevacizumab treatment for advanced NSCLC patients might be helpful for identifying patients who can obtain clinical benefit from bevacizumab. And the obvious increase of LDH level during treatment may be an early marker of the resistance to bevacizumab before imaging detection. Although our findings still need to be validated in prospective trials, the estimation of serum level of LDH might provide additive value for early evaluation of the response to bevacizumab.

In the new era of targeted therapy, checkpoint inhibitors, including nivolumab and pembrolizumab, have shown encouraging results with regard to overall response rates, OS, and

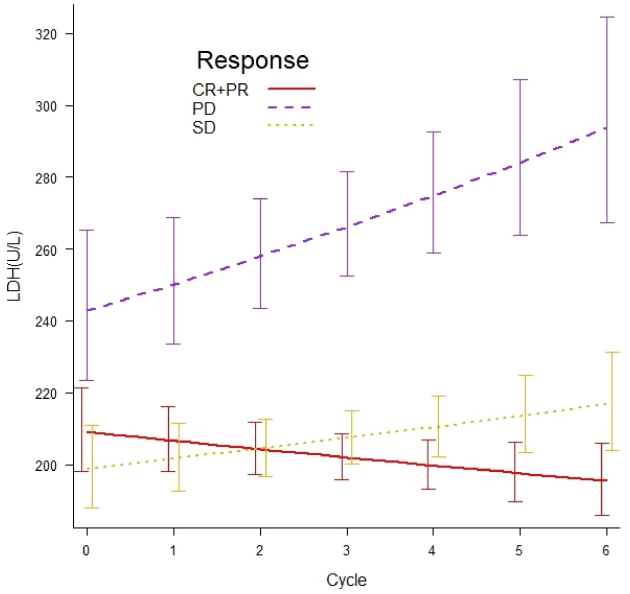


Figure 3 Predictive LDH over time according to response status.
Note: The plot of the mixed-effect model to predict LDH by response status (CR/PR, SD, and PD) over time.
Abbreviations: CR, complete response; PR, partial response; LDH, lactate dehydrogenase; SD, stable disease; PD, progression disease.

PFS in advanced NSCLC.[5–7] Interestingly, VEGF not only promotes angiogenesis but also acts as a key mediator in inhibiting T-cell infiltration and helping tumor cells escape from immune surveillance.[31] Blockage of VEGF was also found to increase T-cell numbers beyond lessened vascularity and then inhibit the tumor growth.[32] Thus, combination of antiangiogenic therapy and immunotherapy is considered promising, and several trials are ongoing to evaluate the clinical benefits from bevacizumab combined with checkpoint inhibitors in several cancers, such as colorectal cancer (NCT02876224), NSCLC (NCT02681549), renal cell carcinoma (NCT03066427), and recurrent solid tumors (NCT02857920). Consequently, the observation of LDH changes during bevacizumab treatment might highlight the importance of exploring the time point at which the immunotherapies could be administrated.

Our study also has some limitations. First, this was a retrospective study carried out in a single center with limited patients, and so we cannot fully exclude information collection bias, because of it not being planned ahead of time. Second, we cannot totally control for all possible risk factors for cancer patients. Also, the level of LDH can be influenced by several factors, even with the balance of other factors. The exact mechanism underlying the correlation between LDH and angiogenesis must also be solved through further investigations.

Conclusion

Our results indicated that dynamic CHG were superior to baseline LDH in predicting outcomes for NSCLC patients treated with bevacizumab. Patients experiencing reduction

of serum LDH level during treatment might achieve more clinical benefits from bevacizumab. Nevertheless, further prospective studies are required to validate the role of LDH kinetics in predicting the response and survival of NSCLC patients treated with bevacizumab.

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Disclosure

The authors report no conflicts of interest in this work.

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