

## Leukaemia Section

### Mini Review

# Germinal center B-cell-like diffuse Large B-cell Lymphoma (GCB) DLBCL

Luis Miguel Juárez Salcedo, Samir Dalia

Principe de Asturias University Hospital, Madrid, Spain; Dr.luisjuarez@gmail.com (LMJC);  
Oncology and Hematology, Mercy Clinic Joplin, Joplin, MO, USA; sdalia@gmail.com (SD)

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## Abstract

Review on Germinal center B-cell-like diffuse Large B-cell Lymphoma (GCB) DLBCL, with data on clinics, and genes.

### KEYWORDS

Diffuse Large B-cell Lymphoma, Germinal center

## Identity

### Other names

(GCB) DLBCL

## Clinics and pathology

### Disease

Diffuse large B-cell lymphoma (DLBCL) accounts for approximately 30% to 40% of all non-Hodgkin lymphoma (NHL) cases. (Sujobert P, et al., 2016) Gene expression profiling (GEP) studies have identified  $\geq 2$  distinct molecular subtypes, termed germinal center B-cell (GCB) and activated B-cell (ABC), which are believed to represent lymphomas arising from different stages of lymphoid differentiation. (Alizadeh AA, et al., 2000; Rosenwald A, et al., 2002) The GCB DLBCL represent approximately 50% of DLBCL. (Karmali R, et al., 2017).

GCB DLBCLs are thought to arise from normal germinal center B cells and show features that are consistent with germinal center B cell derivation. (Alizadeh AA, et al., 2000; Rosenwald A, et al., 2002) These harbor oncogenetic hits typical such as t(14:18) translocation, the mutations of epigenetic modifiers (EZH2, KMT2D) or mutations in the genes encoding the S1PR2 receptor or its signal transduction protein GNA13. (Sehn L, et al., 2015)

This subtype has a cure rate of about 70 to 80% with currently available immune chemotherapy regimens like R-CHOP, R-DHAP, R-ICE or DA-EPOCH-R. (Thieblemont C, et al., 2011; Delarue R, et al., 2013; Cunningham D, et al., 2013)

### Etiology

GCB DLBCLs are believed to derived from lymphoid cells residing in the germinal center and therefore express genes normally detected in germinal center B cells, such as CD10, LMO2 and the transcriptional repressor Bcl6. (Béguelin W, et al., 2013; Sujobert P, et al., 2016; Lenz G et al. 2008) Approximately 30% to 40% of GCB DLBCLs have a t(14:18) translocation, 30% have REL amplifications, 20% have mutations of the histone methyltransferase EZH2 and 10% have a deletion of the PTEN, all of which are virtually never seen in ABC DLBCL. (Pfeifer M, et al., 2013; Morin RD, et al., 2011; Pasqualucci L, et al., 2011)

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### Epidemiology

The median age is 70 years old (occur in children and adults). The incidence is between 25-30% of adult NHL's (western countries), with slight male predominance.

### Pathology

GC-DLBCL is described as CD-10 positive, Bcl-6 positive and MUM-1 negative. (Sujobert P, et al., 2016)

### Treatment

It is the most curable subtype, with a 5-year overall survival (OS) rate of nearly 75%. The GC subtype has a cure rate of about 70 to 80% with currently available therapies. The infusional regimen of dose-adjusted etoposide, cyclophosphamide, doxorubicin, vincristine, prednisone, and rituximab (DA-EPOCH-R) or Hyper CVAD-R, have yield promising results especially in the GC- DLBCL subtype. (Petrich AM, et al., 2014) Similarly, R-CHOP, R-DHAP and R-ICE could be valuable options of treatment. (Delarue R, et al., 2013; Cunningham D, et al., 2013). In the new era of targeted therapy, it could soon benefit from inhibitors of the EZH2, Bcl-2 and Bcl-6 oncoproteins.

### Genetics

GC-DLBCL largely express gene products, such as Bcl-6, GCSAM (HGAL) and LMO2 that define normal germinal center B cells within the germinal center light zone. (Alizadeh AA, et al., 2000; Rosenwald A, et al., 2002) Malignant GC-DLBCL clones continue to undergo somatic hypermutation of their variable immunoglobulin heavy chain gene and have often switched IgH classes that are mediated by AID, an enzyme that is characteristically expressed at high levels in germinal center B cells. (Lossos IS, et al., 2000) The GC-DLBCL subtype is characterized by low level of NF- $\kappa$ B activation and its survival is not dependent on NF- $\kappa$ B. (Davis RE, et al., 2001; Dal Porto JM, et al., 2004)

Translocation of BCL2 and/or MYC genes, are commonly observed in GC-DLBCL. These translocation lead to constitutive activation of c-MYC and the anti-apoptotic Bcl-2 protein and to a malignant transformation by preventing terminal differentiation or blocking apoptosis. (Shaffer 3rd AL, et al., 2012) 20% have gain of function mutations of the histone methyltransferase EZH2, which is a master regulator of the GC-DLBCL phenotype and cooperates, partly with Bcl-2 and BCL6 to mediate lymphomagenesis. Is also characterized by downregulation of the phosphatase and tensin homologue (PTEN) and concomitant

upregulation of phosphatidylinositol-3-kinase (PI3K) signaling pathway. (Sehn L, et al., 2015)

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