IVYSPRING INTERNATIONAL PUBLISHER

International Journal of Medical Sciences

2019; 16(4): 556-566. doi: 10.7150/ijms.27610

Research Paper

Clinical Significance of *BCL2*, C-*MYC*, and *BCL6* Genetic Abnormalities, Epstein-Barr Virus Infection, CD5 Protein Expression, Germinal Center B Cell/Non-Germinal Center B-Cell Subtypes, Co-expression of MYC/BCL2 Proteins and Co-expression of MYC/BCL2/BCL6 Proteins in Diffuse Large B-Cell Lymphoma: A Clinical and Pathological Correlation Study of 120 Patients

Choo-Yuen Ting[1]✉, Kian-Meng Chang[1], Jew-Win Kuan[3], Jameela Sathar[1,2], Lee-Ping Chew[2,4], Oy-Leng Jacqueline Wong[5], Yusri Yusuf[5], Lily Wong[6], Ahmad Toha Samsudin[7], Mohd Nurjaya Bin Mohd Pana[7], , Suk-Kam Lee[8], Navarasi S. Raja Gopal[8], Rita Puri[1], Tee-Chuan Ong[1], Samsol Kamal Bahari[1], Ai-Sim Goh[9], Ching- Soon Teoh[9]

1. Department of Hematology, Hospital Ampang, Ministry of Health Malaysia.
2. Clinical Research Centre, National Institutes of Health, Ministry of Health Malaysia.
3. Department of Medicine, Faculty of Medicine and Health Sciences, University Malaysia Sarawak.
4. Department of Medicine, Hospital Umum Sarawak, Ministry of Health Malaysia.
5. Department of Pathology, Hospital Umum Sarawak, Ministry of Health Malaysia
6. Department of Medicine, Queen Elizabeth Hospital, Ministry of Health Malaysia.
7. Department of Pathology, Queen Elizabeth Hospital, Ministry of Health Malaysia.
8. Department of Pathology, Hospital Pulau Pinang, Ministry of Health Malaysia.
9. Department of Medicine, Hospital Pulau Pinang, Ministry of Health Malaysia.

✉ Corresponding author: Email: chooyuen@moh.gov.my; Tel: +603 26155555, extension: 6886

Received: 2018.06.02; Accepted: 2018.07.29; Published: 2019.04.20

Abstract

Background: Clinical significance of germinal center B-cell (GCB) and non-GCB sub-categorization, expression of MYC, BCL2, BCL6, CD5 proteins and Epstein Barr virus encoded RNA (EBER) positivity in diffuse large B-cell lymphoma (DLBCL) remain controversial. Could these biomarkers accurately identify high risk DLBCL patients? Are MYC, BCL2 and BCL6 proteins expression feasible as baseline testing to predict *c-Myc*, *BCL2* or *BCL6* gene rearrangements?

Aims: To investigate prognostic values of GCB/non-GCB sub-categorization, Double Protein Expression Lymphoma (DPL), Triple Protein Expression Lymphoma (TPL), positivity of CD5 protein and EBER in patients with DLBCL disease. To evaluate correlation between *BCL2* , *c-Myc* and *BCL6* gene rearrangements with BCL2, MYC and BCL6 proteins expression.

Methods: Diagnostic tissue samples of 120 DLBCL patients between January 2012 to December 2013 from four major hospitals in Malaysia were selected. Samples were subjected to immunohistochemical staining, fluorescent in-situ hybridization (FISH) testing, and central pathological review. Pathological data were correlated with clinical characteristics and treatment outcome.

Results: A total of 120 cases were analysed. Mean age of diagnosis was 54.1 years ± 14.6, 64 were males, 56 were females, mean follow up period was 25 months (ranged from 1 to 36 months). Of the 120 cases, 74.2% were non-GCB whereas 25.8% were GCB, 6.7% were EBER positive, 6.7% expressed CD5 protein, 13.3% were DPL and 40% were TPL. The prevalence of c-*Myc*, *BCL2*, *BCL6* gene rearrangements were 5.8%, 5.8%, and 14.2%, respectively; and 1.6% were Double Hit Lymphoma (DHL). EBER positivity, DPL, TPL, c-*Myc* gene rearrangement, *BCL2* gene rearrangement, extra copies of *BCL2* gene and *BCL6* gene rearrangement were associated with shorter median overall survival (P<0.05). IPI score was the significant determinants of median overall survival in DPL and TPL (P<0.05). CD5 protein expression and GCB/non-GCB sub-categorization did not affect treatment outcome (P>0.05). Overall, *c-Myc*, *BCL2* and *BCL6* gene rearrangements showed weak correlation with expression of MYC, BCL2 and BCL6 proteins (P>0.05). Fluorescent *in situ* hybridization is the preferred technique for prediction of treatment outcome in DLBCL patients.

Conclusion: *c-Myc*, *BCL2*, and *BCL6* gene rearrangements, EBER expression, DHL, TPL and IPI score are reliable risk stratification tools. MYC, BCL2 and BCL6 proteins expression are not applicable as baseline biomarkers to predict *c-Myc*, *BCL2*, and *BCL6* gene rearrangements.

Key words: diffuse large B-cell lymphoma, *c-Myc, BCL2* and *BCL6* gene rearrangements, diffuse large B-cell lymphoma with CD5 protein expression, diffuse large B-cell lymphoma with positive EBER expression, non-germinal center B-cell subtype, Asia