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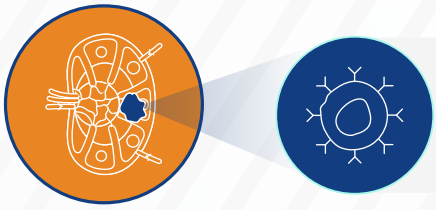
Clinical and Molecular Heterogeneity of Diffuse Large B-Cell Lymphomas

Why an individualised approach to patient management is much needed



Lymphomas constitute a heterogeneous group of neoplasms caused by the clonal expansion of lymphoid cells[1]

They are histologically classified as Hodgkin or non-Hodgkin lymphoma (NHL), with NHL accounting for 90% of cases[1]

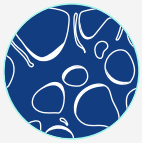
Three most common NHL types

Diffuse large B-cell lymphomas (DLBCL)

Follicular lymphoma (FL)

Peripheral T-cell lymphoma (PTCL)

NHLs have varying genetic fingerprints that correspond to:



Epigenetics – FL

Singalling – ABC-DLBCL

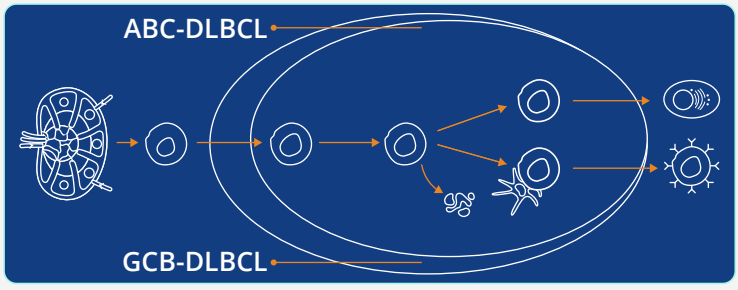
DNA repair/ integrity – Mantle cell lymphoma (MCL)

Transcription factors – Burkitt lymphoma (BL)

DLBCL is the most common type of NHL, accounting for 30%-40% of cases[2], and exhibits significant heterogeneity within a patient, between patients, and in a population

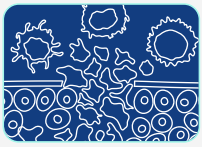
DLBCL responds well to immunochemotherapy. However, nearly one-third of patients experience relapsed/refractory disease[4]

Subtypes based on the cell of origin (COO)[5]



- Germinal-centre B-cell (GCB) → Better prognosis
- Activated B-cell (ABC) → Worse prognosis
- Unclassified → Intermediate prognosis

Patients diagnosed with the same DLBCL COO subtype may respond differently to treatments due to the following factors[6]



- Intratumor heterogeneity
- Variations in tumor microenvironment
- Differences in drug sensitivity
- Proportion of tumor-infiltrating T-cells

It is, therefore, important to understand the specific clinical and molecular features of DLBCL to select an appropriate treatment strategy

Visit https://b-cell-malignancies.knowledgehub.wiley.com/ for additional resources

Mutational landscape of DLBCL and molecular subtypes

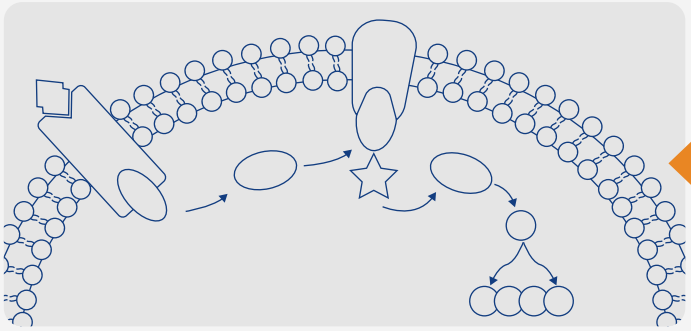
Classification based on genomic rearrangements[5]

Chromosomal translocations in MYC, BCL2, and/or BCL6

Double-hit or triple-hit high-grade B-cell lymphomas

Classification based on molecular signatures

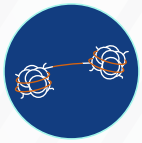
Signalling pathways altered in lymphoma progression[7]



- Bruton's tyrosine kinase (BTK)
- Spleen tyrosine kinase (SYK)
- Phosphoinositide 3-kinase (PI3K)/AKT/mammalian target of rapamycin (mTOR)
- Janus kinase-signal transducer and activator of transcription (JAK-STAT)
- NOTCH
- Nuclear factor-κB (NF-κB)
- Ubiquitin-proteasome pathway (UPP)

Genetic alterations and mechanisms of pathogenesis in DLBCL

Aberrant somatic hypermutations[4]



Chromatin/histone modifiers[4]

- Methyltransferase – KMT2D (MLL2), EZH2
- Acetyltransferase – CREBBP/EP300

Transcription factors[4]

- BCL6, FOXO1

Tumor microenvironment alterations[8]

- GC-like
- Mesenchymal
- Inflammatory
- Depleted

Immune surveillance bypass[4]

- Downregulation of MHC class-II expression
- Programmed death ligands (PD-Ls)

B-cell migration[4]

- S1PR2, GNA13, ARHGEF1, and P2RY8 TNFRSF14

Molecular subtypes and association with COO and prognosis[5]

Subtype	*Genetic alterations*	COO prototype	Signaling mechanism	Prognosis
MCD	*MYD88* and *CD79B* *BCl2* amplification	ABC	B-cell receptor signalling NF-κB immune pathway activation	Poor
EZB	*EZH2* mutation and *BCL2* translocation *MYC* rearrangement *KMT2D (MLL2)* *CREBBP* *EP300*	GCB	Deregulation of histone modification	Intermediate
BN2	*BCL6* structural alterations and *NOTCH2* mutations *BCL10* *PD-L-1/2*	ABC GBC NC	NOTCH activation Immune surveillance evasion	Intermediate
N1	*NOTCH1* mutations	ABC		Poor
A53	Chromosome*17p* deletion and *TP53* mutations		Chromosomal aberration Cell growth	Intermediate
ST2	Mutations in *SGK1, TET2, SOCS1, DUSP2, STAT3* and *BRAF*	NC	JAK-STAT ERK signalling	Good

Existing and emerging treatment strategies

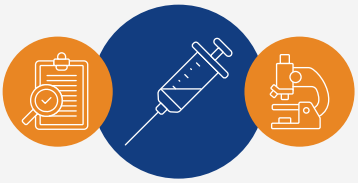
Available treatments[9]

Standard treatment[5]

R-CHOP chemo-immunotherapy regimen (rituximab-cyclophosphamide, doxorubicin, vincristine, and prednisone) with or without radiotherapy

Although R-CHOP has been shown to be safe and effective, 45%–50% of patients experience a relapse

Treatment of relapsed/refractory disease



Salvage chemotherapy with autologous stem cell transplant (ASCT)[7]

- R-ICE (rituximab plus ifosfamide, carboplatin, and etoposide)
- R-DHAP (rituximab plus dexamethasone, cytarabine, and cisplatin)
- R-GDP (rituximab plus gemcitabine, dexamethasone, and cisplatin)[7]

Many patients do not respond to salvage chemotherapy and ASCT, underscoring the need for novel treatment alternatives

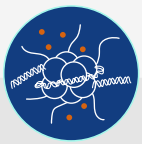
Non-chemotherapy-based options[2,7]

Inhibiting targets from signalling pathway through BCR signalling inhibition[7]

BTK inhibitors (BTKis): Ibrutinib, acalabrutinib, zanubrutinib, and tirabrutinib

- Activation of BCR signalling activates downstream MAPK, PI3K, and NF-κB pathways via BTK
- BTK inhibition has been shown to decrease the expression of the anti-apoptotic proteins – BCL-2, BCL-XL, and MCL-1, thereby promoting cell death

- PI3K-AKT-mTOR inhibition[7] – idelalisib, temsirolimus
- JAK-STAT inhibition[7] – itacitinib
- NOTCH inhibition[7] – CB-103
- NF-κB inhibition[7] – pevonedistat

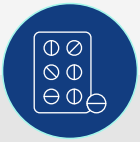


Inhibition of histone modifiers:
- Histone deacetylase and methyl transferase inhibitors

Chimeric antigen receptor T-cell therapy

Tafasitamab, an anti-CD19 antibody

Immune checkpoint inhibitors:
- Nivolumab
- Pembrolizumab



Selinexor, an oral selective inhibitor of XPO1:
- Induces the nuclear accumulation of tumor suppressor proteins
- Reduces the accumulation of oncoproteins like Bcl2

Bispecific T-cell engager therapy (BiTEs):
- Mosunetuzumab, glofitamab, and epcoritamab

Antibody-drug conjugates (ADCs):
- Brentuximab vedotin (BV) and polatuzumab vedotin (PoV)
- Novel ADCs against CD22, CD25, and CD27 are currently being tested

International Prognostic Indices are used to assess the prognosis and treatment outcomes of patients with DLBCL, determined by[10]:

- Age
- Lactate dehydrogenase
- Performance status
- Number of extranodal sites
- Ann Arbor stage

Prognosis can vary significantly with the molecular subtype of DLBCL

Molecular alterations impact the treatment response of DLBCL and can act as predictive biomarkers that guide diagnosis and impact treatment decisions

Profiling of circulating tumor DNA is an emerging non-invasive technique for the diagnosis and monitoring of disease progression and treatment response[11]

An integrated approach combining clinical, phenotypic, and molecular features can:
- Provide a more accurate prediction of prognosis
- Allow better risk stratification of patients[12]

Conclusions[1-12]

- In B-cell lymphomas, biological heterogeneity exists between different subtypes and between patients with the same subtype
- Including DLBCL molecular subtypes in diagnostic and classification methods can improve risk stratification and prediction of prognosis
- Healthcare professionals (HCPs) must take into account the distinct molecular signature of a particular DLBCL when determining the best course of treatment
- One treatment may not work for all patients. The heterogeneous nature of DLBCL warrants an individualised treatment approach to improve patient outcomes
- HCPs must select subsequent treatments for high-risk relapsed patients based on the clinical features of the tumor and patient-specific characteristics, such as comorbidities and age
- Prognostic indices that include both COO classification and molecular signatures can provide a more accurate prediction of outcomes

Key takeaway

Adopting an individualised patient approach that accounts for the variations across the molecular subtypes of DLBCL and treatment responses can help improve the recovery rate and decrease the occurrence of DLBCL relapse

References:

1. Jamil A, and Mukkamalla SKR. Lymphoma. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2023.
2. Susanibar-Adaniya, S., & Barta, S. K. (2021). 2021 Update on diffuse large B cell lymphoma: A review of current data and potential applications on risk stratification and management. *American Journal of Hematology, 96*(5), 617-629.
3. Cheson, B. D., Nowakowski, G., & Salles, G. (2021). Diffuse large B-cell lymphoma: new targets and novel therapies. *Blood Cancer Journal, 11*(4), 68.
4. Pasqualucci, L., & Dalla-Favera, R. (2018) Genetics of diffuse large B-cell lymphoma. *Blood, 131*(21), 2307-2319.
5. Morin, R. D., Arthur, S. E., & Hodson, D. J. (2022) Molecular profiling in diffuse large B-cell lymphoma: why so many types of subtypes? *British Journal of Haematology, 196*(4), 814-829.
6. Roider, T., Seufert, J., Uvarovskii, A., Frauhammer, F., Bordas, M., Abedpour, N., ... & Dietrich, S. (2020). Dissecting intratumour heterogeneity of nodal B-cell lymphomas at the transcriptional, genetic and drug-response levels. *Nature Cell Biology, 22*(7), 896-906.
7. Wang, L., Qin, W., Huo, Y. J., Li, X., Shi, Q., Rasko, J. E. J., Janin, A., & Zhao, W. L. (2020). Advances in targeted therapy for malignant lymphoma. *Signal Transduction and Targeted Therapy, 5*(1), 15.
8. Kotlov, N., Bagaev, A., Revuelta, M. V., Phillip, J. M., Cacciapuoti, M. T., Antysheva, Z., ... & Cerchietti, L. (2021). Clinical and biological subtypes of B-cell lymphoma revealed by microenvironmental signatures. *Cancer Discovery, 11*(6), 1468-1489.
9. Danilov, A. V., Magagnoli, M., & Matasar, M. J. (2022). Translating the biology of diffuse large B-cell lymphoma into treatment. *The Oncologist, 27*(1), 57-66.
10. Crombie, J. L., & Armand, P. (2020). Diffuse large B-cell lymphoma's new genomics: the bridge and the chasm. *Journal of Clinical Oncology, 38*(30), 3565..
11. Lauer, E. M., Mutter, J., & Scherer, F. (2022). Circulating tumor DNA in B-cell lymphoma: technical advances, clinical applications, and perspectives for translational research. *Leukemia, 36*(9), 2151-2164.
12. Weber, T., & Schmitz, R. (2022). Molecular subgroups of diffuse large B cell lymphoma: Biology and implications for clinical practice. *Current Oncology Reports, 24*(1), 13-21.

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