ARTICLE

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LMO2 expression is frequent in T-lymphoblastic leukemia and correlates with survival, regardless of T-cell stage

Kerri-Ann Latchmansingh[1,5], Xiaoqiong Wang[2,5], Ramiro E. Verdun[3], Mario L. Marques-Piubelli[4], Francisco Vega[2], M. James You[2], Jennifer Chapman[1] and Izidore S. Lossos[3]✉

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T- lymphoblastic leukemia/lymphoma (T-LL) is an aggressive malignancy of immature T-cells with poor overall survival (OS) and in need of new therapies. LIM-domain only 2 (LMO2) is a critical regulator of hematopoietic cell development that can be overexpressed in T-LL due to chromosomal abnormalities. Deregulated LMO2 expression contributes to T-LL development by inducing block of T-cell differentiation and continuous thymocyte self-renewal. However, LMO2 expression and its biologic significance in T-LL remain largely unknown. We analyzed LMO2 expression in 100 initial and follow-up biopsies of T-LL from 67 patients, including 31 (46%) early precursor T-cell (ETP)-ALL, 26 (39%) cortical and 10 (15%) medullary type. LMO2 expression was present in 50 (74.6%) initial biopsies with an average of 87% positive tumor cells (range 30–100%). LMO2 expression in ETP, medullary and cortical T-LLs was not statistically different. In patients with biopsies after initial therapy, LMO2 expression was stable. LMO2 expression was associated with longer OS ($p = 0.048$) regardless of T-lymphoblast stage or other clinicopathologic features. These findings indicate that LMO2 is a promising new prognostic marker that could predict patients' outcomes and potentially be targeted for novel chemotherapy, i.e. PARP1/2 inhibitors, which have been shown to enhance chemotherapy sensitivity in LMO2 expressing diffuse large B cell lymphoma (DLBCL) tumors by decreasing DNA repair efficiency.

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INTRODUCTION

T-lymphoblastic leukemia/lymphoma (T-LL) is a rare and aggressive but biologically heterogeneous malignancy arising from T-cell precursors. T-LL accounts for 10–15% of pediatric and 20–25% of adult lymphoblastic leukemias and remains a significant clinical challenge given the inability to cure many patients and the significant toxicity of current therapies[1–4]. T-LL has been subdivided into four intrathymic differentiation stages by its antigen expression profile, including pro-T, pre-T, cortical T and medullary T[3]. Early T-cell precursor ALL (ETP-ALL), a more recently emerged immunophenotypic subtype that includes many previously classified pro-T or pre-T cases, is now recognized as a unique subtype and is associated with high risk of treatment failure[4–6]. However, these immunophenotypic subgroups have a heterogeneous and overlapping genetic landscape and do not correlate well with prognosis. In the last decade, genomic and transcriptomic studies have identified major disease-driving pathways involved in pathogenesis of T-LL and identified distinct biological groups associated with clinical outcomes[7].

LIM-domain only 2 (LMO2) is a cysteine-rich protein that plays a critical role in the regulation of hematopoietic cell development and is the core of the transcriptional T-cell acute lymphocytic leukemia protein 1 (TAL1) complex. *LMO2* is expressed in early T-cell progenitors and is normally switched off during T-lymphocyte differentiation[8–11]. LMO2 can be aberrantly overexpressed in T-LL as a result of translocations involving T-cell receptor (TCR) genes [t(11;14)(p13;q11), t(7;11)(q35;p13)], small chromosomal deletions [del(11)(p12-p13)] in the vicinity of *LMO2* locus, rare translocations involving non-TCR genes, or following retroviral integration upstream of the *LMO2* locus during treatment of X-linked severe combined immunodeficiency syndrome[12–15]. Recent studies in diffuse large B cell lymphoma (DLBCL) have identified the critical role of LMO2 in DNA repair and revealed that high LMO2 expression in tumor cells induces accumulation of DNA double-stranded breaks, contributing to tumor cell genetic instability by means of homologous recombination deficiency, and making them more amenable to chemotherapy and augmentation of tumor cell killing by Poly (ADP-ribose) polymerase (PARP) inhibitor therapy[16]. However, LMO2 protein expression and its correlation with clinicopathological features and prognosis in T-LL remain largely unknown.

In this study, we assessed LMO2 expression in a large cohort of 100 biopsies from 67 patients with T-LL composed of neoplastic T-lymphoblasts at various differentiation stages and correlated LMO2 expression with other clinicopathological characteristics and survival. Our results indicate that LMO2 is a promising biomarker that predicts T-LL patients' prognosis and provide data

[1]Department of Pathology and Laboratory Medicine, Division of Hematopathology, University of Miami/Sylvester Comprehensive Cancer Center & Jackson Memorial Hospital, Miami, FL, USA. [2]Department of Hematopathology, The University of Texas MD Anderson Cancer Center, Houston, TX, USA. [3]Department of Medicine, Division of Hematology, University of Miami/Sylvester Comprehensive Cancer Center & Jackson Memorial Hospital, Miami, FL, USA. [4]Department of Translational Molecular Pathology, The University of Texas MD Anderson Cancer Center, Houston, TX, USA. [5]These authors contributed equally: Kerri-Ann Latchmansingh, Xiaoqiong Wang. ✉email: ilossos@med.miami.edu

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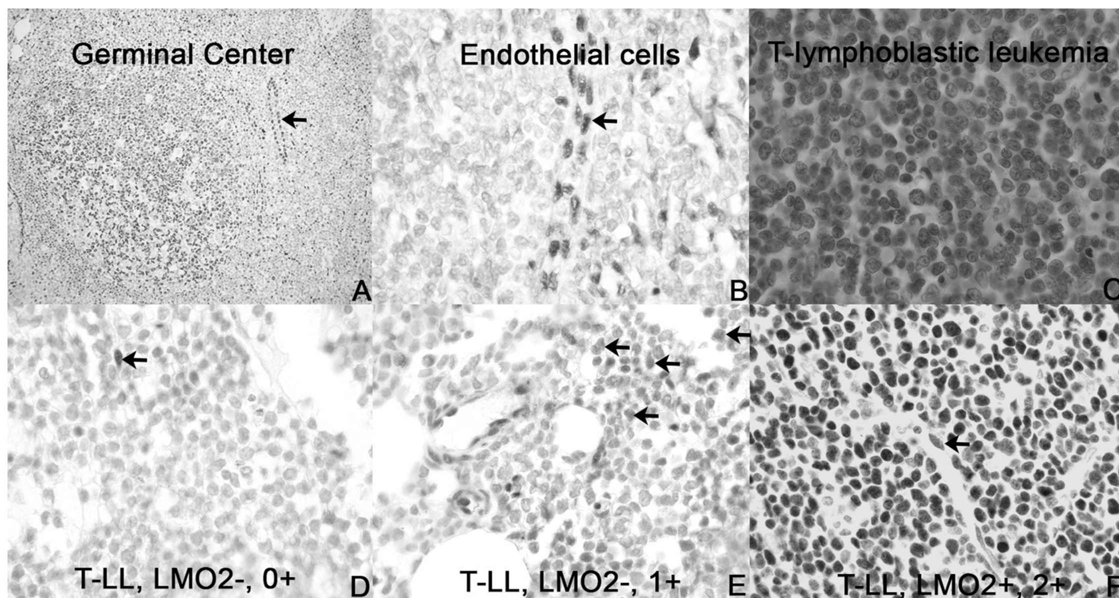

Fig. 1 Grading of LMO2 immunohistochemistry staining in T-LL. In normal tonsil, LMO2 immunohistochemistry staining shows strong nuclear positivity in **A** germinal center B cells (IHC, x40) and (**B**) endothelial cells (IHC, x100), while LMO2 is negative in **B** surrounding normal T-cells (IHC, x100) (**C**). An example of T lymphoblastic leukemia (T-LL) extensively involving bone marrow (Hematoxylin & Eosin stain, x100). **D** T-LL with negative LMO2 expression. In this example, lymphoblasts are negative for LMO2 while scattered endothelial cells (arrow), as internal positive control, are positive for LMO2 (IHC, x100). **E** T -LL with weak (1+) and variable expression of LMO2. **F** T-LL with diffuse and strong (2+) expression of LMO2 in >90% of lymphoblasts.

to support the need for further investigation into whether this marker can be used as a potential therapeutic target.

MATERIALS AND METHODS

Patient selection

We retrospectively searched the pathology databases of the University of Miami/Jackson Memorial Hospital (UM/JMH) and MD Anderson Cancer Center (MDACC) for cases of T-LL diagnosed between the years of 2006 and 2020. Slides were retrieved from file and diagnoses were reviewed by expert hematopathologists (JC, FV, JY). Clinicopathological data including age, sex, site of involvement, cytogenetic and mutational status, tumor stage, therapy, and response were collected for each patient. Subsequent biopsies showing persistent or relapsed disease were also collected and reviewed when available.

Immunophenotypic studies

Immunohistochemical (IHC) stains and flow cytometry studies were performed as part of the initial clinical workup and was confirmed by review of original IHC slides and/or flow cytometry scatterplots for the purposes of this work. IHC for at least CD3, CD7, CD4, CD8, TdT and CD1a were performed in all cases with available material either at the time of original diagnosis and/or for the purposes of this work if not performed originally. IHC was performed in formalin-fixed, parrafin-embedded tissue sections of either bone marrow core biopsy or clot section and was performed in our clinical IHC lab using clinically validated protocols and automated instruments (Leica BOND III, Leica Biosystems Ltd. Newcastle, UK). Immunohistochemical staining for LMO2 (Ventana, Tuscon, Arizona, United States) was performed in all cases for the purposes of this manuscript. For each case, neoplastic T-cells were categorized into one of three groups; early T-precursor (ETP), cortical or medullary, based on protein expression as determined by IHC in each case[3].

Cytogenetic analysis

Conventional cytogenetic analysis was performed on G-banded metaphase cells prepared from unstimulated patient specimen cell cultures using standard techniques. Twenty metaphases were analyzed, when available, and the results were reported using the 2016 International System for Human Cytogenetic Nomenclature.

Molecular studies

Bone marrow aspirate specimens originating at the UM/JMH were assessed by integrated genomic RNA/DNA profiling at Foundation Medicine using the Foundation One Heme assay (https://www.foundationmedicine.com/test/foundationone-heme) or at Genoptix Medical Laboratory using the lymphoid molecular profiling panel (https://neogenomics.com/test-menu/legacy-lymphoid-molecular-profile). Bone marrow aspirate specimens originating from MDACC were assessed for molecular abnormalities using an in-house clinically validated 28-gene panel Ultra-Rapid Reporting of GENomic Targets (URGENTseq)[17].

Determining expression of LMO2

Individual cells were considered LMO2 positive if definitive nuclear staining was identified. Cells were scored as negative, weak positive or strong positive based on comparison with internal control endothelial cell nuclei, as follows: absence of LMO2 expression was scored as 0; LMO2 expression weaker than that of endothelial cells was considered weak (1+) and staining equal to or stronger than that of endothelial cells was considered strong (2+) (Fig. 1). LMO2 expression in each tumor was scored as negative or positive based on a 30% cutoff following the precedent used to assess a variety of other proteins in hematopoietic neoplasms as well as LMO2 expression in DLBCL[18]. The percentage of tumor cells expressing LMO2 at each intensity of expression were recorded in each case by counting 300 cells per case. H score for LMO2 expression was calculated for each case using the formula H score = [(%0+) x 1] + [(%1+) x 2] + [(%2+) x 3][19].

For cases in which coexpression of CD3 and LMO2 was difficult to determine due to either low blast counts or increased LMO2 uptake by non-neoplastic hematopoietic cells, a dual CD3/LMO2 immunostaining was performed on formalin-fixed paraffin-embedded tissue slides. Dual immunohistochemistry was performed using 3,3′-diaminobenzidine (DAB) chromogen for visualization of the nuclear antigen (LMO2) and a red chromogen for visualization of the membrane or cytoplasmic antigen (CD3). In each dual assay, the normal protocol for the LMO2 assay was performed, directly followed by the normal protocol for CD3, in a sequential fashion (Fig. 2). In cases with low blast counts, which were usually post therapy cases, blasts were assessed for LMO2 expression using dual LMO2/CD3 staining. A cutoff of 30% was applied for the cases reviewed by dual CD3/LMO2 staining. To ensure that normal T-cells were not included, this assessment was performed only in foci containing TdT or CD34 positive blasts that could also be identified in routine H&E stain.

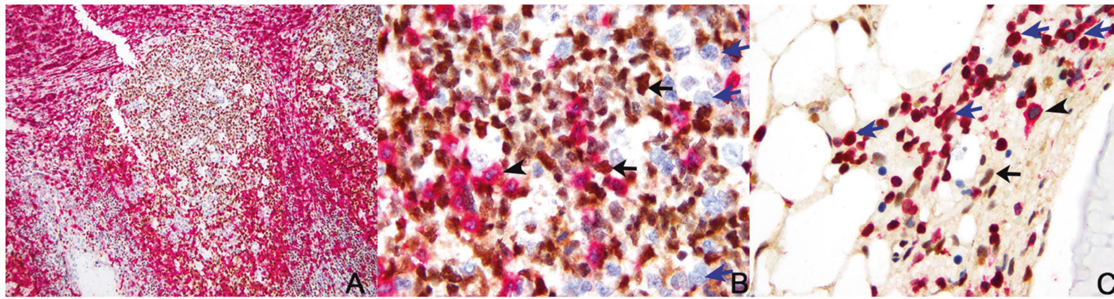

Fig. 2 Dual immunohistochemistry for LMO2 (brown chromogen) and CD3 (red chromogen). Dual immunohistochemistry staining pattern of LMO2 and CD3 in normal tonsil (**A**, x40; B, x100). Germinal center B cells express strong LMO2 and are negative for CD3 (**B**, arrow). T cells express CD3 and are negative for LMO2 (**B**, arrowhead). Histiocytes are negative for CD3 and LMO2 (**B**, blue arrow). **C** An example of T-LL minimally involving bone marrow. Neoplastic lymphoblasts coexpress LMO2 and CD3 (blue arrow, x100), while endothelial cells staining with LMO2 (arrow) and normal T-cells staining with CD3 (arrowhead), as internal control.

Statistical analysis

Distributions of demographic and clinical or pathological characteristics were listed as frequency and percent. They were compared by LMO2 expression using the chi-square test or Fisher's exact test. Continuous variables were compared using the Gehan-Breslow-Wilcoxon test. Overall survival (OS) was defined as the time from diagnosis to death. Curves for OS were estimated using the Kaplan-Meier method and cox regression was used to compare continuous variable. All statistical analyses were performed using GraphPad Prism 6.0 (GraphPadSoftware; https://www.graphpad.com) and IBM SPSS Statistics for Windows, version 24 (IBM Corp., Armonk, N.Y.,USA). A *p*-value <0.05 was considered significant (95% confidence interval [CI]).

RESULTS

A total of 100 biopsies of T-LL were identified in 67 patients including cases diagnosed in bone marrow biopsies as T-lymphoblastic leukemias (59 patients) and cases diagnosed as T-lymphoblastic lymphomas in extramedullary sites (8 patients). The initial diagnostic biopsy was included for all patients in this study. Patients had an average age of 35 years (range 8–77 years) and male:female ratio of 2.1. Sites of involvement that were biopsied at the time of initial diagnosis included bone marrow (59), mediastinal mass (4), lymph nodes (3) and nasopharyngeal mass (1). Histopathologic data are summarized in Table 1. T-LL subtypes included 31 ETP (46%), 26 cortical (39%) and 10 medullary (15%). In patients with more than one biopsy over time, T-LL classification as ETP, cortical or medullary did not change.

Cytogenetic abnormalities were identified in 24 of 43 tested cases (56%), the most common being complex karyotype, which was noted in 16/43 (37%), while deletion 6 was the most common simple cytogenetic abnormality observed in 4/44 cases (9%). Sequencing analysis was available in 11 cases and showed the most common mutated gene to be *NOTCH1* (10/11, 91%), followed by *WT1* (3/11, 27%), with *CD36*, *TP53* and *PIK3CA* mutations respectively identified in 2/11 cases each (18%). Mutations in *ARID1A*, *B2M*, *CDKN2A/B*, *DNMT3A*, *EP300*, *EZH2*, *IKZF2*, *IL7r*, *JAK1*, *JAK3*, *KIT*, *NF1*, *PHF* and *REL* were also identified.

Fifty cases (74.6%) were positive for LMO2 expression. Representative images are showed in Fig. 1C, F. Among LMO2 positive cases, the average percent of positive cells per case was 87% (range 30–100%) and average H score was 244 (range 134–300). Seventeen (25%) cases were LMO2 negative of which 14 (82%) showed complete absence of LMO2 staining (H score 100) and 3 (18%) showed only dim/variable staining (1+) in <30% of tumor cells. In 24 patients with multiple biopsies over time and after therapy, LMO2 expression extent and intensity was similar in initial and subsequent biopsies in all cases. LMO2 expression was more common in ETP-T-LL (27/31, 87%), than medullary (7/10, 70%) or cortical (16/26, 62%), but the difference was not statistically significant. LMO2 expression also did not correlate significantly with patient age, site of involvement, or other clinicopathologic features. Whether LMO2 expression correlates with mutation and/or cytogenetic abnormalities in T-LL is not established in this analysis and would require additional cases to be analyzed.

Sixteen (24%) patients were lost to follow-up; one following bone marrow transplant and the remaining shortly after diagnosis or during treatment. Detailed follow-up clinical data from the remaining 51 (76%) patients showed that 37 (73%) were deceased due to disease or treatment related complications, while 14 (26%) were either in complete remission or currently receiving treatment, six of which had already received bone marrow transplant. Of the 37 deceased patients, 12 were post-transplant with intractable disease as the major cause of death, followed by complications related to immunosuppression. The remaining 25 (68%) patients were unable to achieve long-standing complete remission and were not eligible for transplant. Twenty-eight (76%) of the deceased had tumors that were LMO2 positive. LMO2 expression was associated with longer OS in 65 patients with follow-up data who were treated with curative intent with multiagent chemotherapy regimens ($p = 0.048$) (Fig. 3), regardless of T-lymphoblast stage or other clinicopathologic features. Information on progression free survival was not available for many patients.

DISCUSSION

T-LL is an aggressive malignancy of immature T-cells characterized by accumulations of genetic abnormalities that affect T-cell development. The prognosis is very poor as compared to other acute lymphoblastic leukemia/lymphomas with an overall survival of 3 years; thus new, targeted therapies are needed[1–3,7]. T-LL is characterized genetically by recurrent cytogenetic abnormalities in 50–70% of cases, most frequently involving the alpha or delta region of the T-cell receptor (TCR) gene at 14q11.2, the beta locus at 7q35, or the gamma locus at 7p14-15[3]. Usually, translocations in these chromosomal regions result in transcriptional dysregulation of the partner gene, frequently a transcription factor, as it comes under the transcriptional regulation of the TCR locus. Deregulation of transcription factors following this mechanism, as well as mutational abnormalities of *CDNK2A/2B*, *NOTCH1*, epigenetic factors and other signaling abnormalities also characterize the heterogeneous genetic landscape of T-LL[20–22].

Abnormal persistent expression of LMO2 is also implicated in tumorigenesis of T-LL[23–26]. The LMO2 transcription start site is located in close proximity to the 11p13 T-cell translocation cluster, a site where disease defining recurrent translocations of T-LL occur. Genetic abnormalities affecting *LMO2* occur in approximately 13 and 21% of pediatric and adult T-LL, respectively, making this one of the most frequently affected transcription

Table 1. Clinicopathologic features of patients.

Patient	Age (years)	Site of diagnostic biopsy	T-cell stage	LMO2% positivity, H score	LMO2 expression (≥30% is +)	Karyotype	Mutations	Survival status	Disease status
1	40	BM	ETP	283	+	Complex	*NOTCH1, WT1*	D	
2	20	BM	ETP	287	+	Complex	*NOTCH1*	D	
3	36	BM	ETP	292	+	Complex		D	
4	37	BM	ETP	298	+	46,XY,del6[10]		D	
5	40	BM	ETP	286	+	Complex		D	
6	22	BM	ETP	284	+	46,XY		D	
7	18	BM	ETP	292	+	Complex		D	
8	45	BM	ETP	288	+	Complex		D	
9	59	BM	ETP	179	+	46,XY		A	CR
10	59	BM	ETP	294	+	Complex		D	
11	57	BM	ETP	282	+	46,XY		L	
12	8	BM	ETP	292	+	Complex		L	
13	19	BM	ETP	290	+	46,XY		D	
14	22	BM	ETP	300	+	46,XX		A	CR
15	29	BM	ETP	294	+	N/A		D	
16	24	BM	ETP	184	+	N/A		L	
17	43	BM	ETP	296	+	N/A		L	
18	45	BM	ETP	298	+	Complex		L	
19	46	BM	ETP	296	+	N/A		D	
20	48	BM	ETP	287	+	N/A		D	
21	12	BM	ETP	284	+	N/A		D	
22	45	BM	ETP	268	+	t(2;11), monosomy 7		A	CR
23	22	BM	ETP	251	+	N/A		D	
24	20	Left groin lymph node	ETP	292	+	N/A		A	PD
25	58	BM	ETP	200	+	46,XX	*ARID1A, B2M, DNMT3A, REL, WT1*	A	PD
26	54	Cervical lymph node	ETP	271	+	N/A		A	CR
27	40	Cervical lymph node	ETP	292	+	N/A		L	
28	53	BM	Cortical	134	+	46,XX	*NOTCH1*	D	
29	38	BM	Cortical	149	+	46,XY, t(10;14)	*NOTCH1, NF1, PHF6*	A	PD
30	23	BM	Cortical	288	+	46,XX		L	
31	23	BM	Cortical	244	+	46,XY		D	
32	39	BM	Cortical	209	+	Complex		D	
33	29	BM	Cortical	290	+	Complex		D	
34	71	BM	Cortical	240	+	46,XY,del6[10], del7[10]		D	
35	44	BM	Cortical	284	+	46,XY		D	

Table 1. continued

Patient	Age (years)	Site of diagnostic biopsy	T-cell stage	LMO2% positivity, H score	LMO2 expression (≥30% is +)	Karyotype	Mutations	Survival status	Disease status
36	35	BM	Cortical	298	+	Complex		L	
37	36	BM	Cortical	292	+	46,XY		A	CR
38	26	BM	Cortical	296	+	46,XX		A	CR
39	20	BM	Cortical	298	+	46,XX,del6,i(9)[2]		D	
40	19	BM	Cortical	153	+	46,XY	*EP300, EZH2, NOTCH1*	A	CR
41	25	BM	Cortical	259	+	t(11;14)		D	
42	23	BM	Cortical	181	+	46,XY		L	
43	25	BM	Cortical	193	+	N/A		L	
44	44	BM	Medullary	193	+	46,XY		D	
45	53	BM	Medullary	274	+	Complex		A	CR
46	77	BM	Medullary	294	+	46,XY,del6[10]		D	
47	36	BM	Medullary	158	+	Complex		D	
48	53	BM	Medullary	266	+	46,XY		D	
49	22	BM	Medullary	212	+	N/A		L	
50	16	BM	Medullary	236	–	46,XY		D	
51	51	BM	ETP	100	–	N/A		L	
52	53	BM	ETP	122	–	N/A		L	
53	36	BM	ETP	100	–	N/A		L	
54	27	BM	ETP	124	–	46,XY	*NOTCH1, JAK1, JAK3, WT1, IL7r*	D	
55	32	BM	Cortical	100	–	Complex	*NOTCH1, TP53, KIT*	D	
56	27	BM	Cortical	108	–	46,XY	*NOTCH1, TP53*	D	
57	73	BM	Cortical	100	–	47,XX,t(7;9),+20 [9]		D	
58	20	BM	Cortical	107	–	Complex		D	
59	46	BM	Cortical	108	–	N/A		A	PD
60	34	Mediastinal mass	Cortical	104	–	N/A		D	
61	19	Nasopharyngeal mass	Cortical	103	–	N/A		A	CR
62	26	Mediastinal mass	Cortical	102	–	N/A	*PIK3CA, CD36, CDKN2A/B, NOTCH1*	D	
63	36	Mediastinal mass	Cortical	101	–	N/A		L	
64	27	Mediastinal mass	Cortical	102	–	N/A		D	
65	22	BM	Medullary	104	–	N/A	*NOTCH1-TCRB* fusion, *IKZF2, PIK3C, CD36*	A	PD
66	8	BM	Medullary	100	–	N/A		D	
67	8	BM	Medullary	100	–	N/A		L	

BM Bone marrow, *ETP* Early T-cell precursor, *(+)* Positive, *(–)* Negative, *N/A* Not applicable, *A-Alive* D-Deceased, *L* Lost to follow-up, *CR* Complete Remission, *PD* Persistent Disease.

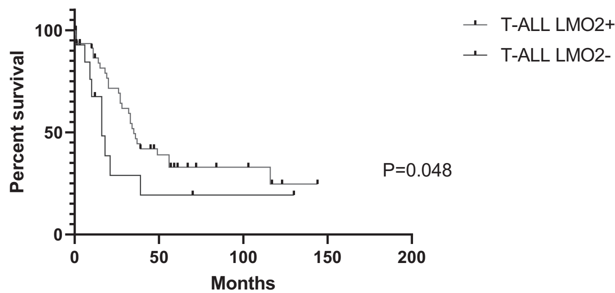

Fig. 3 Overall Survival of T-lymphoblastic leukemia correlated with LMO2 expression. T-ALL with LMO2 expression have a longer overall survival compared with T-ALL without LMO2 expression ($p = 0.048$).

factors in T-LL[27]. Deregulated expression of LMO2 contributes to development of T-LLs by inducing T-cell differentiation block and continuous thymocyte self-renewal[26,27]. Recent studies in DLBCL have identified the critical role of LMO2 in DNA repair and that high LMO2 expression in tumor cells induces accumulation of DNA double-stranded breaks, contributing to tumor cell genetic instability by means of homologous recombination deficiency. The latter may predispose the cells to increased sensitivity to chemotherapy and can augment tumor cell killing by Poly (ADP-ribose) polymerase (PARP) inhibitor therapy[16,28]. However, LMO2 protein expression, and its correlation with clinicopathological features and prognosis in T-LL have been largely unknown. We note that a recent case report was published detailing successful treatment of T-LL with *BRCA1* mutation with PARP inhibitor after failure of multiple lines of therapies[29]. LMO2 expression was not analyzed in this case.

Our findings provide support that LMO2 expression is common in T-LL, occurring in 74.6% of unselected cases. Moreover, when T-LL are positive for LMO2, expression is usually extensive (average of 87% of cells positive) and strong (average H score 244). LMO2 expression appears to be stable and, in this series, did not change in response to therapy or over time in biopsies of relapsed and/or persistent disease, indicating that expression can be determined at initial diagnosis or at the time of persistent/relapsed disease.

We have previously reported that in B-cell acute lymphoblastic leukemia (B-ALL), high LMO2 RNA expression correlated with better overall survival in adult patients and constituted a favorable independent prognostic factor in B-ALL with normal karyotype[30]. Herein we show that LMO2 protein expression also correlates with OS in T-LL patients regardless of T-lymphoblast stage or other clinicopathologic features, suggesting that LMO2 expression may affect the efficiency of DNA repair mechanisms and predisposes these tumor cells to a higher sensitivity to chemotherapy, as has been shown in LMO2 expressing DLBCL. These findings justify the need for further investigation into T-LL expressing LMO2 in order to establish novel therapies exploiting DNA repair deficiencies, which have lower toxicity in normal cells than do the currently available chemotherapy agents, such as PARP1/2 inhibitors.

DATA AVAILABILITY

The datasets generated and/or analyzed during the current study are not publicly available but are available from the corresponding author on request.

REFERENCES

1. Litzow, M. R. & Ferrando, A. A. How I treat T-cell acute lymphoblastic leukemia in adults. *Blood* **126**, 833–841 (2015).
2. Hunger, S. P. & Mullighan, C. G. Acute lymphoblastic leukemia in children. *N. Engl J Med* **373**, 1541–1552 (2015).
3. Borowitz M. J., et al., editor. WHO classification of tumours of haematopoietic and lymphoid tissues. 4 ed. 209–212 (IARC: Lyon, 2017).
4. Morita, K. et al. Outcome of T-cell acute lymphoblastic leukemia/lymphoma: focus on near-ETP phenotype and differential impact of nelarabine. *Am J Hematol* **96**, 589–598 (2021).
5. Zhang, J. et al. The genetic basis of early T-cell precursor acute lymphoblastic leukaemia. *Nature* **481**, 157–163 (2012).
6. Jain, N. et al. Early T-cell precursor acute lymphoblastic leukemia/lymphoma (ETP-ALL/LBL) in adolescents and adults: a high-risk subtype. *Blood* **127**, 1863–1869 (2016).
7. Belver, L. & Ferrando, A. The genetics and mechanisms of T cell acute lymphoblastic leukaemia. *Nat Rev Cancer* **16**, 494–507 (2016).
8. Org, T. et al. Scl binds to primed enhancers in mesoderm to regulate hematopoietic and cardiac fate divergence. *EMBO J* **34**, 759–777 (2015).
9. Li, L. et al. Nuclear adaptor Ldb1 regulates a transcriptional program essential for the maintenance of hematopoietic stem cells. *Nat Immunol* **12**, 129–136 (2011).
10. Dik, W. A. et al. New insights on human T cell development by quantitative T cell receptor gene rearrangement studies and gene expression profiling. *J Exp Med* **201**, 1715–1723 (2005).
11. Herblot, S., Steff, A. M., Hugo, P., Aplan, P. D. & Hoang, T. SCL and LMO1 alter thymocyte differentiation: inhibition of E2A-HEB function and pre-T alpha chain expression. *Nat Immunol* **1**, 138–144 (2000).
12. Van Vlierberghe, P. et al. The cryptic chromosomal deletion del(11)(p12p13) as a new activation mechanism of LMO2 in pediatric T-cell acute lymphoblastic leukemia. *Blood* **108**, 3520–3529 (2006).
13. Rahman, S. et al. Activation of the LMO2 oncogene through a somatically acquired neomorphic promoter in T-cell acute lymphoblastic leukemia. *Blood* **129**, 3221–3226 (2017).
14. Morishima, T. et al. LMO2 activation by deacetylation is indispensable for hematopoiesis and T-ALL leukemogenesis. *Blood* **134**, 1159–1175 (2019).
15. Goossens, S. et al. ZEB2 and LMO2 drive immature T-cell lymphoblastic leukemia via distinct oncogenic mechanisms. *Haematologica* **104**, 1608–1616 (2019).
16. Parvin, S. et al. LMO2 confers synthetic lethality to PARP inhibition in DLBCL. *Cancer Cell* **36**, 237–249 e236 (2019).
17. Patel, K. P. et al. Ultra-rapid reporting of GENomic targets (URGENTseq): clinical next-generation sequencing results within 48 h of sample collection. *J Mol Diagn* **21**, 89–98 (2019).
18. Natkunam, Y. et al. LMO2 protein expression predicts survival in patients with diffuse large B-cell lymphoma treated with anthracycline-based chemotherapy with and without rituximab. *J Clin Oncol* **26**, 447–454 (2008).
19. Fedchenko, N. & Reifenrath, J. Different approaches for interpretation and reporting of immunohistochemistry analysis results in the bone tissue - a review. *Diagn Pathol* **9**, 221 (2014).
20. Girardi, T., Vicente, C., Cools, J., De & Keersmaecker, K. The genetics and molecular biology of T-ALL. *Blood* **129**, 1113–1123 (2017).
21. Liu, Y. et al. The genomic landscape of pediatric and young adult T-lineage acute lymphoblastic leukemia. *Nat Genet* **49**, 1211–1218 (2017).
22. Chen, B. et al. Identification of fusion genes and characterization of transcriptome features in T-cell acute lymphoblastic leukemia. *Proc Natl Acad Sci USA* **115**, 373–378 (2018).
23. Chambers, J. & Rabbitts, T. H. LMO2 at 25 years: a paradigm of chromosomal translocation proteins. *Open Biol* **5**, 150062 (2015).
24. Nam, C. H. & Rabbitts, T. H. The role of LMO2 in development and in T cell leukemia after chromosomal translocation or retroviral insertion. *Mol Ther* **13**, 15–25 (2006).
25. Neale, G. A., Mao, S., Parham, D. M., Murti, K. G. & Goorha, R. M. Expression of the proto-oncogene rhombotin-2 is identical to the acute phase response protein metallothionein, suggesting multiple functions. *Cell Growth Differ* **6**, 587–596 (1995).
26. El Omari, K. et al. Structure of the leukemia oncogene LMO2: implications for the assembly of a hematopoietic transcription factor complex. *Blood* **117**, 2146–2156 (2011).
27. Jevremovic, D., Roden, A. C., Ketterling, R. P., Kurtin, P. J. & McPhail, E. D. LMO2 is a specific marker of T-lymphoblastic leukemia/lymphoma. *Am J Clin Pathol* **145**, 180–190 (2016).
28. de Jong, M. R. W. et al. Identification of relevant drugable targets in diffuse large B-cell lymphoma using a genome-wide unbiased CD20 guilt-by association approach. *PLoS One* **13**, e0193098 (2018).
29. Xue S. et al. Olaparib combined with chemotherapy for treatment of T-cell acute lymphoblastic leukemia relapse after unrelated umbilical cord blood transplantation. *Leuk Lymphoma*, **63**, 478–482 (2022).
30. Malumbres, R. et al. LMO2 expression reflects the different stages of blast maturation and genetic features in B-cell acute lymphoblastic leukemia and predicts clinical outcome. *Haematologica* **96**, 980–986 (2011).

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AUTHOR CONTRIBUTIONS

K.-A.L.: Performed research, managed data, wrote manuscript, X.W.: Performed research, managed data, wrote manuscript, R.E.V.: Conceived hypothesis, wrote manuscript, M.L.M.-P.: managed the data and wrote the manuscript, F.V.: Performed research, managed data, wrote manuscript, M.J.Y.: Performed research, managed data, wrote manuscript, J.C.: Performed research, managed data, wrote manuscript, I.S.L.: Conceived hypothesis, performed research, managed data, wrote manuscript.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

This study was performed after IRB approval at the University of Miami and University of Texas MD Anderson Cancer Center.

COMPETING INTERESTS

ISL reports personal fees from Janssen Biotech, Janssen, Seattle Genetics, Verastem, and Karyopharm outside the submitted work. Remaining authors have no conflicts of interest to report.

ADDITIONAL INFORMATION

Correspondence and requests for materials should be addressed to Izidore S. Lossos.

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