

# Non-Hodgkin lymphoma: A review of treatment options and the limitations for diffuse large B-cell lymphoma (DLBCL)

Thanthong Kobkarnsakul \*

\* Shrewsbury International School, Bangkok, Thailand 10120

Email: 2022tao.k@shrewsbury.in.th

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## Abstract:

Non-Hodgkin lymphomas are lymphomas that have a wide range of molecular and characteristics. The basis for developing treatments is for precise diagnosis, meticulous staging of the disease, and identifying adverse prognostic factors. Chemoimmunotherapy is frequently used as the initiating treatment, however therapy involving radiation may be utilized for patients that are in the early stages of the disease. Although the response rate of patients to the remedies are relatively high, relapsing of the disease tends to be common. Therefore, additional therapies such as stem cell transplantation, are frequently required. Due to the fact that various subgroups of the lymphoid malignancies still prevail and are irremediable using the latest management approaches, currently the conduction of objective trials are undergoing in order for the identification of newer therapeutics with promise in this disease. Personalised medicine promises that it will improve a patient's survival of the disease. However, further investigation must take place involving challenges and pitfalls of precision medicine.

*Keywords* — Chemotherapy, diffuse large B-cell lymphoma, lymphomas, non-Hodgkin lymphomas, targeted therapy

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## I. INTRODUCTION

Lymphomas are hematological cancers which can be categorized into two sub-groups: Non-Hodgkin lymphomas (NHL) and Hodgkin lymphoma (HL) (1). NHL are caused by loci encoding lymphoid antigen receptors with cellular proto-oncogenes, which can be distinguished by chromosomal translocations (2, 3). NHL is a malignancy that originates from lymphoma, which accounted for roughly 90% of all lymphoma malignancy (4). Depending on its origin, NHL can be grouped into B-cell lymphomas or T-cell and NK-cell lymphomas (4). Diffuse large B-cell lymphoma (DLBCL) and follicular lymphomas (FLs) are the two most common types of NHL, which DLBCL account for 30–40% in countries in western countries, and FLs account for 20–30% of lymphomas in western countries (4-6).

Combination chemotherapy regimens are commonly recommended to treat NHL (5, 6). Typical examples of chemotherapy are cyclophosphamide, vincristine and doxorubicin (5, 7). If NHL becomes refractory lymphoma, and does not get better with the initial treatment, chemotherapy may have to be coursed at a higher dose or combined with other interventions (8-10). However, the intensive chemotherapy destroys bone marrow, which could cause various side effects to arise (8). Therefore, combining targeted therapy such as rituximab with standard chemotherapy could improve treatment outcomes for NHL patients (10). This paper aims to focus on non-Hodgkin lymphoma by raising awareness of its treatment options and the limitations of each different form of treatment. Also, promote the understanding of the mechanism of drug resistance of these malignant clones and provide precision medicine approaches that could be a

promised therapy for treatment outcomes and improving patients' quality of life.

## **II. PATHOPHYSIOLOGY OF NON-HODGKIN LYMPHOMA**

Lymphoma develops from immune cells at diverse differentiating phases (11). The two types of lymphocytes, T and B are able to act as precursors of lymphomas (1, 12, 13). NHL is a cancer type that is commonly found globally. The pathophysiology of a heterogeneous class of malignant lymphoid tumours still required more information to identify. Associations between multiple infirmities and diagnosing lymphoma were identified, immunodeficiency was one of the conditions that has been recognised to have high tendency for the development of NHL (11). Sjogren syndrome and rheumatoid arthritis are autoimmune diseases that beget a solid relationship to develop B cell lymphomas (11). Apart from that, infectious diseases for instance EBV, HTLV-I, HIV, HCV, *Helicobacter pylori*, and human herpesvirus 8 were reported to involve in aetiology of both HLs and NHL (14). NHL therapy is derived from combination chemotherapy regimens (5, 6). The combining of a monoclonal antibody to the CD20 gene, such as rituximab has proven to improve the patients' therapeutic outcomes and prolonged overall survival (15, 16). The differentiation of treatment responsiveness for male and female patients was leading to the development of a gender-based treatment regimen (17-19). Front-line or salvage therapies in several lymphoid malignancies can be yielded response rates by autologous and allogeneic hematopoietic stem cell transplants (20-22). Sex hormones are involved in lymphoid malignancies (23). Therefore, several *in vitro* experiments have been studied on the relationship between sex hormone and the development of NHL. Epidemiologically, there was a study reported that there has been a correlation between NHL occurrence and sex hormones (24-26). In addition, women had an inverse correlation between multiple pregnancies and live births and risk of diffuse large B-cell lymphoma (27, 28). Apart from the factors above, unlike most solid tumours, which have a high degree of genetic instability, lymphomas have a

comparatively stable genome (4). While typical genetic modifications serve as a pathway for DNA damage to produce lymphoma, they allow non-Hodgkin lymphomas to be categorised. Rather than that, chromosomal translocations are involved, which are frequently found in haemopoietic system cancers (4, 29). With multiple factors promoting the aggressiveness of NHL. Therefore, the understanding of molecular aspects will help manage more effective treatment. Given that multiple factors contribute to the aggressiveness of NHL, understanding the molecular basis will aid in managing more effective treatment.

### *A. Mutation of a single gene*

Approximately one in ten of all FL cases is associated with specific genetic mutations that affect how patients respond to treatment. Notably, the TP53 mutation had association with a substandard prognosis in both the pre-and-post-rituximab treatment (30). Consistent with their poor prognosis, TP53 mutations were more prevalent in patients with disease progression or histologic transformation from follicular to diffuse-type NHL (30, 31).

The polycomb repressive complex 2 (PRC2) is a biomarker and a target for therapies since the histone methyltransferase EZH2 is both the catalytic subunit of PRC2 and a target for therapies (32, 33). An approximation of 25% of all FLs initially diagnosed have EZH2 mutations (most commonly affecting residue Y641) (34-36). Heterozygous EZH2 mutations result in increased trimethylation of histone H3 lysine 27 (H3K27me3), an epigenetic mark of repressed gene expression that induces lymphomagenesis *in vivo* when combined with the overexpression of BCL2 (36, 37). Additionally, pro-survival BCL-2 proteins, which include B-cell leukaemia/lymphoma-2 (BCL-2/BCL2), myeloid cell leukaemia-1 (MCL-1/MCL1), and B-cell lymphoma-extra large (BCL-XL/BCL2L1), are generally overexpressed in B-NHL and play a vital role in lymphoma pathogenesis, disease progression, and drug resistance (38).

Lymphoma, like all cancers, is characterised by genetic changes that disrupt the balance between proliferation and apoptosis. Particular lymphocytes, such as B lymphocytes, are especially susceptible to

DNA getting damaged throughout the germinal centre reaction, as somatic hypermutation and class-switch recombination affect the immunoglobulin genes (39). Biologically diverse DLBCL was more comprehensively studied, resulting in sub-classification (39). According whole-genome expression profiling (GEP), DLBCL can be classed in relation to the cell of origination, which is in most cases the germinal centre B-cell-like (GCB) but maybe active B-cell-like (ABC) and primary mediastinal B-cell lymphoma (40). ABC-type DLBCL carries a significantly worse prognosis, with GCB-type DLBCL being slightly better (40). Moreover, cytogenetic trials identified a MYC translocation (mainly of the GCB type) in DLBCL pain, which was correlated with a poor prognosis especially those with BCL2 translocation in the presence of a concurrent translocation (40). The overexpression in ABC types DLBCL of MYC and BCL 2 through other mechanisms is also seen (41, 42).

Several independent groups have recently reported the mutational landscapes observed in the GCB and ABC/non-GCB subgroups. ABC-type lymphomas are enriched with activated BCR and TLR signaling pathways, activating transcription factors  $\text{NF}\kappa\text{B}$ , playing a vital role in lymphomagenesis, for TNFAIP3, CD79A/B, CARD11, MYD88, BCL10, MALT1 and BCL6 (43, 44). The genetic alters associated with histone modifiers such as MLL2, EZH2, CREBBP, EP330 and PTEN were shown to be predominantly GCB subtypes, BCL2 and BCL6 (45, 46). In particular, a large portion of the genetic changes were not excluded from any of the subtypes. In addition to the activations of various oncogenic signals namely, JAK/STAT, RAS/MAPK, and PI3K/AKT/mTOR, inflammatory cytokines or cell growth factors generated in the microenvironment may be used in both types without genetic changes in tumour cells (47). Therefore, these genetic factors and intracellular signaling are among the most critical factors in promoting aggressive lymphoma.

#### ***B. Molecular mechanisms of lymphoma develop resistance to drugs***

Many drugs approved for lymphoma treatment were reported to be ineffective as cancer cells develop resistance. Such drugs, for instance, chemotherapeutics and monoclonal antibodies, are also reported. The molecular mechanism involved in the resistance of drugs can be classified into two main mechanisms: cancer cell-intrinsic and cancer cell-extrinsic mechanisms (48). Inalienable drug resistance is more often than not related to pre-existing components that mechanical actions of the anticancer agents (e.g., CD20-negative lymphomas will not react to anti-CD20 rituximab) (16). In cases where the resistance is obtained, ordinarily it is related to quantifiable anti-tumour adequacy due to the disposal of drug-sensitive lymphoma cells with resulting brief clinical abatement of the infection. Hence, consequent relapsing of the lymphoma is, for the most part, considered cancer cell resistance to drugs which drive the remission.

#### ***C. Stem-like features and cancer cell resistance***

The stem-like features of lymphoma are more intangible to explain compared to solid tumours (49). The easy criteria to identify side population cells was the capability of cancer in the exportation of Hoechst 33342 dye. Side populations are regularly enhanced in cells that initiate lymphoma, characterised by expanded self-renewal and clonogenicity (50). Cells in the side population express elevated degrees of different ATP-binding cassette (ABC) transporter family members, counting multidrug resistance protein 1 (MDR1), contributing to their sedate safe phenotype (49, 51, 52).

#### ***D. Hypoxia-Induced Changes***

In the presence of oxygen, few forms of lymphoma can survive and proliferate, but several of these do so in low-oxygen environments such as sizable necrotic lymphoma masses, malignant effusions, or bone marrow (53). Lymphoma cells must learn to adapt to stressors such as hypoxia, acidosis, elevated levels of reactive oxygen species (ROS), and nutrient deficiency (54). Hypoxia is one of several widely recognised factors contributing to the survival of tumour cells and induces a highly complex manner of chemoresistance in every classification of malignant disorders (53).

Hypoxia-inducible factors (HIFs) are critical as part of the cascade of phenotypic changes affiliated with hypoxia, in the two cell types: lymphoma and non-malignant in the tumour microenvironment (53, 54). VEGF transactivated by HIF1 $\alpha$  plays an autocrine and paracrine role in sprouting angiogenesis and is predominantly active in the tumour microenvironment for the malignant lymphoid and benign cells, respectively (53). Blood vessel chaos causes repeating thrombotic and hemorrhagic events, whereas unorganised lymphatic vessels cause intracellular pressure to increase, which allows for collagen fibre deposition (55). Tissue-resident macrophages activated by hypoxia and localised to areas of low oxygen exposure such as bone marrow begin to produce pro-inflammatory cytokines and enlist the help of immune system cells other than malignant tumours (55). Together, hypoxic, fibrotic, and pro-inflammatory niches adjacent to necrotic tissues create a microenvironment that is favourable for the continuation of malignant lymphoid cells and induce cells to develop resistance to drugs (53).

### **III. RECOMMENDED TREATMENT FOR NON-HODGKIN LYMPHOMA**

Chemotherapy is the utilization of anti-cancer drugs either through intravenous injection (IV) or by intake through the mouth. This treatment is extremely handy in the treatment of lymphoma as it travels through the bloodstream, reaching all parts of the body. Chemotherapeutic drugs that have been previously implemented in order to treat NHL, are Alkylating agents such as cyclophosphamide and Ifosfamide (56, 57). Other types of drugs are corticosteroids, platinum drugs, purine analogs, anti-metabolites, anthracyclines, and others (Vincristine, Etoposide, Bleomycin) are also used (56). Usually, a combination of drugs from different groups are used to treat patients. CHOP is amongst the most common combinations, consisting of cyclophosphamide, doxorubicin, vincristine and prednisone (56). Moreover, another frequent combination is called CVP (56). Other methods and drugs that have been used for the treatment of NHL include targeted therapies (CD20 and CD52 monoclonal antibodies), transplants of stem cells,

and even surgery (56, 58-60). However, drug resistance has frequently hampered efforts to combat or even eliminate malignant lymphoma cells, leading to unmet medical needs for relapsed or treatment-refractory disease.

### **IV. PRECISION MEDICINE**

Although Precision medicine (PM) is not a novel notion, combining this strategy with the treatment intervention could promote better therapeutic outcomes for various aggressive cancers. Immunochemotherapy has significantly caused the advancement of the lymphoma treatment results. However, it is still a toxic therapy that may cause grave long-term side-effects and does not benefit all patients. In order to attempt to address this problem, clinical research strives towards the development of targeted therapies with increased efficiency, less adverse effects, and to be able to accurately predict therapeutic responsiveness by identifying biomarkers. The therapeutic arsenal for hematologic cancers has been expanding greatly, due to the approval of the tyrosine kinase inhibitor imatinib for chronic myeloid leukemia and the molecularly targeted agent all-trans retinoic acid for acute promyelocytic leukemia.

With a vast number of signal transduction inhibitors available, it has allowed for a remarkable opportunity to enhance cancer therapy and its precision, due to their ability to select and target kinases and distinctive cellular proteins. Centered on the previously indicated differences amongst GCB- and non-GCB type DLBCL, the disparity between the results of the targeted strategies are expected. At practically all levels in the intracellular signalling cascade, both the BCR- and TLR-pathways, which are significant in non-GCB DLBCL and lead to NF $\kappa$ B activation, are accessible to treatments (39). Dasatinib (LYN-inhibitor), ibrutinib (BTK-inhibitor), fostamatinib (SYK-inhibitor), or enzastaurin (PKC-inhibitor) can all be used to block the BCR pathway upstream. Currently, BTK appears the most propitious target; in a phase I/II study, ibrutinib demonstrated an ORR of 41% in ABC-type but merely 5% in GCB-DLBCL (61, 62). Ibrutinib is currently undergoing investigation in combination with first-line R-CHOP treatment in a randomised

phase III trial enrolling patients with non-GCB DLBCL (63). Developing inhibitors that target the IRAK kinases, which are downstream of MYD88, is currently underway. Indirect NF $\kappa$ B -inhibition with the proteasome inhibitor bortezomib should as well be more efficacious in ABC-subtype DLBCL (43, 44). Results are similar for lenalidomide, which inhibits IRF4 and has been shown to have a higher efficiency in non-GCB RR-DLBCL than in GCB-subtype (63). Promisable targets in GCB-DLBCL involve paths of PI3k/AKT/ mTOR(activated by inactivation of PTENs), BCL6 and methyltransferase of EZH2 (39, 64). Epigenetic manipulation by a BET bromodomain inhibitor can indirectly target the overexpressing of the MYC oncogene (through translocations to the GCB-like DLBCL or through other mechanisms to the ABC-like DLBCL). Histone modifying agents (e.g. vorinostat) show potential to treat lymphomas with CREBBP/EP300 mutations, with an ORR of 20%–30% in unselected RR-DLBCL (39, 64). Researchers have discovered a way to target the over-expressed anti-apoptotic protein BCL2 using BH3 mimetics, for instance GDC-199 (65). Since malignant lymphoid cells boost their growth and survival by utilizing several oncogenic signalling pathways, pragmatic combinations that are based on mechanisms of targeted agents are needed in order to enhance the efficacy of treatment. However, it may potentially lead to an increase in toxicity.

## **V. DISCUSSION**

The advancement of targeted therapies in DLBCL will result in a paradigm shift away from broad-spectrum polychemotherapy and more mechanical-based therapeutic combinations. Currently, the greatest unmet demand in therapy exists in patients with high-risk DLBCL. Several obstacles must be overcome before further steps could be taken.

Translational research is required in order to grasp lymphomagenesis in greater detail as well as assisting with the identification of driver mutations in lymphoma subtypes (61). Addressing issues of clonal diversity and the evolution of clones must be done. Selective evolutionary processes can result in distinct subclones, with every single one having a distinct profile of mutated genes (35). Heterogeneity

in this disease can be observed in patients by looking at differences among DLBCL patients, between the primary disease, and relapse by examining their mutational profiles across different lymphoma locations (33). Due to the enormous capacity of subsequent generation sequencing technology (NGS), there is a possibility to blueprint each and every of the genes that are linked with lymphoma, thus disentangling the whole 'DLBCL mini-genome' (61, 66-68). Additionally, the genetic deficiencies in the microenvironment that contribute to lymphomagenesis and resistance to therapy can undergo evaluation (68). Pharmacogenomics, pharmacokinetics, pharmacodynamics, and therapeutic drugs are required to be monitored in order for the optimisation of the dosage and dosing schedule of these neoteric medications (62). Numerous researches are being conducted to certify the possibility of combining targeted therapies with the intention of obstructing signalling cascades on multiple levels, such as by blocking negative/positive feedback loops. Adequately defining the sensitivity and specificity of the biomarkers, before the incorporation of such markers into clinical settings is a necessity (69). Interpreting and integrating data, subsequently translating it into clinically relevant druggable sites, are critical phases in personalised medicine.

However, if it is not addressed adequately, the growing of information may result in an escalation of the divergence of science, veering away from the patient. A logical next step would be to conduct a pathway-driven analysis using computational systems biology methods. Cross-talking between paths may cause the complication of Black and White conclusions from analysis based on pathways, and it may be essential to follow parallel "co-target" accessories to overcome mechanisms of drug resistance (62).

Finally, lymphomagenesis is not solely a genetic phenomenon (68). Thus, to gain a global perspective and comprehensive understanding of tumour evolution and optimise therapeutic procedures, the integration of genomic data with proteomic, and practical comprehension via an integrative systems biology approach would be essential.

## CONCLUSIONS

Over the last 20 years, our comprehension and understanding of lymphomas and the landscaping of therapeutic treatment choices for patients with such malignancies has substantially rocketed. As a result of this, the proportion of cases that were cured successfully with current forms of remedies are rising continually. What is more is that in cases of patients with lymphomas that have relapsed, multiple novel treatment modalities and targeted agents have been introduced into clinical practices, while countless more are undergoing further testing through various clinical trials. In several subtypes of lymphoma, an era of risk-stratified therapy that is able to be tailored to each patient with a basis on molecular and cytogenetic prognostic markers. Nevertheless, an in-depth grasp of the mechanical aspects underlying the recurrence of the disease, that includes lymphoma cell plasticity and clonal evolution would allow for the pioneering and further clinical tests of other forms of potent targeted drug therapies in the near future. The integration of synthetic immunotherapy and CAR T-cell technology, may lead to diseases that are currently deemed treatment-refractory to be eradicated.

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