LMO2 Protein Expression Predicts Survival in Patients With Diffuse Large B-Cell Lymphoma Treated With Anthracycline-Based Chemotherapy With and Without Rituximab

Yasodha Natkunnam, Pedro Farinha, Eric D. Hsi, Christine P. Hans, Robert Tibshirani, Laurie H. Sehn, Joseph M. Connors, Dita Gratzing, Manuel Rosado, Shuchun Zhao, Brad Pohlman, Nicholas Wongchaowart, Martin Bast, Abraham Avidor, Ginette Schiby, Arnon Nagler, Gerald E. Byrne, Ronald Levy, Randy D. Gascoyne, and Izidore S. Lossos

ABSTRACT

Purpose
The heterogeneity of diffuse large B-cell lymphoma (DLBCL) has prompted the search for new markers that can accurately separate prognostic risk groups. We previously showed in a multivariate model that LMO2 mRNA was a strong predictor of superior outcome in DLBCL patients. Here, we tested the prognostic impact of LMO2 protein expression in DLBCL patients treated with anthracycline-based chemotherapy with or without rituximab.

Patients and Methods
DLBCL patients treated with anthracycline-based chemotherapy alone (263 patients) or with the addition of rituximab (80 patients) were studied using immunohistochemistry for LMO2 on tissue microarrays of original biopsies. Staining results were correlated with outcome.

Results
In anthracycline-treated patients, LMO2 protein expression was significantly correlated with improved overall survival (OS) and progression-free survival (PFS) in univariate analyses (OS, $P = .018$; PFS, $P = .010$) and was a significant predictor independent of the clinical International Prognostic Index (IPI) in multivariate analysis. Similarly, in patients treated with the combination of anthracycline-containing regimens and rituximab, LMO2 protein expression was also significantly correlated with improved OS and PFS (OS, $P = .005$; PFS, $P = .009$) and was a significant predictor independent of the IPI in multivariate analysis.

Conclusion
We conclude that LMO2 protein expression is a prognostic marker in DLBCL patients treated with anthracycline-based regimens alone or in combination with rituximab. After further validation, immunohistologic analysis of LMO2 protein expression may become a practical assay for newly diagnosed DLBCL patients to optimize their clinical management.

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INTRODUCTION

Gene expression profiling has been used to determine prognostic subgroups in diffuse large B-cell lymphoma (DLBCL). The pivotal study of Alizadeh et al led to the discovery that the overall survival (OS) is significantly longer in DLBCL patients with a gene expression profile similar to that of normal germinal center (GC) B cells. This result suggests that the cell of origin has an impact on clinical outcome. Several models have been developed based either on RNA or protein expression to predict survival in DLBCL patients; however, a consensus on how to stratify DLBCL patients has not been achieved. To avoid the limitations of fresh tissue and for ease of use in routine clinical practice, many recent studies have also focused on the use of immunohistochemistry to identify risk groups.

From gene expression studies, LMO2 mRNA expression emerged as the strongest single predictor of superior outcome in DLBCL patients in a multivariate model based on the expression of six genes. We developed a monoclonal anti-LMO2 antibody and documented that the LMO2 protein is expressed in normal GC B cells and in a subset of GC-derived B-cell lymphomas. Here, we examined whether LMO2 protein expression, as assessed in archival diagnostic biopsies from 263 DLBCL patients who were treated with anthracycline-based regimens, can predict outcome. The addition of the...
anti-CD20 monoclonal antibody rituximab to anthracycline-based chemotherapy (cyclophosphamide, vincristine, doxorubicin, and prednisone [CHOP]) was recently shown to improve the survival of DLBCL patients. Therefore, we analyzed the impact of LMO2 protein expression in 80 DLBCL patients treated with rituximab plus CHOP (R-CHOP) to test its prognostic value in the rituximab era.

**Patient Selection**

A total of 343 specimens were studied; 263 specimens were from patients treated with anthracycline-containing chemotherapy (CHOP or CHOP-like regimens) and were contributed from the British Columbia guidelines that instituted R-CHOP as the standard therapy as of March 1, 2001, as previously described in detail, and now have had clinical follow-up through March 15, 2007. The specimens were selected based on the following criteria: diagnosis of de novo DLBCL clinically presenting at stage I, II, III, or IV; availability of tissue obtained at diagnosis before the initiation of therapy; treatment with a curative intent with an anthracycline-containing regimen with or without rituximab; and availability of follow-up and outcome data at the treating institution. Patients with primary mediastinal large B-cell lymphoma or involvement of CNS at presentation were not included in this study. None of the patients in the current study were included in our previous studies of gene expression profiling that led to the derivation of the six-gene model.

Institutional review board approval was obtained from all participating institutions. In all patients chosen for this study, information was available about staging of the disease by physical examination, bone marrow biopsy, and computed tomography of the chest, abdomen, and pelvis. Patients were staged according to the Ann Arbor system. Because the clinical data were collected retrospectively, criteria commonly used for prospective studies, such as normal renal and liver functions, absence of comorbid conditions, and good performance status, were not applied for patient selection. The following clinical and laboratory data were available at the time of diagnosis: age, sex, performance status, stage, number of extranodal sites involved, serum lactate dehydrogenase level, and the presence or absence of systemic (“B”) symptoms. Given this information, International Prognostic Index (IPI) scores could be determined in 256 of the patients treated with anthracycline-based regimens and in all 80 patients who received R-CHOP. Patients were categorized into either a low-risk group (IPI score, 0 to 2) or a high-risk group (IPI score, 3 to 5). None of the patients had a known history of HIV infection or other forms of immunosuppression. Follow-up information was obtained from the patients’ medical records and included response to initial therapy based on the Cheson criteria, OS, and progression-free survival (PFS).

Histologic sections were reviewed to confirm the diagnoses and were compatible with features of DLBCL according to the WHO classification of hematopoietic tumors. Pathologists from the five participating institutions (Y.N., P.F., E.D.H., C.P.H., D.G., N.W., A.A., G.S., G.E.B., and R.D.G.) were involved in the review of patients from each of their centers. One pathologist (Y.N.) reviewed all patients.

**Tissue Microarrays and Immunohistochemistry**

Standardized methods for tissue fixation (10% buffered formalin) and processing were used at all participating centers. Tissue microarrays (TMAs) were obtained from the British Columbia Cancer Agency, Cleveland Clinic Foundation, and University of Nebraska Medical Center. A TMA of patients from the University of Miami and Chaim-Sheba Medical Center was constructed using a tissue arrayer (Beecher Instruments, Silver Spring, MD), as previously described. Two to four representative cores were selected for机构 arraying to maximize informative cores based on characteristic morphology without prior knowledge of immunohistologic staining results. Sections of 4 to 5 μm were cut from TMAs, placed on glass slides, and baked for 1 hour at 60°C. Immunohistochemistry for LMO2 protein was performed in one laboratory, and staining in greater than 30% of lymphoma cells was assigned a

**Table 1. Patient and Disease Characteristics**

<table>
<thead>
<tr>
<th>Variable</th>
<th>CHOP-Like Regimen (n = 263)</th>
<th>R-CHOP Regimen (n = 80)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. of LMO2-Positive Patients (n = 140)</td>
<td>No. of LMO2-Negative Patients (n = 123)</td>
</tr>
<tr>
<td>Mean age, years</td>
<td>63.4</td>
<td>63.0</td>
</tr>
<tr>
<td>Stage</td>
<td></td>
<td></td>
</tr>
<tr>
<td>I-II</td>
<td>68</td>
<td>60</td>
</tr>
<tr>
<td>III-IV</td>
<td>72</td>
<td>63</td>
</tr>
<tr>
<td>ECOG performance status</td>
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<td></td>
</tr>
<tr>
<td>0-1</td>
<td>116</td>
<td>88</td>
</tr>
<tr>
<td>2 or more</td>
<td>24</td>
<td>35</td>
</tr>
<tr>
<td>Lactate dehydrogenase</td>
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<td></td>
</tr>
<tr>
<td>Normal</td>
<td>74</td>
<td>55</td>
</tr>
<tr>
<td>&gt; Normal</td>
<td>66</td>
<td>68</td>
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<tr>
<td>No. of extranodal sites</td>
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<tr>
<td>&gt; 1</td>
<td>31</td>
<td>34</td>
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<tr>
<td>0-2</td>
<td>80</td>
<td>71</td>
</tr>
<tr>
<td>3-5</td>
<td>55</td>
<td>50</td>
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</tbody>
</table>

Abbreviations: CHOP, cyclophosphamide, vincristine, doxorubicin, and prednisone; R-CHOP, rituximab plus cyclophosphamide, vincristine, doxorubicin, and prednisone; NS, not significant; ECOG, Eastern Cooperative Oncology Group; IPI, International Prognostic Index.

*P values were obtained using Student’s t test for age and Pearson’s χ² test with Yates continuity correction for all other variables; values of P < .05 are considered statistically significant.

**Abbreviations:**
- CHOP: cyclophosphamide, vincristine, doxorubicin, and prednisone
- R-CHOP: rituximab plus cyclophosphamide, vincristine, doxorubicin, and prednisone
- NS: not significant
- ECOG: Eastern Cooperative Oncology Group
- IPI: International Prognostic Index

*IPH scores were available for 256 of 263 CHOP patients and all 80 R-CHOP patients.
Fig 1. LMO2 protein expression correlates with overall survival (OS) and progression-free survival (PFS) in patients with diffuse large B-cell lymphoma (DLBCL) treated with anthracycline-based chemotherapy. Kaplan-Meier curves of (A) OS and (B) PFS in 263 patients with DLBCL show that LMO2 protein expression correlates with longer OS \((P = .018)\) and PFS \((P = .010)\); Kaplan-Meier curves of (C) OS and (D) PFS in 151 patients with DLBCL with low clinical risk (International Prognostic Index [IPI] score, 0 to 2) grouped on the basis of LMO2 protein expression show that LMO2 protein expression correlates with longer OS \((P = .041)\) and PFS \((P = .041)\). Pos, positive; Neg, negative.

Table 2. Multivariate Analysis of LMO2 Protein Expression With OS and PFS As Dependent Variables in DLBCL Patients Treated With Anthracycline-Based Chemotherapy and R-CHOP

<table>
<thead>
<tr>
<th>Variable</th>
<th>CHOP-Like Regimen</th>
<th>R-CHOP Regimen</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OS</td>
<td>P</td>
</tr>
<tr>
<td>IPI</td>
<td>3.61</td>
<td>.001</td>
</tr>
<tr>
<td>LMO2</td>
<td>-2.21</td>
<td>.027</td>
</tr>
</tbody>
</table>

Abbreviations: OS, overall survival; PFS, progression-free survival; DLBCL, diffuse large B-cell lymphoma; CHOP, cyclophosphamide, vincristine, doxorubicin, and prednisone; R-CHOP, rituximab plus cyclophosphamide, vincristine, doxorubicin, and prednisone; IPI, International Prognostic Index.
positive score based on our and other prior studies of immunohistologic prognostic markers in DLBCL.\(^7\,\text{,}\,16-18\) LMO2 staining showed a robust and primarily nuclear signal, and staining intensity did not vary among normal and neoplastic lymphoid cells. The distinction between positive and negative specimens was relatively straightforward.\(^7\) Two hematopathologists (Y.N. and D.G.) independently scored the TMAs of 263 CHOP-treated patients with a concordance rate of 96%. Discrepancies were resolved over a double-headed microscope. Two hematopathologists (Y.N. and P.F.) independently scored the TMA of 80 R-CHOP–treated patients with a concordance rate of 100%.

**Statistical Analysis**

OS was defined as the time interval between the date of diagnoses and the date of death or last follow-up. PFS was defined as the time interval between the date of initial diagnosis and the date of disease progression or death from any cause, whichever came first, or date of last follow-up evaluation. Survival curves were estimated using the product-limit method of Kaplan-Meier and

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**Fig 2.** LMO2 protein expression correlates with overall survival (OS) and progression-free survival (PFS) in diffuse large B-cell lymphoma (DLBCL) patients treated with rituximab plus cyclophosphamide, vincristine, doxorubicin, and prednisone (R-CHOP). Kaplan-Meier curves of (A) OS and (B) PFS in 80 DLBCL patients treated with R-CHOP show that LMO2 protein expression correlates with longer OS \((P = .007)\) and PFS \((P = .018)\); Kaplan-Meier curves of (C) OS and (D) PFS in 49 patients with DLBCL of low clinical risk (International Prognostic Index [IPI] score, 0 to 2) grouped on the basis of LMO2 protein expression show that LMO2 protein expression correlates with longer OS \((P = .041)\) and PFS \((P = .037)\). Pos, positive; Neg, negative.
were comparing using the log-rank test. Multivariate regression analysis according to the Cox proportional hazards regression model, with OS or PFS as the dependent variable, was used to adjust for the effect of immunohisto logic staining and IPI. The t test or Pearson's χ² test with Yates continuity correction, as indicated, was used to compare the clinical characteristics between LMO2-positive and LMO2-negative patient groups. P < .05 was considered significant.

### RESULTS

#### Patient Characteristics

For analyses of the prognostic impact of LMO2 protein expression in patients treated with anthracycline-based regimens, 263 informative DLBCL patients whose ages ranged from 18 to 93 years (median age, 66 years) were studied. The follow-up period ranged from 5 days to 237 months (median, 46 months), and 161 patients (61%) had died. For analyses of the prognostic impact of LMO2 protein expression in patients treated with R-CHOP, 80 informative DLBCL patients whose ages ranged from 20 to 82 years (median, 58 years) were studied. The follow-up period for R-CHOP–treated patients ranged from 1 to 71 months (median, 54 months), and 24 patients (30%) had died. Patient and disease characteristics for both cohorts of patients, including the five clinical parameters that comprise the IPI, are listed in Table 1.

#### Immunohistologic Findings

Staining for LMO2 protein was present in 140 (53%) of 263 patients treated with CHOP-like regimens and in 44 (55%) of 80 patients treated with R-CHOP. The relationships between the expression of LMO2 protein and clinical characteristics are listed in Table 1. LMO2-positive and -negative patients treated with CHOP-like regimens differed significantly in performance status, whereas LMO2-positive and -negative patients treated with R-CHOP differed significantly in the number of extranodal sites (Table 1).

#### Outcome According to LMO2 Protein Expression in DLBCL Patients Treated With Anthracycline-Based Chemotherapy

The relationships between LMO2 protein expression and patient clinical outcomes were examined (Fig 1). The median OS and PFS times for patients in the R-CHOP group were not yet reached. By the log-rank test, LMO2 protein expression was significantly correlated with both improved OS (P = .007) and PFS (P = .030; Figs 2A and 2B). In a multivariate Cox regression analysis that included IPI scores and LMO2 protein expression with OS and PFS as the dependent variables, LMO2 protein expression remained a significant predictor of both OS (P = .009) and PFS (P = .028; Table 2). LMO2 protein expression correlated with a longer 4-year OS rate when compared with patients who lacked LMO2 protein expression (82% v 56%, respectively; P = .030). Similarly, the 4-year PFS rate was significantly longer in patients expressing the LMO2 protein compared with those who lacked its expression (72% v 47%, respectively; P = .010). To examine whether the prognostic significance of LMO2 expression in R-CHOP–treated patients is also independent of the IPI, we performed a multivariate Cox regression analysis that included IPI scores and LMO2 with OS or PFS as the dependent variables. LMO2 expression was an IPI-independent prognostic marker for both OS and PFS, whereas IPI did not reach independent significance in this multivariate analysis (Table 2). Analysis of OS and PFS in the subgroup with low IPI scores among patients treated with R-CHOP demonstrated that patients with LMO2-positive tumors had significantly better OS (P = .041) and PFS (P = .037) compared with patients with LMO2-negative tumors (Figs 2C and 2D). A similar trend was observed in patients with high IPI scores; however, the difference in OS and PFS did not reach statistical significance, probably because of the small number of patients with a high IPI score.

#### Comparison of LMO2 Expression With Other Immunohistologic Markers

Previously, Hans et al18 demonstrated that an immunohistologic algorithm based on the expression of CD10, BCL6, and MUM1/IRF4 proteins can be used to predict survival in DLBCL patients treated with CHOP-like regimens without addition of rituximab. Therefore, to compare the predictive power of LMO2 protein expression with the
who were classifiable into germinal center (GC) and non-GC subtypes based on the immunohistologic (IHC) algorithm using CD10, BCL6, and MUM1/IRF4 staining.

There was also no significant association between patient outcome and GC and non-GC subgroups of DLBCL classified by the immunohistologic algorithm according to the CD10, BCL6, and MUM1/IRF4 expression. CD10 and MUM1/IRF4 proteins and patient outcome (Table 3). But there was no significant correlation between the expression of both LMO2 and BCL6 proteins and patient outcome (Table 3).

Expression of BCL6 protein correlated with a superior OS (P = .007), but there was no significant correlation between the expression of CD10 and MUM1/IRF4 proteins and patient outcome (Table 3).

In addition, we examined whether the combined expression of LMO2 and BCL6 proteins correlated with an improved patient outcome. Kaplan-Meier curves of (A) OS and (B) PFS in 187 patients treated with cyclophosphamide, vincristine, doxorubicin, and prednisone (CHOP) – like regimens according to the expression of both LMO2 and BCL6 proteins are shown (BCL6 staining was available in 252 of 263 patients). The overall log-rank test for the three curves had a P = .194. Patients with expression of either LMO2 or BCL6 (but not both) have a significantly better OS (P = .007) and PFS (P = .001) compared with patients who do not express both markers. Patients with expression of both LMO2 and BCL6 have significantly better OS (P = .001) and PFS (P < .001) compared with patients who do not express both markers. Pos, positive; Neg, negative.

Fig 3. The expression of LMO2 and BCL6 proteins correlates with longer overall survival (OS) and progression-free survival (PFS) in patients with diffuse large B-cell lymphoma. Kaplan-Meier curves of (A) OS and (B) PFS in 187 patients treated with cyclophosphamide, vincristine, doxorubicin, and prednisone (CHOP) – like regimens who were classifiable into germinal center (GC) and non-GC subtypes based on the immunohistologic (IHC) algorithm using CD10, BCL6, and MUM1/IRF4 staining show no significant correlation with patient outcome (OS, P = .194; PFS, P = .455). Kaplan-Meier curves of (C) OS and (D) PFS in 252 patients treated with CHOP-like regimens according to the expression of both LMO2 and BCL6 proteins are shown (BCL6 staining was available in 252 of 263 patients). The overall log-rank test for the three curves had a P = .001. Patients with expression of either LMO2 or BCL6 (but not both) have a significantly better OS (P = .007) and PFS (P = .001) compared with patients who do not express both markers. Patients with expression of both LMO2 and BCL6 have significantly better OS (P < .001) and PFS (P < .001) compared with patients who do not express both markers. Pos, positive; Neg, negative.
outcome. The overall log-rank test for the three curves had a $P = .001$ (Figs 3B and 3C). Patients who expressed both LMO2 and BCL6 proteins had a significantly better OS ($P < .001$) and PFS ($P < .001$) compared with patients who lacked the expression of both markers. Furthermore, the expression of either LMO2 or BCL6 was also found to confer a superior OS ($P = .007$) and PFS ($P = .001$) compared with the lack of expression of both proteins.

In R-CHOP–treated patients, neither BCL6 protein expression nor GC B-cell phenotype based on the immunohistologic algorithm of Hans et al.$^{18}$ was significantly correlated with OS or PFS ($P > .05$). Thus, in our cohort of R-CHOP–treated patients, LMO2 protein expression emerged as the only predictive marker among patients tested in this study.

**Discussion**

The GC provides a microenvironment in which naïve B cells proliferate and diversify their antigen receptors to produce high-affinity antibodies.$^{20-23}$ It is well recognized that dysregulation of these steps of normal B-cell ontogeny plays an important role in the genesis of GC-derived B-cell lymphomas.$^{24}$ DLBCL with a gene expression profile similar to that of GC B cells exhibits a more favorable clinical outcome.$^{1}$ Therefore, immunohistologic markers associated with a GC phenotype are also likely to be associated with a better clinical outcome in patients with DLBCL. Indeed, this provided the basis for an immunohistologic model based on the expression of CD10, BCL6, and MUM1/IRF4 proteins.$^{18}$ Here, we investigated the impact on DLBCL prognosis of another marker of GC lymphocytes. We show that LMO2 protein expression has prognostic significance in DLBCL, as was previously noted for LMO2 mRNA expression.$^{6}$ Furthermore, we confirmed the prognostic value of LMO2 protein expression in an independent cohort of patients with DLBCL treated with R-CHOP. The latter cohort of patients demonstrated that the prognostic impact of LMO2 is unaffected by the addition of rituximab to the treatment of DLBCL patients.

LMO2 was the strongest single predictor of superior outcome in DLBCL patients in a multivariate model that we had constructed based on the expression of six genes.$^{8}$ The LMO2 gene encodes a transcription factor that regulates key events in erythropoiesis, angiogenesis, and embryogenesis.$^{25-28}$ Mice deficient in LMO2 die as a result of failure of yolk sac erythropoiesis, whereas chimeric mice show that LMO2 plays a role in the development of all bone marrow–derived hematopoietic lineages.$^{29}$ This gene is of relevance in lymphoid and myeloid leukemias resulting from the deregulated expression of LMO2 as caused by chromosomal translocations and insertion mutations.$^{30-33}$ Subsequently, LMO2 was shown to be overexpressed in DLBCL of the GC type.$^{3}$ Using a novel monoclonal anti-LMO2 antibody, we recently confirmed that LMO2 protein is expressed in GC-derived B-cell lymphomas, normal human bone marrow hematopoietic lineages, and leukemias.$^{3}$ To date, no acquired genetic aberrations are known that account for the overexpression of LMO2 in DLBCL; in these cases, its expression is possibly a reflection of the cell of origin or may be associated with a specific function of LMO2 that is as yet unknown. Previous studies have demonstrated that different binding partners interact with LMO2 protein in multiprotein transcriptional complexes.$^{25-28}$ Therefore, it is likely that, in GC B cells, the LMO2 protein interacts with a discrete set of transcription factors to exert specific effects in these cells.

Protein expression studies from several institutions have explored the clinicopathologic and molecular diversity of DLBCL; however, they have yielded conflicting results.$^{5,17,18,34,35}$ Thus, validation of results in independent groups of patients and reassessment in the postrituximab era are necessary. Our findings show that LMO2 protein expression has prognostic significance in two independent cohorts of DLBCL patients treated with anthracycline-based regimens with and without rituximab. Furthermore, the predictive power of LMO2 protein expression in patients treated with CHOP-like regimens added value to the predictive power of BCL6 protein expression and was superior to the immunohistologic algorithm based on the expression of CD10, BCL6, and MUM1/IRF4 proteins previously shown to predict survival in DLBCL patients treated in the prerituximab era. The expression of the LMO2 protein, unlike the BCL6 protein, retained its predictive power in patients treated with R-CHOP. Whether the lack of BCL6 protein expression to predict outcome in patients treated with R-CHOP was a result of the small numbers of patients analyzed in this study or a result of treatment with rituximab needs further evaluation in additional large studies of R-CHOP–treated patients.

In conclusion, we show that, similar to its mRNA expression, LMO2 protein expression is significantly correlated in univariate and multivariate analyses with improved OS and PFS in DLBCL patients treated with anthracycline-based chemotherapy with and without rituximab. Multivariate analyses show that LMO2 protein expression is an IPI-independent predictor of OS and PFS. Further confirmation of these observations in independent cohorts of unselected DLBCL patients treated with R-CHOP is needed before this marker may be applied in routine clinical practice.

**Authors’ Disclosures of Potential Conflicts of Interest**

The author(s) indicated no potential conflicts of interest.

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References


