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A genetic predictive model for precision treatment of diffuse large B-cell lymphoma with early progression

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Abstract

Background: Early progression after the first-line R-CHOP treatment leads to a very dismal outcome and necessitates alternative treatment for patients with diffuse large B-cell lymphoma (DLBCL). This study aimed to develop a genetic predictive model for early progression and evaluate its potential in advancing alternative treatment.

Methods: Thirty-two hotspot driver genes were examined in 145 DLBCL patients and 5 DLBCL cell lines using next-generation sequencing. The association of clinical features, cell-of-origin, double expression, positive p53 protein, and gene alterations with early progression was analyzed, and the genetic predictive model was developed based on the related independent variables and assessed by the area under receiver operating characteristic. The potential of novel treatment based on the modeling was investigated in in-vitro DLBCL cell lines and in vivo xenograft mouse models.

Results: The frequency of *CD79B* (42.86% vs 9.38%, $p = 0.000$) and *PIM1* mutations (38.78% vs 17.71%, $p = 0.005$) showed a significant increase in patients with early progression. *CD79B* and *PIM1* mutations were associated with complex genetic events, double expression, non-GCB subtype, advance stage and unfavorable prognosis. A powerful genetic predictive model (AUROC = 0.771, 95% CI: 0.689–0.853) incorporating lactate dehydrogenase levels (OR = 2.990, $p = 0.018$), *CD79B* mutations (OR = 5.970, $p = 0.001$), and *PIM1* mutations (OR = 3.021, $p = 0.026$) was created and verified in the other cohort. This modeling for early progression outperformed the prediction accuracy of conventional International Prognostic Index, and new molecular subtypes of MCD and Cluster 5. *CD79B* and *PIM1* mutations indicated a better response to inhibitors of BTK (ibrutinib) and pan-PIM kinase (AZD 1208) through repressing activated oncogenic signaling. Since the two inhibitors failed to decrease BCL2 level, BCL2 inhibitor (venetoclax) was added and demonstrated to enhance their apoptosis-inducing activity in mutant cells with double expression.

Conclusions: The genetic predictive model provides a robust tool to identify early progression and determine precision treatment. These findings warrant the development of optimal alternative treatment in clinical trials.

Keywords: Diffuse large B-cell lymphoma, Early progression, CD79B, PIM1

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