Nonimmunoglobulin (non-Ig)/BCL6 gene fusion in diffuse large B-cell lymphoma results in worse prognosis than Ig/BCL6

Takashi Akasaka, Chiyoko Ueda, Masayuki Kurata, Hiroshi Akasaka, Hirohiko Yamabe, Takashi Uchiyama, and Hitoshi Ohno

Introduction

Diffuse large B-cell lymphoma (DLBCL) constitutes a heterogeneous spectrum of non-Hodgkin’s lymphoma (NHL) with diverse molecular genetic abnormalities. The 3 most common genetic lesions associated with chromosomal translocations are rearrangements of cMYC, BCL2, and BCL6 proto-oncogenes resulting from t(8;14)(q24;q32) (translocation of chromosome 8, long arm, region 2, band 4, to chromosome 14, long arm, region 3, band 2); t(14;18)(q32;q21); and 3q27 abnormalities, respectively. Many studies have focused upon whether these molecular lesions are associated with particular clinical features and whether they can predict the response and outcome for the treatment. The BCL6 gene was first identified at the breakpoints on 3q27 involved in t(3;14)(q27;q32) and t(3;22)(q27;q11), and rearrangements of the gene have been observed in up to 35.5% of patients with DLBCL. An earlier study showed that the BCL6 rearrangement more frequently occurs in extranodal DLBCL than in node-based disease and is correlated with a favorable clinical outcome, although later studies failed to confirm these observations.

In contrast to other B-cell NHL, (B-NHL)-associated translocations, the BCL6 translocation is unique in that it can involve not only Ig genes but also a number of non-Ig loci as partners. The molecular anatomy of the BCL6 gene rearrangements in 39 cases with diffuse large B-cell lymphoma (DLBCL) by long-distance polymerase chain reaction–based assays was determined. The results showed that Ig genes were affected in 21 cases; non-Ig genes, 15 cases; a deletion of more than a 1-kb segment, 2 cases; and a point mutation, 1 case. Comparative studies between the 21 cases with Ig gene partners and the 17 cases with non-Ig gene partners, including 2 cases with the deletion, showed that the overall survival of the latter group of patients was significantly inferior to that of the former (P = .0440), and the estimated 2-year overall survival rates were 58.3% vs 17.6% (P = .005).

Non-Ig/BCL6 fusion is a poor prognostic indicator of DLBCL, and DLBCL with BCL6 translocation could be subclassified according to the individual partner locus and/or gene. (Blood. 2000;96:2907-2909)
Table 1. Clinical features of 3 DLBCL cases with BCL6 translocation affecting the 3q26-27 locus

<table>
<thead>
<tr>
<th>Case no.</th>
<th>Sex/age</th>
<th>Stage/PS</th>
<th>Involved organs at presentation</th>
<th>LDH (IU)</th>
<th>Treatment</th>
<th>Outcome</th>
<th>Survival (d)</th>
</tr>
</thead>
<tbody>
<tr>
<td>90</td>
<td>70/M</td>
<td>III/1</td>
<td>Lymph nodes</td>
<td>735</td>
<td>CHOP, radiation</td>
<td>CR-R-PD</td>
<td>630</td>
</tr>
<tr>
<td>880</td>
<td>59/M</td>
<td>IV/1</td>
<td>Lymph nodes, spleen, bone marrow, liver</td>
<td>1950</td>
<td>LSG4*</td>
<td>PD</td>
<td>30</td>
</tr>
<tr>
<td>910</td>
<td>35/F</td>
<td>IVE/3</td>
<td>Lymph nodes, breasts, ovary, uterus</td>
<td>737</td>
<td>Mastectomy, CHOP, high-dose chemotherapy</td>
<td>PR-R-PD</td>
<td>501</td>
</tr>
</tbody>
</table>

PS indicates performance status; LDH, lactic dehydrogenase; M, male; F, female. CHOP indicates cyclophosphamide, doxorubicin, vincristine, and prednisone. CR indicates complete remission; PR, partial remission; R, relapse; and PD, progressive disease. Details of the clinical features of case no. 910 were described previously.27

*LSG4 is the multidrug regimen proposed by the Japan Lymphoma Study Group.
Diverse partners of BCL6 translocation could affect clinical behavior of DLBCL

We recently showed that the non-Ig/BCL6 translocation results in replacement of its 5'-noncoding region with heterogeneous promoters, which are activated by a variety of stimuli including cell cycle control, changes in the physical environment, and the response to cytokines. Therefore, it is possible that non-Ig partners have influence on the pattern of BCL6 deregulation in a different fashion from Ig and thereby affect the clinical behavior of DLBCL patients carrying the corresponding BCL6 translocation. Table 1 summarizes 3 DLBCL patients with the BCL6 translocation involving the 3q26-27 locus. It is apparent that these patients had homogeneous clinical features, ie, they presented with an advanced disease, a high lactate dehydrogenase level, and a resistance to chemo-radiotherapy. This observation suggested that DLBCL with the BCL6 translocation could be subclassified according to the individual partner locus and/or gene, although the responsible gene of the 3q26-27 locus is currently unknown. Our study suggests that the non-Ig/BCL6 fusion is a poor prognostic indicator of DLBCL, but additional studies of larger cohorts of uniformly treated patients, performed in a prospective fashion, will be required to confirm our findings.

References

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