The Spectrum of MYC Alterations in Diffuse Large B-Cell Lymphoma

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Keywords

Diffuse large B-cell lymphoma · MYC · Double-hit lymphoma · Double-expressor-diffuse large B-cell lymphoma · MYC translocations

Abstract

MYC, as a powerful transcription factor, plays a vital role in various cancers. The clinical significance of MYC alterations in diffuse large B-cell lymphoma (DLBCL) has been investigated for a long time. In this study, we comprehensively summarize the different alterations of MYC in DLBCL, including MYC overexpression, MYC translocations, MYC mutations, and increased gene copy number of MYC. Noteworthy, lone MYC overexpression or MYC translocation is not significantly associated with poor clinical outcomes, and their detrimental effects depend on the genetic alterations of BCL2 or BCL6. Both double-expressor DLBCL (DE-DLBCL), defined as overexpression of MYC and BCL2 proteins, and double-hit lymphoma (DHL), defined as a dual translocation of MYC together with BCL2 or BCL6, represent the distinct subgroups of DLBCL with inferior clinical outcomes. The mechanism may be that MYC activation induces cell proliferation, without the threat of the apoptotic brake in the presence of BCL2 overexpression. In addition, most of MYC mutations are present with favorable prognosis, and the nonsignificant effect

of MYC copy number amplification has been observed. It has been proved that cyclophosphamide, doxorubicin, vincristine, and prednisone plus rituximab show limited effects for DHL or DE-DLBCL, and the rituximab plus dose-adjusted etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin seem to be efficacious for DHL. The novel therapy is urgently needed for clinical improvement in DHL and DE-DLBCL.

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Introduction

Non-Hodgkin lymphoma is one of the top 10 causes of cancer mortality and diffuse large B-cell lymphoma (DLBCL) comprises approximately 30–50% of Non-Hodgkin lymphoma [1, 2]. DLBCL is a heterogeneous disease and can be identified as 2 molecular subtypes, termed germinal center B-cell-like (GCB) and activated B cell (ABC, or non-GC) [3]. Patients with the GCB subtype usually have better prognosis than those with the ABC subtype [4]. Rituximab in combination with cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) is the backbone of DLBCL treatment, but about 50% of DLBCL will relapse after R-CHOP treatment and 30% will succumb to this disease [5, 6]. Various genetic

and epigenetic alterations are associated with DLBCL genesis and development [3]. GCB DLBCL is preferentially involved in *MYC* translocation, *BCL2* translocation, and *PTEN* deletion, whereas ABC DLBCL is characterized by chronic active B cell receptor (BCR) signaling and NF- κ B deregulation [3, 7].

MYC gene, encoding the important transcription factor MYC, is located on the long arm of chromosome 8 (8q24) and under the transcription control of immunoglobulin (IG) gene [8]. *MYC* plays a pivotal role in tumor pathogenesis and development, with a wide range of biological activities, including apoptosis, growth, proliferation, differentiation, migration, and cellular metabolism [9–12]. *MYC* can bind the sequence-specific genes and drive their transcriptions to induce the oncogenic potentials of many cancers [13]. Aberrant activation of *MYC* can lead to the progress of various malignancies, including neuroblastoma, medulloblastoma, breast cancer, pancreatic ductal adenocarcinoma, and ovarian cancer [12, 14–19]. *MYC* alterations may be due to copy number gain, transcriptional/post-transcriptional events, epigenetic phenomena, or chromosomal translocations [12, 20]. A plethora of articles have exploited *MYC*-related biological progresses and their effects on clinical outcomes in DLBCL, but no comprehensive knowledge of *MYC* alterations including *MYC* overexpression, *MYC* translocations, increased *MYC* copy number, and *MYC* mutations in DLBCL has been conducted [12, 21]. This review will comprehensively conclude the potent effects of different *MYC* alterations and the treatment of DLBCL associated with *MYC* alterations.

MYC Overexpression in DLBCL

MYC protein can be detected in about 40% of whether newly diagnosed DLBCLs or relapsed patients [8]. Although many studies have reported that DLBCL patients with *MYC* overexpression were associated with inferior prognosis, the underlying mechanism is probably associated with the other genetic alterations in these patients, and the effect of lone *MYC* overexpression is probably not significant as we expected [20, 22]. *MYC* overexpression can induce significant DNA damage and then lead to the apoptosis of cancer cell by increasing the expression of P53. Based on the *MYC*-driven lymphoma with transgenic mouse models, the tumors induced by E μ -myc transgene, with *MYC* overexpression, were generally clonal, and further study demonstrated that deregulated *MYC* promoted apoptosis by activating oncogenic stress

response pathways. Therefore, the development of DLBCL requires additional oncogenic alteration to overcome the apoptosis [13]. It has been proved that the alterations of *BCL2* and *BCL6* can induce the oncogenic effect of *MYC* activation [20, 22].

A recent excellent review has summarized that the co-expression of *MYC* and *BCL2* is a poor biomarker for prognosis in DLBCL [8]. *BCL2*, an antiapoptosis protein, can maintain cell viability by inhibiting apoptosis response. In normal lymphoid cells, genetic insults or oxidative stress inhibits *BCL2* to promote apoptosis by increasing the expression of proteins of the BH3 family. In malignant lymphoma cells, overexpression of *BCL2* caused by chromosomal translocations and increased gene copy number suppresses the apoptosis and promotes the malignant proliferation of lymphoma cells and finally accelerates the *MYC*-induced lymphomagenesis [23, 24]. About 30% of DLBCL harbor both *BCL2* and *MYC* overexpression, which is defined as double-expressor DLBCL (DE-DLBCL) [25]. Compared to DLBCL patients without double expression, DE-DLBCL patients are more likely to have old age at diagnosis, advanced stages, B symptoms, high international prognostic index (IPI), and inferior prognosis in R-CHOP treated patients [3]. In addition, over 50% of relapsed/refractory DLBCL are DE-DLBCL [26]. In Savage et al. [27] study with a median follow-up of 6.8 years, DE-DCBCL treated by R-CHOP had a higher risk of central nervous system (CNS) relapse compared to the nondual expressers (2-year risk, 9.7 vs. 2.2%; $p = 0.001$), independent of CNS-IPI score and cell of origin. According to Joel et al. [20] review, the 5-year overall survival (OS) of DE-DLBCL was about 30–45%, while the control was about 66–75%. Recently, Green et al. [25] identified the double hit score, a sum of the immunoreactivity scores of *MYC* and *BCL2*, 1 (positive) or 0 (negative). Double hit score 2 represented both *BCL2* and *MYC* overexpression (DE-DLBCL) and was associated with lower complete response rate ($p < 0.004$), shorter OS ($p < 0.001$), and shorter progression-free survival (PFS; $p < 0.001$) [25]. Furthermore, some studies suggested that the prognostic value of DE-DLBCL was superior to cell of origin classification in the primary CNS DLBCLs [28, 29].

DE-DLBCL is more common in ABC-subtype disease (33–46% ABC vs. 17% GCB); intriguingly, the prognostic significance of DE-DLBCL is more prominent in the GCB-subtype [20]. Furthermore, overexpression of *MYC* and *BCL2* in DLBCL is mainly induced by activation of BCR and NF- κ B signaling in the ABC patients, while are caused by the translocation of *MYC* and *BCL2* in the GCB

patients [30]. These findings indicate that targeting BCR and NF- κ B signaling may be effective in ABC-DE-DLBCL [31]. The clinical outcomes of DE-DLBCL treated with RCHOP are intermediate between DLBCL without MYC/BCL2 alterations and DLBCL with MYC and BCL2 co-translocations [25].

Immunohistochemical (IHC) detection for DE-DLBCL is simple and efficient and is necessary to take into routine. How to define the “positive expression” of IHC results has become a tough problem. According to different studies, the positive value of MYC and BCL2 ranges from 30 to 70 and 0 to 70%, respectively. In addition, the technical biases, such as the sensitivity of antibody and the differences of manufactures, also result in the variability of IHC score. Nowadays, it is accepted that the positive values of MYC and BCL2 are 40 and 50%, respectively, because of their close correlation with clinical outcomes, but the values are not the screening thresholds of FISH test for translocation [32].

MYC Translocation in DLBCL

MYC Translocation Requires the Second Hit to Serve as a “Vicious” Role

MYC translocation is reported in 7–21% of DLBCL [33, 34]; and MYC translocation to an *IG* locus, present in about 5% of DLBCL, induces the constitutively active transcription of MYC under the *IG* promoter and causes the highest expressions of MYC mRNA and protein [8]. Copie-Bergman et al. [34] detected the MYC status in 774 DLBCL patients treated by R-CHOP using FISH testing and found that MYC-*IG* patients had shorter OS in comparison with MYC-negative patients, while no survival differences were observed between MYC-non-*IG* and patients without MYC translocations. The dosage effect may explain that the MYC overexpression with a MYC-*IG* translocation has the worse clinical outcomes compared to other subtypes of translocations [33, 34]. Kluk et al. [35] study reported that DLBCL patients with MYC protein expression $\geq 50\%$ were identified to have MYC translocations, whereas Green et al. [25] study showed that MYC protein expression $\geq 70\%$ could be speculated to be with MYC translocations. Moreover, no MYC translocations were found in DLBCL patients without MYC expression [36].

The prognostic effect of the isolated MYC translocation without other gene translocations appears controversial [8, 34]. A recent retrospective research analyzed 347 de novo DLBCL patients treated by R-CHOP and

demonstrated that MYC translocations occurred in 19% of GCB-DLBCL patients and 11% ABC-DLBCL and was significantly associated with the worse time to progression whether in GCB-DLBCL or ABC-DLBCL [21]. Cuccini et al. [37] study found that MYC translocation was present in 17% of relapsed/refractory DLBCL prospectively treated by R-ICE or R-DHAP and compared to DLBCL patients without MYC translocations, DLBCL patients with MYC translocations showed as a higher lactico-deshydrogenase level ($p = 0.0006$) and shorter 4-year PFS (18 vs. 42%, $p = 0.0322$) and OS (29 vs. 62%, $p = 0.0113$) which was consistent with another study. However, it was recently reported that 74% of MYC-translocated DLBCL harbored a “second hit” defined as either BCL2 and BCL6 translocations or TP53 mutations, and the clinical effects of MYC rearrangement may be induced by the underlying double hit [20]. A large clinical cohort conducted by Johnson et al. [32] found that 5-year OS was $>90\%$ in DLBCL patients with MYC translocations but without BCL2 expression [8, 32]. In addition, Alexandra et al. [38] study also pointed out that the prognosis of MYC translocations in DLBCL depended on the second hit and if without the BCL2 and BCL6 translocations or TP53 mutations, the clinical outcomes of MYC-translocated DLBCL patients were excellent, with 90% remaining in remission beyond 8 years. So, the “vicious” effect of MYC translocations is significantly dependent on the second hit. Both BCL2 and BCL6 overexpression can lead to dysregulation of the apoptotic response [39]; therefore, the possible mechanism is that the other genetic aberrations are able to overcome the proapoptotic effects induced by MYC aberrations. Based on these findings, DLBCL with positive MYC expression should be conducted for the FISH to detect MYC, BCL2, and BCL6 translocations; and including analysis for TP53 mutations is much better.

Double-Hit Lymphoma Is Significantly Associated with Poor Prognosis

Double-hit lymphoma (DHL) is defined as the high-grade B-cell lymphomas with MYC translocations and either BCL2 or BCL6 translocations by the newest version of world health organization classification, a separate subtype with an aggressive entity [7]. According to the 2016 revision of the world health organization classification, this subtype is morphologically heterogeneous and can have morphological features of blastoid, Burkitt lymphoma, DLBCL, and intermediate between DLBCL and Burkitt lymphoma [13]. And more, about 65% of DHL patients harbored translocations of MYC

and *BCL2*; 14% were with translocations of *MYC* and *BCL6*, and the remaining 21% had all 3 translocations, called as triple-hit lymphoma (THL) [40]. In clinical setting, it is demonstrated that DHL patients have the advanced lactate dehydrogenase level, IPI score, disease stage, and poor clinical outcomes [8, 24]. In addition, DHLs were associated with CNS involvement with 4–7% of patients at the risk of CNS relapse/progression [3, 24]. Although a big overlap exists between DHL and DE-DLBCL, they have the differences in some regards. Over 90% of DHLs were in GCB-DLBCL, whereas over 60% of DE-DLBCLs occurred in ABC-DLBCL [41]. Noteworthy, almost 20% of DHL patients were not with *MYC* and *BCL2* overexpression, and this part of patients were associated with better clinical prognosis compared to DE-DLBCL patients [42].

Furthermore, concurrent *MYC* and *BCL2* translocations seem different to *MYC* and *BCL6* translocations. The studies conducted by Ye et al. [43] and Copie-Bergman et al. [34] demonstrated that *MYC* and *BCL2* cotranslocations were associated with inferior outcomes compared to *MYC* and *BCL6* cotranslocations in DLBCL treated by R-CHOP. In contrast, Landsburg et al. [40] reported that patients with *MYC* and *BCL6* cotranslocations were significantly associated with worse median OS (14.5 months) than *MYC* and *BCL2* cotranslocations or THL (34.8 and 17.2 months, respectively). Therefore, more studies are needed to evaluate whether the clinical effects of 2 subtypes of DHL are equivalent in DLBCL. The clinicopathological characteristics and outcomes of THL were similar to the DHL patients [36]. As stated above, simultaneous *MYC* and *BCL2* translocations are more common than *MYC* and *BCL6* DHL and THL; and hence, the double hit of *MYC* and *BCL2* translocations in DLBCL will be the focus of attention.

No Detection Standard for MYC Translocations has been Established

The gold standard for detecting DHL is FISH, but FISH costs much and is difficult to be operated. Nowadays, there is no standard guidance on which DLBCL patients require FISH testing. A recent study reported when *MYC* expression level was $\geq 30\%$ by IHC, the FISH testing was needed [44]; however, other studies reported some patients with *MYC*-rearranged DLBCL could have the protein level below the threshold [45]. And according to Wang et al. [46] study, when FISH testing was only conducted in DLBCL patients with $>40\%$ of *MYC* expression, about 20% of the *MYC*-rearranged patients might be missed. Therefore, it is necessary to perform FISH testing

in every newly diagnosed DLBCL and if patients are confirmed with *MYC* translocations, it is recommended to conduct FISH testing for *BCL2* and *BCL6* [21].

MYC Mutations in DLBCL

MYC mutations in DLBCL were not as well investigated as *MYC* translocations. Xu-Monette et al. [47] study identified *MYC* mutations in 750 DLBCL patients using Sanger sequencing and demonstrated that 33.3% of patients harbored *MYC* mutations at the DNA level and 16.1% at the protein level (nonsynonymous mutations). The further results showed that *MYC* T58 and F138 mutations, which were only in 2% of DLBCL, were associated with *MYC* translocations and significantly associated with poor clinical outcomes. Most of the nonsynonymous mutations were associated with better prognosis compared to *MYC* translocations [4, 47]. It may be because the nonsynonymous mutations of *MYC* hamper the oncogenic functions of *MYC* in DLBCL. In addition, Ennishi et al. [21] research observed that the hotspot mutations of *MYC*, defined as >2 single nucleotide variants, had no significant association with clinical outcomes of GCB-DLBCL, while no hotspot mutations were identified in ABC-DLBCL. In other words, most *MYC* mutations are passenger mutations instead of driver mutations during genesis and development of DLBCL [4].

Increased Gene Copy Number of MYC in DLBCL

Increased *MYC* gene copy number exists in 8–20% of DLBCL patients and is not definitely associated with increased *MYC* protein expression [5, 8, 48]. *MYC* copy number amplification is more common in GCB-DLBCL than ABC-DLBCL [21]. The studies of *MYC* copy amplification in DLBCL are limited, and the existing data draw the conflicting results about the prognosis of increased copy number of *MYC* in DLBCL.

Landsburg et al. [49] study including 22 DLBCL patients with *MYC*-amplification, 87 patients with single-hit, and 127 patients without *MYC* amplification or translocation, reported that *MYC*-amplified DLBCL had similar 2-year OS to the *MYC*-negative ones. Bryn et al. [5] study also reported that no distinct differences were observed between DLBCL with increased *MYC* gene copy number (33 cases) and DLBCL with no *MYC* aberrations (43 cases). However, some studies reported that *MYC* extra copy was associated with inferior prognosis [21, 50].

Quesada et al. [50] retrospective study demonstrated that within 80 DLBCL patients with MYC overexpression, MYC amplification was associated with inferior OS and more interestingly, patients with double or triple extra copy lymphoma (defined by MYC and BCL2 and/or BCL6 amplification) have similar prognosis to these DHL or THL. In addition, Valera et al. [51] study pointed out that the role of MYC extra copy in DLBCL was affected by the copy number of MYC gene. The nonsignificant effect of MYC copy number amplification can be explained by the no evident relationship between high MYC expression and increased copy number [21].

Treatment for DHL and DE-DLBCL

Intensified Chemotherapy May Be Only Choice

A retrospective study demonstrated that DHL patients treated with RCHOP had significantly inferior outcome compared to DLBCL without MYC/BCL2 alterations (5-year PFS: 18 vs. 65%; 5-year OS: 27 vs. 71%), and those with DE-DLBCL also showed worse outcomes (5-year PFS: 32% and 5-year OS: 36%) [32]. Combined with other larger retrospective studies, the R-CHOP in DLBCL is suboptimal for DHL and DE-DLBCL [52–54].

Petrich et al. [52] conducted a large retrospective study to explore R-CHOP and other intensive induction regimens among 311 DHL patients, and the results demonstrated that patients treated by intensive induction regimens had better median PFS in comparison with R-CHOP therapy (7.8 vs. 21.6 months; $p = 0.001$), but no OS benefit. The initial results of a prospective clinical trial of rituximab plus dose-adjusted etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin (DA-R-EPOCH) on MYC translocated DLBCL ($n = 52$), which included 14 DHL patients and 24 patients with overexpressed BCL2, showed that within a median follow-up of 14 months, the PFS was 87% for DHL, suggesting that compared to RCHOP, DA-R-EPOCH could induce higher clinical response rate [53]. A meta-analysis of 11 studies involving 394 DHL patients indicated that DA-R-EPOCH reduced the risk of progression compared to R-CHOP, but no OS difference was observed [54]. In spite of no OS benefit, the institutional experience of MD Anderson Cancer Center still highlighted the importance of DA-R-EPOCH in the treatment of DHL [55]. However, not all intensified chemotherapy therapies for DHL are favorable [56]. The intensification of therapy, rituximab, high-dose methotrexate, and cytarabine regimen (R-hyper-CVAD) has been reported to not

affect the clinical outcomes [57, 58]. Therefore, by far, DA-R-EPOCH seems the most favorable chemotherapy with a higher complete response rate than R-CHOP and the less adverse effects compared to the other high-dose chemotherapies [52]. Although intensive induction regimens show prospects in treatment of DHL, most of these DHL patients are elderly and/or frail, which make them unavailable to the high-dose chemotherapy [56]. Thus, the more effective therapies are urgently needed for DHL.

No grand-scale studies were analyzed specifically for treatment of DE-DLBCL. A small retrospective clinical trial encompassing 16 DE-DLBCL patients showed that the relapse rate in R-CHOP groups was significantly higher than it in DA-R-EPOCH group (80 vs. 18%, $p = 0.042$) [59]. However, subgroup analysis from Cancer and Leukemia Group B 50303 trial and the GOYA trial demonstrated that no extra benefits were observed in DE-DLBCL patients treated with intensive chemotherapy in comparison with R-CHOP [24]. As a result of the limited data, the decision to determine which one of R-CHOP and intensive chemotherapy cannot be made for DE-DLBCL.

Because of the increased possibility of CNS invasion in DHL and DE-DLBCL patients, the CNS prophylaxis is strongly considered. Whereby, DA-R-EPOCH with CNS prophylaxis was empirically recommended [56]. However, the ultimate decision still needs the prospective clinical trials in DHL and DE-DLBCL patients.

As for consolidative hematopoietic stem cell transplant (SCT) for DHL/DE-DLBCL patients, the available data are also limited, and the results are not optimistic [56]. Some retrospective studies demonstrated that autologous SCT (ASCT) during first complete remission after chemotherapy failed to get an improvement of PFS and OS in DHL [52, 60]. Recently, a large clinical trial about ASCT in DHL patients who achieved first complete remission following completion of R-CHOP or intensive therapy demonstrated that 3-year relapse-free survival and OS rates showed no significant difference between ASCT ($n = 62$) and non-ASCT patients ($n = 97$; 3-year relapse-free survival rate: 75 vs. 89%, $p = 0.12$; 3-year OS rate: 85 vs. 91%, $p = 0.74$) [61]. However, the study by Maura et al. [62] suggested that transplant consolidation followed with high-dose chemotherapy could contend against the poor prognostic effect of DE-DLBCL among young and/or fit DLBCL patients regardless of whether in first line or first relapse.

Conclusively, although intensive induction regimens for DHL or DE-DLBCL are accepted by most centers,

Table 1. Clinical features and treatments of DLBCL with MYC alterations

MYC alterations in DLBCL	Clinical associations	Special treatments
MYC translocations (7–21%) Sole MYC rearrangement DHL (5–6%)	Clinical prognosis is dependent on the second hit GCB-subtype, high IPI score, advanced stages, CNS involvement, and poor prognosis	– DA-R-EPOCH with CNS prophylaxis is empirically recommended. Clinical trials is especially encouraged
MYC overexpression (40%) Sole MYC overexpression DE-DLBCL (30%)	Clinical prognosis is dependent on the second hit ABC subtype, high IPI score, advanced stages, higher risk of CNS relapse, and poor prognosis	– Refer to the treatments of DHL
MYC mutation (33.3%)	Most MYC mutations are passenger mutations	–
Increased MYC copy number (8–20%)	Nonsignificant clinical effect	–

The percentages shown above: the percentage of the total DLBCL. DLBCL, diffuse large B-cell lymphoma; ABC, activated B cell-like; GCB, germinal center B cell-like; IPI, international prognostic index; DE-DLBCL, MYC/BCL2 dual protein expression; DHL, MYC and BCL2 double translocations; DA-R-EPOCH, rituximab plus dose-adjusted etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin.

firm conclusions from prospective clinical trials designed for DHL are urgently needed. Besides, the new targeted drugs for DHL or DE-DLBCL targeting oncogenic alterations are urgently needed.

Drugs Targeting MYC

Although targeting MYC directly has been explored for several decades, thus far no effective drugs have been produced [63]. As MYC protein seems “undruggable,” diverse compounds have been developed to inhibit activities of MYC in various ways, including destroying the interaction between MYC and MAX and suppressing the MYC-dependent transcription [64]. Targeting MYC-regulated transcription has been studied for a long time. HDACs are recruited to the promoter regions of MYC-mediated genes to promote the transcription of MYC-targeted genes. Thus, HDAC inhibitors will lead to the decreased expression of MYC-targeted genes, including MYC itself [63, 65]. Inhibition of PI3K pathway has also been demonstrated to deregulate MYC activities by suppressing MYC gene transcription [63, 66]. Although single-agent HDAC or PI3K inhibitor has not shown effective antitumor activity in DLBCL, synergistic lethality of HDAC and PI3K inhibitors has been observed in DLBCL xenograft tumors [67]. A recent phase I clinical trial demonstrated that the dual HDAC and PI3K inhibitor, CUDC-907, showed encouraging and durable antitumor activity in MYC-altered DLBCL patients [42, 68]. And the phase II clinical trial of CUDC-907 is ongoing [26]. Be-

sides, bromodomain and extra-terminal motif inhibitors can prevent the transcription regulated by MYC and then inhibit the cancer cell proliferation [26]. The bromodomain and extra-terminal motif bromodomain inhibitor, JQ1, has demonstrated anti-tumor effects by repressing MYC and its target genes in MYC-driven lymphomas in vitro and vivo, including MYC-rearranged DLBCL [69]. Based on the speculation that targeting the curial effectors in deregulated MYC activity may induce the synthetic lethality, inhibitors of kinases in cell cycle progress, including CDKs inhibitors, CHK1 inhibitors, and aurora kinase inhibitors, also show prospects in treatment of MYC-rearranged DLBCL [13]. In conclusion, clinical trials evaluating novel regimens will be the preferred choice for DE-DLBCL and DHL.

Conclusion

Here, we conclude the clinical characteristics and treatments of DLBCL with MYC alterations, including MYC overexpression, MYC translocations, MYC copy number amplification, and MYC mutations (Table 1). The prognostic effect of lone MYC translocation or MYC overexpression is still in controversy, and the dominant view is that lone MYC translocation or MYC overexpression does not induce the poorer clinical outcomes compared to the MYC-negative DLBCL patients. DE-DLBCL and DHL have been proved to be significantly

associated with poor clinical prognosis. Most of *MYC* mutations are present with favorable prognosis, and the nonsignificant effect of *MYC* copy number amplification has been observed; and nevertheless, the effects of *MYC* mutations and increased *MYC* copy number may depend on the mutation subtypes and the copy number, respectively. Based on the existent data, the available treatment for DHL and DE-DLBCL is the intensified chemotherapy, especially DA-R-EPOCH. And it is urgently needed to develop the novel-targeted drugs for DHL and DE-DLBCL.

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Statement of Ethics

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Disclosure Statement

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Y.X. consulted literature and wrote the paper. X.Z. gave advices.

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