ORIGINAL ARTICLE

Germinal-Center B-Cell-Like (GCB) DLBCL Versus Activated B-Cell-Like (ABC) DLBCL: Biology and Treatment Approach

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ABSTRACT

Diffuse large B-cell lymphoma (DLBCL) is the most common type of malignant lymphoma characterized by the expression of CD20 that led to the development of type I and type II anti-CD20 which in combination with traditional chemotherapy played a major role in disease control and prolongation of overall survival. Primary mediastinal B-cell lymphoma, germinal center B-cell like and activated B-cell lymphoma are the major subtype of DLBCL, however, every subtype respond to immune-chemotherapy in a different way with different survival periods as well. The former finding provoked scientists to reveal the genes and pathways implicated in the pathogenesis in order to lead the diagnosis with both immune-histochemistry and gene profile as well.

Key words: germinal center, activated B-cell, diffuse large B-cell lymphoma, biology, treatment.

INTRODUCTION

Diffuse large B-cell lymphoma (DLBCL) is the most common subtype of malignant lymphoma which characterized by heterogeneity with respect to clinical presentation, morphology, and molecular pathogenesis (1). The emerging of gene profiling demonstrated several subtypes of DLBCL depending on gene expression (2). According to their gene expression profiles these subtypes were classified into: germinal-center B-cell-like (GCB) DLBCL, activated B-cell-like (ABC) DLBCL, and primary mediastinal B-cell lymphoma (PMBL). Those subtypes differ in both gene expression profiles and the oncogenic pathways they use; therefore, they show differences in overall survival following standard treatment (3, 4). Most patients with GCB DLBCL respond well to a combination approach of the anti-CD20 antibody rituximab and chemotherapy, however, more than 50% of ABC DLBCL patients fail to have the same response (4) that is why we need to know more about the precise pathogenesis of those patients in order to improve both understanding and treatment approach.

Molecular pathogenesis of GCB DLBCL

GCB DLBCLs originate from germinal center B-cells (5). These cells along with the normal germinal center B-cells share the expression of many genes especially BCL-6 and LMO2 (6). Another evidence for their germinal-center derivation is provided by the fact that GCB DLBCLs frequently show ongoing somatic hypermutation of their variable immunoglobulin heavy chain gene that is mediated by AID, an enzyme that is characteristically expressed at high levels in germinal-center B-cells (7). In 45% of GCB DLBCL case, at (14; 18) translocation juxtaposing the BCL2 (the anti-apoptotic oncogene) and the IgH locus is detectable leading to constitutive activation of the BCL2 protein. However, this abnormality is not detectable in ABC DLBCL cases (5). Phosphatase and tension homologue (PTEN) is found to be deregulated. The phosphatidylinositol 3-kinase (PI3K) signaling cascade is initiated with the phosphorylation of phosphatidylinositol 4, 5 bisphosphate (PIP2) to phosphatidylinositol 3, 4, 5 trisphosphate (PIP3) leading to cell growth and survival (8).

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The conversion of PIP2 into PIP3 is highly regulated by PTEN which is able in turn to reduce PIP3 into PIP2, therefore, PTEN loss leads to PIP3 accumulation with a subsequent activation of AKT and mTOR leading to a further cell growth (9). A heterozygous or homozygous deletion of PTEN is found in about 15% of GCB DLBCL cases which indicates an important role of PTEN PI3K pathway in the pathogenesis process. MDM2 a negative regulator of the tumor suppressor gene P53 is found to be amplified as well as deletions in other suppressor genes such as TP73 and ING1 (10).

Molecular Pathogenesis of ABC DLBCL

According to the gene profiles of ABC DLBCL studies suggest that this subtype is Derived from B cells that are in the process of differentiating into plasma cells (Figure 2) (5) and most genes characteristically expressed by normal germinal-center B-cells are down-regulated in ABC DLBCL. However, these are an up-regulation of many genes normally expressed in plasma cells(11).

The main manifestation of ABC DLBCL is the complete blockade of final plasma cell differentiation (12). More than 25% of ABC DLBCL samples harbor inactivating mutations of PRDM1 that encodes BLIMP1 (12) which promotes plasmacytic differentiation by terminating the expression of most mature B-cell differentiation genes (13). BLIMP1 expression is also depressed by the ETS transcription factors and mainly SPID which is found to be amplified in 26% of samples (14).

Lam et al as well as Ruland et al showed that the NF-kB family of transcription factors is implicated in the pathogenesis of ABC DLBCL. This family has several members such as: RelA, RelB, c-Rel, NF-kB1 and NF-kB2 which are able to form both homodimers and heterodimers that are kept inactive by binding to inhibitory proteins of the IkB family. Upon NF-kB activation by different stimuli, IkBs are degraded by IkB kinases leading to NF-KB phosphorylation and transactivation of the target genes (15). Figure 1 illustrates the pathogenesis of GCB and ABC DLBCL.

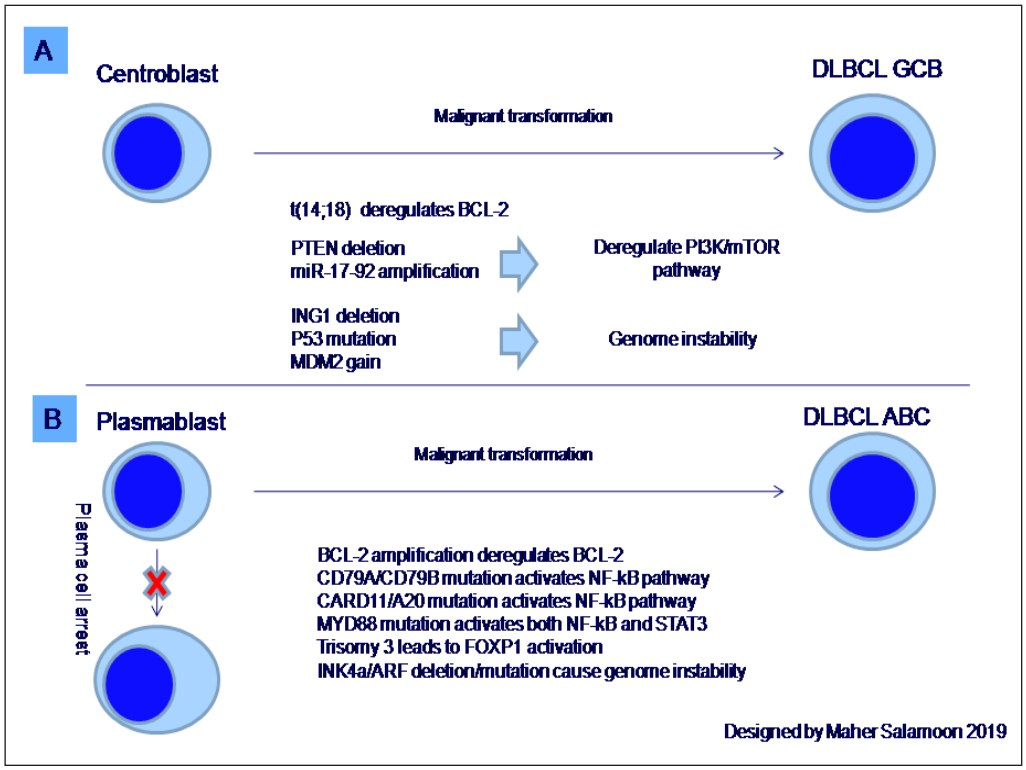

Figure 1. Pathogenesis of Both GCB DLBCL and ABC DLBCL

(A) GCB DLBCL is derived from a centroblast residing in the germinal center. T(14;18) deregulates BCL-2. PTEN deletion along with miR-17-92 amplification leads to deregulation of PI3K/mTOR pathway. INF1 deletion, P53 and MDM2 gain cause genomic instability.

(B) ABC DLBCL is derived from a plasmablast that lost the ability to differentiate into plasma cell. The whole mark of pathogenesis is the deregulation of the anti-apoptotic oncogene BCL-2 and the activation of NF-kB pathway.

Primary Mediastinal B-Cell Lymphoma (PMBL)

PMBL affect young women with mainly mediastinal presentation. It was considered an isolated entity depending on its special morphologic and clinical manifestations. Because of the morphological similarities between PMBL and classical sclerotic type Hodgkin's disease cHD, it became so hard to put the final diagnosis without a gene profile (5).

PMBL and cHD share around 30% of over expressed genes and they also use the same oncogenic pathway NF-kB (2). However, roughly 50% of PMBL samples harbor an amplification of the chromosomal band 9p24 which can provoke an oncogenic pathway through Jak-2 and consequently STAT transcription factors. Furthermore, SOCS1 a repressor of Jak-2 is found to be deleted in PMBL leaving Jak-2 activity without a real control, the thing that clarifies the potential role of the former pathway in PMBL pathogenesis. The histone demethylase JMJD2C seems to cooperate with JAK2 to modify the PMBL epigenome and thereby promotes survival in PMBL cell lines (17). Ligands of PD receptors on T-cell surface (PD-L1, PD-L2) are up regulated as well which means impairing T-cell and PMBL cells interaction, leading to a very faint cell mediated immunity (5).

Response to treatment

Following standard Anthracyclin-containing regimens, DLBCL subtypes respond in different ways and they have different rates of overall survival as well (5). Even with the introduction of type I anti-CD20 (Rituximab), GCB DLBCL patients are still doing better than those with ABC DLBCL (1) , however, both subtypes get benefit from immune-chemotherapy compared with the standard chemo-alone. Routinely, the International Prognostic Index (IPI) is the criteria of choice used to predict survival upfront at diagnosis in DLBCL patients treated with a combination of Rituximab and Anthracycline-containing regimens(10).

In order to predict survival in a much precise way, three gene signatures were developed called: germinal center B-cell, stromal-1 and stromal-2. The germinal center B-cell has a favorable prognosis containing genes expressed in germinal center cells. In the other hand, stromal-1 and 2 reflect the non malignant cells in the background or more precisely in the microenvironment (10). Stromal-1 is considered favorable demonstrating the histocytic infiltration of the extracellular matrix, while Stromal-2 reflects the blood vessels density and it is considered unfavorable. In order to calculate the survival predictor score, a multivariate model is created for the three genes which work by dividing patients into 4 ranks in order to evaluate progression free survival at 3 years 84%, 69%, 61% and 33% while the overall survival is divided as follows: 89%, 82%, 74% and 48% (14). Another criteria developed by Lossos et al used 6 genes and divided patients into low, intermediate and high risk patients to predict survival, however, all these efforts did not distinguish between GCB and ABC DLBCL (7). Gene profiling using DNA array may help to distinguish between DLBCL and Burkitt's lymphoma the thing that cannot be carried out by conventional methods(18).

How to Classify GCB and ABC?

The international prognostic index (IPI), was confirmed as a prognostic tool to predict response rate, progression free survival and overall survival before and after the introduction of type I anti-CD20 (19). IPI divides patients into four groups (low-risk group, low-intermediate risk group, high-intermediate risk group and high risk group). After the discovery of the cell of origin, Hans et al, published an algorithm classifying DLBCL into ABC and GCB according to both cell of origin and immune-histochemistry (20). The positive predictive value of this algorithm was 87% in GCB and 73% for the non-GCB group with 86% concordance with the gene expression profile (GEP) (20). Choi et al developed another algorithm with much better concordance with GEP reaching 93% (21). Meyer et al compared the prior two algorithms and managed to design the two modified algorithms of both Hans and Choi with concordance of 87% with GEP (22). However, the 2016 revision of WHO classification lymphoid malignancies still recommends the Hans' one (23).

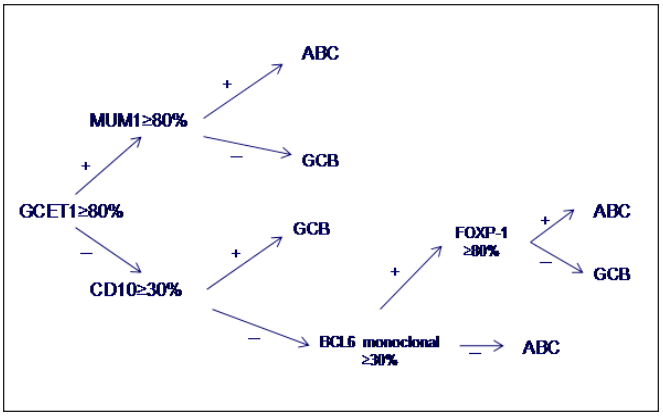

Figure 2. The New IHC algorithm using five markers with 78 out of 84 patients concordance (93%) when compared with the GEP classification. In the other hand Hans' diagram has 86% concordance with the GEP.

The immune-histochemical staining in (Hans algorithm) uses three main markers as illustrated in figure 2: [CD10, Multiple Myeloma Oncogene 1 (MUM1) and polyclonal B-cell lymphoma (BCL-6)] to classify DLBCL into GCB and non-GCB (ABS and unclassified subtypes) (20). Despite the high concordance (80%) between those IHC studies and GEP, many other studies showed conflict results, however, the majority of those previous studies used data from the pre-anti CD20 type II era (24). Only one study conducted by Haarer CF et al

showed a 70% concordance between Hans's method and GEP (25). In order to improve recognition of GC-DLBCL cases, new GC markers are employed to enrich IHC markers in the algorithm such as germinal center B-cell expressed transcript 1 (GCET1) and metastasis associated gene 3 (MTA3) (26,27). Another emerging GC related marker is the LIM domain only 2 (LIMO2) which found to be correlated with better survival (28). GCET1 along with FOXP1 are also used in the new improved algorithm, and GCET1 was found to be highly related to neoplasms related to GC origin (26) which can help distinguishing between GCB and ABC DLBCL. FOXP1 gene on the other hand is highly expressed in ABC DLBCL cases and found to be associated with inferior overall survival, however a percentage of 80% expression was needed to reach the diagnosis of ABC DLBCL as illustrated in the improved algorithm in figure 2 (29).

GCB/ABC DLBCL Treatment Approach

A study conducted by Choi et al, showed a reflection of the improved Hans algorithm on treatment results in term of overall survival (OS) and event free survival (EFS) (30). Patients treated with the standard R-CHOP classified according to Hans's algorithm VS patients treated with the same protocol classified using the new improved protocol (30), better OS of 5 years in patients with GCB compared with those of ABC, however, results showed comparable results at 10 years in which the improved algorithm was employed.

Another study compared four algorithms (Hans, modified Hans, Choi and modified Choi) role in classification and survival prediction in patients with different subtypes of DLBCL, concluded that only Choi algorithm was able to predict OS in both GCB and ABC subgroups (31) and it was also better in defining the GCB subtypes according to the OS. The UK NCRI compared R-CHOP-14 VS R-CHOP-21 in previously untreated 1080 patients with DLBCL and reported no superiority in term of overall survival and progression free survival in the 14 days schedule (32), taking into account that the cell of origin was classified according to the Hans method.

Other trial showed improvement in response and survival in elderly patients treated with Bendamustin plus Rituximab. In a phase II study, addition of Lenalidomide as maintenance after R-CHOP 21 led to an increase in progression free and overall survival (33). Ibrutinib at 560mg/d can be given with R-CHOP as front-line therapy for non-GCB DLBCL as shown in a phase Ib study, however, a phase III study comparing Ibrutinib plus R-CHOP VS CHOP alone is underway (34).

In a study conducted by Ana B-Lopez et al, showed worse progression-free survival and overall survival in patients with non-GCB as calculated using Choi, Visco-Youmg and Hans algorithm, indicating that any of these algorithms would be useful for identifying patients who require alternative therapies to R-CHOP. In the same study, MYC alterations had no impact on clinical outcome in the non-GCB subtype, however, patients of GCB with isolated MYC rearrangement had worse (PFS) and therefore they might benefit from new treatment modalities (35).

DISCUSSION

The new improved Hans algorithm has inspired more researcher to focus on new treatment approaches instead of the old standards taking into consideration the new discovered genes playing roles in ABC and GCB pathogenesis.

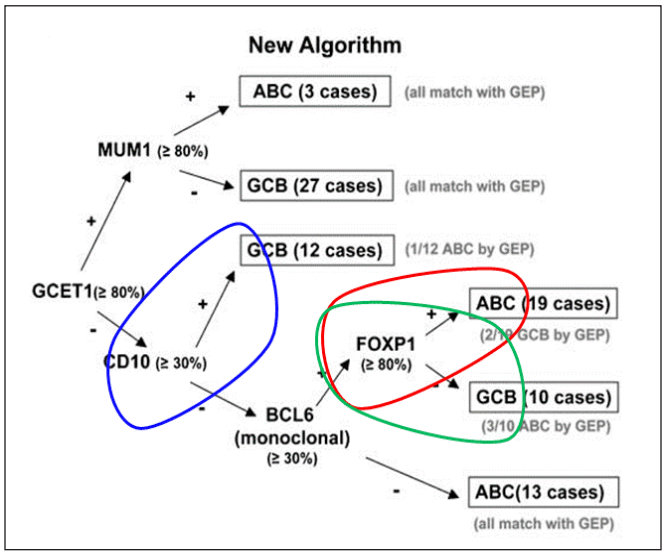

Figure 3. illustrates the improved Hans algorithm with 3 main zones (blue reflecting the way of GCB identification through CD10 positivity, red referring to ABC identification through FOXP1 positivity and green representing GCB diagnosis basing on FOXP1 negativity

Several mutated genes are found to affect the different pathogenic pathways in both GCB and ABC DLBCL reflecting the heterogeneity of these diseases. For instance, there is an association of MYD88 mutations, particularly L265P, with CD79B mutations in ABC, whereas other MYD88 mutations take place in both DLBCL subtypes (36). More interestingly, mutations in the PI3K/AKT/m-TOR pathway were more frequent in GCB DLBCL, and this finding is consistent with signaling activation of PI3K which is frequently associated with loss of PTEN (37).

If we analyze figure 3, we should concentrate on 3 regions:

1- Region of CD10≥30% marked in blue, where only 1 out of 12 patients diagnosed with GCB found to be ABC by GEP, however, weakness is very slight compared with other regions.

2- FOXP1≥80% positivity marked in red led to diagnosis of ABC in 19 patients, however, only two of which found to be GCP by GEP.

3- FOXP1≥80% negativity marked in green led to diagnosis of GCB in 10 patients, however, 3 patients found to be ABC by GEP.

BCL6 negativity along with MUM1 status(+/-) seem to be good check points leading to a perfect compatibility between IHC and GEP irrespective of the modest number of cases.

CONCLUSION

DLBCL is still a heterogeneous disease hiding in its folds and grey zone several discovered and yet undiscovered subtypes. Definitive diagnoses of the main subtypes depends on IHC along with GEP that helps defining the final diagnosis, however, GEP is not a simple procedure, furthermore, it cannot be carried out in all centers. Therefore, efforts are made to improve the capabilities of IHC in reaching the right diagnosis.

The real driving mechanism of carcinogenesis in both GCB and ABC is still hard to reveal especially with the discovery of several pathways implicated in this process, however, despite this progress in gene profiling studies, it is so hard to deliver the right treatment especially for ABC patients who show shorter survival compared with their counterpart GCB.

DISCLOSURE

I declare no conflict of interest

ETHICAL APPROVAL

This article does not contain any studies with animals performed by any of the authors.
This article does not contain any studies with human participants

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