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LETTER TO THE EDITOR

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ABOUT COVER

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ORIGINAL ARTICLE

Observational Study

T-cell immunoglobulin mucin molecule-3, transformation growth factor β, and chemokine-12 and the prognostic status of diffuse large B-cell lymphoma

Hao Wu, Hui-Cong Sun, Gui-Fang Ouyang

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Abstract

BACKGROUND

The effects of T-cell immunoglobulin mucin molecule-3 (Tim-3), transforming growth factor β (TGF-β), and chemokine-12 (CXCL12) expression on the prognosis of patients with diffuse large B-cell lymphoma (DLBCL) have not been elucidated.

AIM

To examine the correlation between Tim-3, TGF-β and CXCL12 expression and DLBCL prognosis.

METHODS

Lymph node tissues of 97 patients with DLBCL and 93 normal-response hyperplastic lymph node tissues treated from January 2017 to May 2019 were selected as the DLBCL and control groups, respectively. The expression of Tim-3, TGF-β, and CXCL12 was detected immunohistochemically. Patients were followed up for 3 years, and progression-free survival was recorded. Cox mult-ifactorial analysis was performed to analyze the risk factors for poor prognosis.

RESULTS

The positive expression rates of Tim-3, TGF-β, and CXCL12 were higher in DLBCL tissues than in non-cancerous (control) tissues ($P < 0.05$). One-year post-surgery, the positive expression rates of Tim-3, TGF-β, and CXCL12 were higher in patients with effective treatment than in those with ineffective treatment ($P < 0.05$). The 3-year progression-free survival of 97 patients with DLBCL was 67.01% (65/97). Univariate analysis revealed that clinical stage, bone marrow infiltration, International Prognostic Index (IPI) score, Tim-3 positivity, TGF-β positivity, and

CXCL12 positivity were associated with poor prognosis ($P < 0.05$). Multivariate Cox regression analysis demonstrated that clinical stage III–IV, bone marrow infiltration, mediate-to-high-risk IPI scores, Tim-3 positivity, TGF-β positivity, and CXCL12 positivity were independent risk factors affecting prognosis ($P < 0.05$).

CONCLUSION

DLBCL tissues exhibit high positive expression of Tim-3, TGF-β, and CXCL12, and a high expression of all three indicates a poor prognosis.

Key Words: T-cell immunoglobulin mucin molecule-3; Transforming growth factor β; Chemokine-12; Diffuse large B-cell lymphoma

Core Tip: Diffuse large B-cell lymphoma (DLBCL) is a malignant tumor with a poor prognosis. T-cell immunoglobulin mucin molecule-3 (Tim-3), transforming growth factor β (TGF-β), and chemokine 12 (CXCL12) can affect the prognosis of solid tumors by participating in the tumor immune escape. Therefore, we analyzed the effects of Tim-3, TGF-β, and CXCL12 expression on DLBCL prognosis. The results suggest that Tim-3 positive, TGF-β positive, and CXCL12 positive are independent risk factors; therefore, they can be used to evaluate the efficacy and prognosis of DLBCL patients.

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INTRODUCTION

Diffuse large B-cell lymphoma (DLBCL) is a biologically heterogeneous malignancy with a high incidence of recurrent lymphoma, high degree of malignancy, and poor overall prognosis[1]. Reportedly, the five-year overall survival (OS) rate of DLBCL treated with a first-line regimen [*i.e.*, rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP)-based immunotherapy] is 63.12%, whereas an OS of 77.31% has been documented following autologous hematopoietic stem cell transplantation, suggesting that 30%–40% of patients experience unsatisfactory therapeutic effects[2]. Exploring prognostic factors and therapeutic targets is crucial for improving the outcomes of patients with DLBCL. T-cell immunoglobulin and mucin domain 3 (Tim-3)[3], transforming growth factor β (TGF-β)[4], and chemokine 12 (CXCL12)[5] are closely associated with immune function, and can affect the prognosis of various solid tumors by participating in tumor immune escape. Considering the limited number of reports examining the role of Tim-3, TGF-β, and CXCL12 expression in DLBCL prognosis, we analyzed the effects of Tim-3, TGF-β, and CXCL12 expression on the prognosis of 97 patients with DLBCL admitted to our hospital from January 2017 to May 2019.

MATERIALS AND METHODS

General information

The DLBCL group included 97 patients with DLBCL admitted to our hospital from January 2017 to May 2019, based on the following inclusion criteria: (1) Initial diagnosis of DLBCL according to the *Chinese Guidelines for Diagnosis and Treatment of Diffuse Large B Cell Lymphoma* (2013 edition)[6]; (2) age > 18 years; (3) no previous preoperative chemoradiotherapy; (4) postoperative R-CHOP chemotherapy with ≥ 6 courses; (5) estimated survival time > 3 month; and (6) informed consent was obtained from all patients. The exclusion criteria were as follows: (1) Conversion from follicular lymphoma; (2) active hepatitis B, human immunodeficiency virus, severe liver and kidney dysfunction, and severe infection; (3) cognitive or mental disorders; (4) allergy to current chemotherapeutic agents; and (5) inability to be followed up or incomplete clinical data. In addition, 93 patients with normal reactive hyperplastic lymph nodes were included in the control group. The DLBCL group comprised 53 males and 44 females, ranging between 18 and 76 years of age (54.36 ± 12.63 years); this group included 48 patients with bone marrow infiltration and 49 without bone marrow infiltration; 41 with clinical stage I–II and 56

with stage III–IV; 54 patients with an Eastern Cooperative Oncology Group score of 0–1 points[7] and 43 with ≥ 2 points; 64 patients with low-risk International Prognostic Index (IPI) scores[8] and 33 with high-risk IPI scores; 50 patients presenting B symptoms (presence of systemic symptoms such as fever, night sweats, and weight loss), and 47 with no B symptoms. The control group consisted of 48 males and 45 females, ranging from 20–83 years of age (56.92 ± 11.08). There were no significant differences in sex and age between the two groups ($P > 0.05$).

Immunohistochemical examination of Tim-3, TGF-β, and CXCL12 expression in lymphoid tissues

Surgically excised tissues were subjected to paraffin embedding, baking, deparaffinization, antigen repair, hydrogen peroxide treatment, and serum closure. Primary antibodies against Tim-3, TGF-β, and CXCL12 were added at concentration ratios of 1:200, 1:100, 1:80, respectively (all purchased from Abcam), incubated overnight at 4 °C, and washed with phosphate-buffered saline. Subsequently, the secondary antibody was added for 30 min, followed by diaminobenzidine staining, hematoxylin staining, dehydration, and transparent sealing. Five high-magnification images were randomly selected using a light microscope. Tim-3, TGF-β, and CXCL12 were localized to the cell membrane and scored as a positive cell ratio (positive cell ratio < 1%, 0 points; 1 point, 1%–24%; 2 points, 25%–49%; > 50%, 3 points) and staining intensity score product to achieve a total score (total score ≥ 4 points was deemed positive)[9].

Follow-up and evaluation

An outpatient review and telephone follow-up were conducted to record the efficacy 1 year after surgery. The review was according to the criteria in *Chinese Guidelines for Diagnosis and Treatment of Diffuse Large B Cell Lymphoma* (2013 edition)[6]: Complete remission, complete disappearance of lesions; partial remission, lesion narrowing of ≥ 50% and no appearance of new lesions; stable disease, lesion size reduction of < 50%; progression or recurrence, lesion size increases by 50% or new lesions appear. Complete remission and partial remission are considered effective, whereas stable disease, progression, or recurrence are considered ineffective. The number of patients with no disease progression, recurrence, or death within three years (calculated from the date of diagnosis) was determined.

Statistical analysis

Data analysis was performed using the SPSS 22.0 software (IBM Corp., Armonk, NY, USA). Normal distribution data were presented as mean ± SD using the independent sample *t*-test and count data as percentages (%). The χ^2 test was performed to compare groups. Statistical significance was set at $P < 0.05$.

RESULTS

Comparison of Tim-3, TGF-β, and CXCL12 expression between cancerous and adjacent tissues

DLBCL tissues exhibited higher expression rates of Tim-3, TGF-β, and CXCL12 than non-cancerous (control) tissues ($P < 0.05$) (Table 1).

Comparison of Tim-3, TGF-β, and CXCL12 expression in patients with effective and ineffective DLBCL therapy

The expression rates of Tim-3, TGF-β, and CXCL12 were higher in patients with effectively treated DLBCL than in those with ineffective treatment ($P < 0.05$), as shown in Table 2.

Univariate Cox analysis of factors affecting patient outcomes

After a 3-year follow-up, 65 of 97 patients with DLBCL exhibited progression-free survival (67.01%), and univariate analysis revealed that clinical stage, bone marrow infiltration, IPI score, and Tim-3, TGF-β, and CXCL12 positivity were associated with poor prognosis ($P < 0.05$), as shown in Table 3.

Multivariate Cox regression analysis of factors affecting patient outcomes

We performed multivariate regression analysis by including statistically significant indicators from the univariate analysis, revealing that clinical stage III–IV, bone marrow infiltration, moderate-to-high risk in IPI score, Tim-3 positivity, TGF-β positivity, and CXCL12 positivity were independent risk factors associated with prognostic survival ($P < 0.05$), as shown in Table 4.

DISCUSSION

DLBCL is a common malignant lymphoma with a poorly understood pathogenesis. Despite continuous progress in clinical diagnosis and available treatments, more than 50% of adult patients still experience

Table 1 Comparison of T-cell immunoglobulin mucin molecule-3, transforming growth factor β, and chemokine 12 expression between cancerous and adjacent tissues, *n* (%)

Groups	Tim-3 positive	TGF-β positive	CXCL12 positive
DLBCL group (n = 97)	73 (75.26)	51 (52.58)	82 (84.54)
Control group (n = 93)	36 (38.71)	23 (24.73)	27 (29.03)
χ^2 value	25.931	15.483	59.806
P value	0.000	0.000	0.000

DLBCL: Diffuse large B-cell lymphoma; Tim-3: T-cell immunoglobulin mucin molecule-3; TGF-β: Transforming growth factor β; CXCL12: Chemokine 12.

Table 2 Comparison of T-cell immunoglobulin mucin molecule-3, transforming growth factor β, and chemokine 12 expression between patients with effective and ineffective after diffuse large B-cell lymphoma treatment, *n* (%)

Groups	Tim-3 positive	TGF-β positive	CXCL12 positive
Effective (n = 51)	47 (92.16)	39 (76.47)	48 (94.12)
Ineffective (n = 46)	26 (56.52)	12 (26.09)	34 (73.91)
χ^2 value	16.4939	24.6236	7.553
P value	0.000	0.000	0.006

Tim-3: T-cell immunoglobulin mucin molecule-3; TGF-β: Transforming growth factor β; CXCL12: Chemokine 12.

early recurrence, progression, and death during the early stage[10]. Although the addition of rituximab to traditional chemotherapy has significantly improved the survival of patients with DLBCL, 30%-40% of patients experience relapse and/or refractory disease and have a poor prognosis. Based on clinical observations, DLBCL exhibits marked heterogeneity, distinct clinical manifestations, chemoradiotherapy responses, prognosis, survival, and other characteristics. Evaluating relevant factors that impact DLBCL prognosis is critical to enabling timely adjustment of treatment options and provide new therapeutic targets. Bone marrow infiltration, IPI score, and Ann Arbor stage were independent prognostic factors. The detection of B cell subtypes, Ki-67 index, and β2-MG had a certain predictive effect on prognosis. Autologous hematopoietic stem cell transplantation is the best treatment for patients with DLBCL. Chemotherapy combined with rituximab can enhance efficacy[11].

Immune deficiency is closely associated with poor prognosis of DLBCL. Tim-3, TGF-β, and CXCL12 are related to the immune function of malignant tumors; however, reports on DLBCL are inconsistent [12]. Tim-3 is a transmembrane protein located on chromosome 5 at position 33.2. This immune molecule can be expressed in various immune cells and non-Hodgkin's lymphoma tissue endothelial cells. Tim-3 mainly inhibits the proliferation and activation of Th1 cells and macrophages and promotes tumor immune escape by binding to its ligand, galectin-9[13]. Reduced Tim-3 expression can enhance the killing function of lymphocytes in DLBCL cells (SUDHL-10), suggesting that Tim-3 has an immunosuppressive function[14]. TGF-β is an immunosuppressor secreted by tumor cells that regulates self-growth, differentiation, and immune function. TGF-β has been shown to inhibit normal T-cell immune-killing function while maintaining regulatory T-cell function to avoid severe autoimmune disease. In animal experiments, DLBCL mice exhibit immunosuppression and dysregulated regulatory T-cell ratios, thus facilitating tumor cell evasion of immune system surveillance and promoting tumorigenesis and progression. CXCL12 is a chemokine secreted by osteoclasts, endothelial cells, and epithelial cells of the central nervous system, and is a pro-inflammatory mediator secreted by cancer-related fibroblasts. CXCL12 regulates neoangiogenesis, tumor cell proliferation, and migration of various solid tumors by binding to chemokine 4 (CXCL4)[15]. Blocking the CXCL12/CXCL4 pathway can enhance tumor T-cell infiltration, reduce regulatory T-cell production, and enhance antitumor activity[16]. CXCL12 expression was markedly heterogeneous in different tumors, indicating the importance of exploring CXCL12 expression in DLBCL.

In this study, we found that Tim-3, TGF-β, and CXCL12 expressions were upregulated in DLBCL tissues. Moreover, patients with DLBCL who were effectively treated exhibited higher expression rates of Tim-3, TGF-β, and CXCL12 than those with ineffective treatment. These findings suggest that Tim-3, TGF-β, and CXCL12 participate in DLBCL occurrence, and the effect of DLBCL chemotherapy can be evaluated to a certain extent. Furthermore, the Tim-3-positive expression rate of tumor-infiltrating T cells was 76.2% in patients with DLBCL. In addition, the progression-free survival of Tim-3-positive patients was lower than that of Tim-3-negative patients[17]; these findings are consistent with those

Table 3 Univariate analysis of factors affecting patient outcomes, *n* (%)

Factors		*n*	Three-year progression-free survival	χ^2 value	*P* value
Sex	Male	53	40 (75.47)	3.784	0.052
	Female	44	25 (56.82)		
Age (yr)	≥ 50	54	37 (68.52)	0.125	0.723
	< 50	43	28 (65.12)		
Bone marrow infiltration	Presence	48	45 (93.75)	30.733	0.000
	Absence	49	20 (40.82)		
B symptom	Presence	50	31 (62.00)	1.172	0.279
	Absence	47	34 (72.34)		
Clinical stages	I-II stage	41	10 (24.39)	58.355	0.000
	III-IV stage	56	55 (98.21)		
ECOG grade	0-1 points	54	34 (62.96)	0.903	0.342
	≥ 2 points	43	31 (72.09)		
IPI grade	Low-risk	64	33 (51.56)	20.307	0.000
	Medium-high risk	33	32 (96.97)		
Tim-3 expression	Positive	73	60 (82.19)	30.760	0.000
	Negative	24	5 (20.83)		
TGF-β expression	Positive	51	49 (96.08)	41.105	0.000
	Negative	46	16 (34.78)		
CXCL12 expression	Positive	82	60 (73.17)	9.103	0.003
	Negative	15	5 (33.33)		

ECOG: Eastern Cooperative Oncology Group; IPI: International Prognostic Index; Tim-3: T-cell immunoglobulin mucin molecule-3; TGF-β: Transforming growth factor β; CXCL12: Chemokine 12.

Table 4 Multivariate Cox analysis affecting patient outcomes

Variables	*r*	SD	Wald	*P* value	OR	95%CI
Bone marrow infiltration	0.820	0.251	10.686	0.001	2.270	1.472-3.934
Clinical stages	1.537	0.419	13.478	< 0.001	4.649	2.940-15.168
IPI score	0.949	0.273	12.074	0.001	2.582	1.626-4.741
Tim-3 expression	1.027	0.279	13.540	< 0.001	2.792	1.744-5.207
TGF-β expression	1.195	0.360	11.010	0.001	3.304	1.954-8.019
CXCL12 expression	1.305	0.401	10.600	0.001	3.688	2.102-10.117

r: Regression coefficient; OR: Odds ratio; CI: Confidence interval; IPI: International Prognostic Index; Tim-3: T-cell immunoglobulin mucin molecule-3; TGF-β: Transforming growth factor β; CXCL12: Chemokine 12; DLBCL: Diffuse large B-cell lymphoma.

observed in the present study. With the continuous progress in R-CHOP chemotherapy, TGF-β expression gradually decreases, indicating that TGF-β is related to DLBCL progression[18]. However, few studies have examined the progression and prognosis of DLBCL in association with CXCL12, and current studies have mainly involved *in vitro* experiments. Ibrutinib can target the CXCL12/CXCL4 chemotaxis axis and inhibit colony formation of stromal cells in the human spinal cord, thus improving drug-resistant DLBCL[19]. Reduced expression of CXCL12/CXCL4 was found to inhibit the growth of DLBCL cell lines in a dose-dependent manner, indicating its potential involvement in the occurrence and progression of DLBCL[20]. In this study, multivariate Cox regression analysis revealed that clinical stage, bone marrow infiltration, IPI score, Tim-3 positivity, TGF-β positivity, and CXCL12 positivity were independent risk factors related to prognostic survival, and clinical stage, bone marrow infilt-

ration, and IPI score were common indicators of poor prognosis that are widely employed in clinical settings. The prognostic impact of Tim-3, TGF-β, and CXCL12 positivity suggested that all three could be effective predictors of prognosis and could be developed as novel clinical therapeutic targets. With the application of clinical anti-CD20 monoclonal antibody drugs, the prognosis of patients with DLBCL has considerably improved. Traditional chemotherapeutic drugs are prone to drug resistance, myelosuppression, and serious infection complications, and immunotherapy has gradually gained momentum as a treatment strategy for DLBCL. CXCL12/CXCL4 can reportedly be blocked, and chemotaxis axis can further disrupt the interaction of PD-1/PD-L1 and improve T-cell infiltration and antitumor activity[21]. Accordingly, combination therapy with a CXCL4 blocker and an immune checkpoint inhibitor may provide a new direction for treating malignancies. Therefore, regulating immune cells through the immunosuppressive factors Tim-3, TGF-β, and CXCL12 may be a clinically valuable strategy for improving the prognosis of DLBCL.

Furthermore, these findings would provide a great reference for observing and predicting the prognosis of DLBCL. However, there are still some limitations to this study: (1) The sample size was small and the sample source was single-center, so it is necessary to further expand the sample size for multicenter studies; and (2) longer follow-up time cannot completely avoid data loss and measurement deviation.

CONCLUSION

In conclusion, Tim-3, TGF-β, and CXCL12 exhibit a high positive expression rate in DLBCL and can be used to evaluate the efficacy and prognosis of R-CHOP chemotherapy. Moreover, these factors could be potential prognostic indicators of DLBCL.

ARTICLE HIGHLIGHTS

Research background

Diffuse large B-cell lymphoma (DLBCL) is a malignant tumor with biological heterogeneity characterized by high recurrence, high malignancy, and poor overall prognosis. Exploring the prognostic factors and therapeutic targets of DLBCL is crucial to improve patient prognosis. T-cell immunoglobulin and mucin domain 3 (Tim-3), transforming growth factor β (TGF-β), and chemokine 12 (CXCL12) are closely related to immune function and can affect the prognosis of various solid tumors by participating in tumor immune escape.

Research motivation

Owing to limited reports on the role of Tim-3, TGF-β, and CXCL12 expression in the prognosis of DLBCL, their effects on the prognosis of DLBCL patients remain unclear.

Research objectives

We investigated the relationship between Tim-3, TGF-β, and CXCL12 expression and DLBCL prognosis.

Research methods

The lymph node tissues of 97 patients with DLBCL and 93 patients with normal reactive hyperplasia were selected as DLBCL and control groups, respectively. The expression of Tim-3, TGF-β, and CXCL12 was detected using immunohistochemistry. The patients were followed up for 3 years, and progression-free survival was recorded. Cox multivariate analysis was used to analyze the risk factors for poor prognosis.

Research results

Clinical stage III–IV, bone marrow infiltration, high-risk IPI score, Tim-3 positivity, TGF-β positivity, and CXCL12 positivity were independent risk factors affecting the prognosis of DLBCL.

Research conclusions

Tim-3, TGF-β, and CXCL12 have high positive expression rates in DLBCL and can be used to evaluate the efficacy and prognosis of R-CHOP chemotherapy. In addition, these factors may serve as potential prognostic biomarkers for DLBCL.

Research perspectives

Future work and clinical research can further validate the accuracy of the experimental results by expanding the sample size and conducting multicenter studies, and ultimately applying the results to the prognostic analysis of DLBCL.

FOOTNOTES

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