International Journal of Scientific Research and Engineering Development-– Volume 4 Issue 5, Sep- Oct 2021

Available at www.ijsred.com

RESEARCH ARTICLE OPEN ACCESS

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

----------**********----------

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**

----------**********----------

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 autoimmunediseases 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, the was a study has 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 NFκβ, 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 GCBsubtypes, 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 HIF1α 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 NFκβ 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 NFκβ -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.

REFERENCES

1. Swerdlow SH, Campo E, Pileri SA, Harris NL, Stein H, Siebert R, et al. The 2016 revision of the World Health Organization classification of lymphoid neoplasms. Blood, The Journal of the American Society of Hematology. 2016;127(20):2375-90.
2. Guo M, Mao X, Ding X. Molecular genetics related to non-Hodgkin lymphoma. Open Life Sciences. 2016;11(1):86-90.
3. Cerosaletti KM, Morrison VA, Sabath DE, Willerford DM, Concannon P. Mutations and molecular variants of the NBS1 gene in non‐Hodgkin lymphoma. Genes, Chromosomes and Cancer. 2002;35(3):282-6.
4. Shankland KR, Armitage JO, Hancock BW. Non-hodgkin lymphoma. The Lancet. 2012;380(9844):848-57.
5. Tilly H, Da Silva MG, Vitolo U, Jack A, Meignan M, Lopez-Guillermo A, et al. Diffuse large B-cell lymphoma (DLBCL): ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Annals of oncology. 2015;26:v116-v25.
6. Ngo L, Hee S-W, Lim L-C, Tao M, Quek R, Yap S-P, et al. Prognostic factors in patients with diffuse large B cell lymphoma: before and after the introduction of rituximab. Leukemia & lymphoma. 2008;49(3):462-9.
7. Marcus RE, Solal-Celigny P, Imrie K, Catalano JV, Dmoszynska A, Raposo JoC, et al. MabThera (Rituximab) Plus Cyclophosphamide, Vincristine and Prednisone (CVP) Chemotherapy Improves Survival in Previously Untreated Patients with Advanced Follicular Non-Hodgkin's Lymphoma (NHL). Blood. 2006;108(11):481.
8. Vose JM, Anderson JR, Kessinger A, Bierman PJ, Coccia P, Reed EC, et al. High-dose chemotherapy and autologous hematopoietic stem-cell transplantation for aggressive non-Hodgkin's lymphoma. Journal of Clinical Oncology. 1993;11(10):1846-51.
9. Miller TP, Dahlberg S, Cassady JR, Adelstein DJ, Spier CM, Grogan TM, et al. Chemotherapy alone compared with chemotherapy plus radiotherapy for localized intermediate-and high-grade non-Hodgkin's lymphoma. New England Journal of Medicine. 1998;339(1):21-6.
10. Greenhalgh J, Bagust A, Boland A, Blundell M, Oyee J, Beale S, et al. Rituximab for the first-line maintenance treatment of follicular non-Hodgkin's lymphoma. Pharmacoeconomics. 2013;31(5):403-13.
11. Ansell P, Simpson J, Lightfoot T, Smith A, Kane E, Howell D, et al. Non‐Hodgkin lymphoma and autoimmunity: Does gender matter? International journal of cancer. 2011;129(2):460-6.
12. Henopp T, Quintanilla‐Martínez L, Fend F, Adam P. Prevalence of follicular lymphoma in situ in consecutively analysed reactive lymph nodes. Histopathology. 2011;59(1):139-42.
13. Gajl-Peczalska KJ, Bloomfield CD, Coccia PF, Sosin H, Brunning RD, Kersey JH. B and T cell lymphomas: Analysis of blood and lymph nodes in 87 patients. The American journal of medicine. 1975;59(5):674-85.
14. Hjalgrim H, Engels EA. Infectious aetiology of Hodgkin and non‐Hodgkin lymphomas: a review of the epidemiological evidence. Journal of internal medicine. 2008;264(6):537-48.
15. Cang S, Mukhi N, Wang K, Liu D. Novel CD20 monoclonal antibodies for lymphoma therapy. Journal of hematology & oncology. 2012;5(1):1-9.
16. Van Meerten T, Hagenbeek A. CD20-targeted therapy: a breakthrough in the treatment of non-Hodgkin's lymphoma. Neth J Med. 2009;67(7):251-9.
17. Bendtsen MD, Jakobsen LH, Jørgensen JM, Johnsen HE, Josefsson PL, Poulsen CB, et al. Gender-Based Differences in Efficacy of Immuno-Chemotherapy for Diffuse Large B-Cell Lymphoma Revisited: A Danish Population-Based Study. Blood. 2017;130(Supplement 1):1561-.
18. Chu MP, Lieffers J, Ghosh S, Belch AR, Chua NS, Fontaine A, et al. Skeletal muscle radio-density is an independent predictor of response and outcomes in follicular lymphoma treated with chemoimmunotherapy. PLoS one. 2015;10(6):e0127589.
19. Brown LM. Survival analysis of Hodgkin lymphoma by age-at-diagnosis and gender based on WHO/REAL disease classification, surveillance epidemiology and end results data 1975–2005: University of North Texas Health Science Center at Fort Worth; 2009.
20. Reddy NM, Oluwole O, Greer JP, Engelhardt BG, Jagasia MH, Savani BN. Outcomes of autologous or allogeneic stem cell transplantation for non-Hodgkin lymphoma. Experimental hematology. 2014;42(1):39-45.
21. Pollack SM, Steinberg SM, Odom J, Dean RM, Fowler DH, Bishop MR. Assessment of the hematopoietic cell transplantation comorbidity index in non-Hodgkin lymphoma patients receiving reduced-intensity allogeneic hematopoietic stem cell transplantation. Biology of Blood and Marrow Transplantation. 2009;15(2):223-30.
22. Van Besien K, Loberiza Jr FR, Bajorunaite R, Armitage JO, Bashey A, Burns LJ, et al. Comparison of autologous and allogeneic hematopoietic stem cell transplantation for follicular lymphoma. Blood. 2003;102(10):3521-9.
23. Prescott J, Lu Y, Chang ET, Sullivan-Halley J, Henderson KD, Clarke CA, et al. Reproductive factors and non-Hodgkin lymphoma risk in the California Teachers Study. PLoS One. 2009;4(12):e8135.
24. Kato I, Chlebowski RT, Hou L, Wactawski‐Wende J, Ray RM, Abrams J, et al. Menopausal estrogen therapy and non‐H odgkin's

lymphoma: A post‐hoc analysis of women's health initiative randomized clinical trial. International journal of cancer. 2016;138(3):604-11.
25. Lu Y, Wang SS, Sullivan‐Halley J, Chang ET, Clarke CA, Henderson KD, et al. Oral contraceptives, menopausal hormone therapy use and risk of B‐cell non‐Hodgkin lymphoma in the California Teachers Study. International journal of cancer. 2011;129(4):974-82.
26. Hosgood HD, Gunter MJ, Murphy N, Rohan TE, Strickler HD. The relation of obesity-related hormonal and cytokine levels with multiple myeloma and non-Hodgkin lymphoma. Frontiers in oncology. 2018;8:103.
27. Lee JS, Bracci PM, Holly EA. Non-Hodgkin lymphoma in women: reproductive factors and exogenous hormone use. American Journal of Epidemiology. 2008;168(3):278-88.
28. Kane EV, Roman E, Becker N, Bernstein L, Boffetta P, Bracci PM, et al. Menstrual and reproductive factors, and hormonal contraception use: associations with non-Hodgkin lymphoma in a pooled analysis of InterLymph case–control studies. Annals of oncology. 2012;23(9):2362-74.
29. Esmeray E, Küçük C. Genetic alterations in B cell lymphoma subtypes as potential biomarkers for noninvasive diagnosis, prognosis, therapy, and disease monitoring. Turkish Journal of Biology. 2020;44(1):1-14.
30. Xu P, Liu X, Ouyang J, Chen B. TP53 mutation predicts the poor prognosis of non-Hodgkin lymphomas: Evidence from a meta-analysis. PLoS One. 2017;12(4):e0174809.
31. Gebauer N, Bernard V, Gebauer W, Thorns C, Feller AC, Merz H. TP53 mutations are frequent events in double-hit B-cell lymphomas with MYC and BCL2 but not MYC and BCL6 translocations. Leukemia & lymphoma. 2015;56(1):179-85.
32. Laugesen A, Højfeldt JW, Helin K. Role of the polycomb repressive complex 2 (PRC2) in transcriptional regulation and cancer. Cold Spring Harbor perspectives in medicine. 2016;6(9):a026575.
33. Yap TA, Winter JN, Leonard JP, Ribrag V, Constantinidou A, Giulino-Roth L, et al. A phase I study of GSK2816126, an enhancer of zeste homolog 2 (EZH2) inhibitor, in patients (pts) with relapsed/refractory diffuse large B-cell lymphoma (DLBCL), other non-Hodgkin lymphomas (NHL), transformed follicular lymphoma (tFL), solid tumors and multiple myeloma (MM). Blood. 2016;128(22):4203.
34. Morin RD, Johnson NA, Severson TM, Mungall AJ, An J, Goya R, et al. Somatic mutations altering EZH2 (Tyr641) in follicular and diffuse large B-cell lymphomas of germinal-center origin. Nature genetics. 2010;42(2):181-5.
35. Weigert O, Weinstock DM. The promises and challenges of using gene mutations for patient stratification in follicular lymphoma. Blood, The Journal of the American Society of Hematology. 2017;130(13):1491-8.
36. Wigle TJ, Knutson SK, Jin L, Kuntz KW, Pollock RM, Richon VM, et al. The Y641C mutation of EZH2 alters substrate specificity for histone H3 lysine 27 methylation states. FEBS letters. 2011;585(19):3011-4.
37. Oh EJ, Yang WI, Cheong J-W, Choi S-e, Yoon SO. Diffuse large B-cell lymphoma with histone H3 trimethylation at lysine 27: another poor prognostic phenotype independent of c-Myc/Bcl2 coexpression. Human pathology. 2014;45(10):2043-50.
38. Tsujimoto Y, Finger LR, Yunis J, Nowell PC, Croce CM. Cloning of the chromosome breakpoint of neoplastic B cells with the t (14; 18) chromosome translocation. Science. 1984;226(4678):1097-9.
39. Young RM, Staudt LM. Targeting pathological B cell receptor signalling in lymphoid malignancies. Nature reviews Drug discovery. 2013;12(3):229-43.
40. Barrans SL, Crouch S, Care MA, Worrillow L, Smith A, Patmore R, et al. Whole genome expression profiling based on paraffin embedded tissue can be used to classify diffuse large B‐cell lymphoma and predict clinical outcome. British journal of haematology. 2012;159(4):441-53.
41. Wang XJ, Medeiros LJ, Lin P, Yin CC, Hu S, Thompson MA, et al. MYC cytogenetic status correlates with expression and has prognostic significance in patients with MYC/BCL2 protein double-positive diffuse large B-cell lymphoma. The American journal of surgical pathology. 2015;39(9):1250-8.
42. Sehn LH, Gascoyne RD. Diffuse large B-cell lymphoma: optimizing outcome in the context of clinical and biologic heterogeneity. Blood, The Journal of the American Society of Hematology. 2015;125(1):22-32.
43. Knittel G, Liedgens P, Korovkina D, Pallasch CP, Reinhardt HC. Rewired NF‐κB signaling as a potentially actionable feature of activated B‐cell‐like diffuse large B‐cell lymphoma. European journal of haematology. 2016;97(6):499-510.
44. Pasqualucci L, Dalla-Favera R. SnapShot: diffuse large B cell lymphoma. Cancer cell. 2014;25(1):132-.
45. Kaur P. Follicular Lymphoma: Definition, Epidemiology, Pathobiology–Lymphomagenesis, Morphology, Variants, Immunophenotype, Prognostic Factors, Transformation. Follicular Lymphoma and Mantle Cell Lymphoma: Springer; 2020. p. 1-47.
46. Horn H, Ziepert M, Becher C, Barth TFE, Bernd H-W, Feller AC, et al. MYC status in concert with BCL2 and BCL6 expression predicts outcome in diffuse large B-cell lymphoma. Blood, The Journal of the American Society of Hematology. 2013;121(12):2253-63.
47. Inan S, Hayran M. Cell signaling pathways related to epithelial mesenchymal transition in cancer metastasis. Critical Reviews™ in Oncogenesis. 2019;24(1).
48. Tameire F, Verginadis II, Koumenis C, editors. Cell intrinsic and extrinsic activators of the unfolded protein response in cancer: Mechanisms and targets for therapy2015 2015: Elsevier.
49. Samadani AA, Norollahi SE, Rashidy-Pour A, Mansour-Ghanaei F, Nemati S, Joukar F, et al. Cancer signaling pathways with a therapeutic approach: An overview in epigenetic regulations of cancer stem cells. Biomedicine & Pharmacotherapy. 2018;108:590-9.
50. Dou J, Wen P, Hu W, Li Y, Wu Y, Liu C, et al. Identifying tumor stem-like cells in mouse melanoma cell lines by analyzing the characteristics of side population cells. Cell biology international. 2009;33(8):807-15.
51. Cho Y, Kim YK. Cancer stem cells as a potential target to overcome multidrug resistance. Frontiers in Oncology. 2020;10:764.
52. Lage H. An overview of cancer multidrug resistance: a still unsolved problem. Cellular and molecular life sciences. 2008;65(20):3145-67.
53. Méndez-Maldonado K, Bonifaz LC, Baay-Guzmán GJ, Aquino-Jarquín G, Zapata-Tarres M, Sadowinski-Pine S, et al. Hypoxia inducible transcription factor (HIF-1) regulates CXCL13 expression: Clinical implications in pediatric non-Hodgkin's lymphoma. Boletín médico del Hospital Infantil de México. 2014;71(1):25-35.
54. Bos R, Van Diest PJ, Van der Groep P, Greijer AE, Hermsen MAJA, Heijnen I, et al. Protein expression of B-cell lymphoma gene 6 (BCL-6) in invasive breast cancer is associated with cyclin D 1 and hypoxia-inducible factor-1 α (HIF-1 α). Oncogene. 2003;22(55):8948-51.
55. Henze A-T, Mazzone M. The impact of hypoxia on tumor-associated macrophages. The Journal of clinical investigation. 2016;126(10):3672-9.
56. Zelenetz AD, Abramson JS, Advani RH. NCCN Guidelines Version 2.2012 Panel Members. Non-Hodgkin's lymphomas. 2012.
57. Ansell SM, Armitage J, editors. Non-Hodgkin lymphoma: diagnosis and treatment2005 2005: Elsevier.
58. Maloney DG. Anti-CD20 antibody therapy for B-cell lymphomas. New England Journal of Medicine. 2012;366(21):2008-16.
59. Gazitt Y, Akay C, Doxey D, Thomas C. Synergy between CD52 and CD20 Antibody-Induced Apoptosis Correlates with the Extent of Co-Expression of CD20 and CD52 Antigens on Mononuclear Cells Derived from Chronic Lymphocytic Leukemia (CLL) and Non-Hodgkin's Lymphoma (NHL) Patients: Implications to Antibody-Based Therapy. American Society of Hematology; 2004.
60. Chanan-Khan A, Islam T, Alam A, Miller KC, Gibbs J, Barcos M, et al. Long-term survival with allogeneic stem cell transplant and donor lymphocyte infusion following salvage therapy with anti-CD52 monoclonal antibody (Campath) in a patient with α/β hepatosplenic T-cell non-Hodgkin's lymphoma. Leukemia & lymphoma. 2004;45(8):1673-5.
61. Intlekofer AM, Younes A. Precision therapy for lymphoma—current state and future directions. Nature reviews Clinical oncology. 2014;11(10):585-96.
62. Roschewski M, Staudt LM, Wilson WH. Diffuse large B-cell lymphoma—treatment approaches in the molecular era. Nature reviews Clinical oncology. 2014;11(1):12-23.
63. Cai Q, Westin J, Fu K, Desai M, Zhang L, Huang H, et al. Accelerated therapeutic progress in diffuse large B cell lymphoma. Annals of hematology. 2014;93(4):541-56.
64. Leslie LA, Younes A. Targeting oncogenic and epigenetic survival pathways in lymphoma. Leukemia & lymphoma. 2013;54(11):2365-76.

65. Barton S, Hawkes EA, Wotherspoon A, Cunningham D. Are we ready to stratify treatment for diffuse large B-cell lymphoma using molecular hallmarks? The oncologist. 2012;17(12):1562.
66. Sujobert P, Le Bris Y, de Leval L, Gros A, Merlio JP, Pastoret C, et al. The need for a consensus next-generation sequencing panel for mature lymphoid malignancies. HemaSphere. 2019;3(1).
67. Van Dijk EL, Auger H, Jaszczyszyn Y, Thermes C. Ten years of next-generation sequencing technology. Trends in genetics. 2014;30(9):418-26.
68. Taylor JG, Gribben JG, editors. Microenvironment abnormalities and lymphomagenesis: Immunological aspects2015 2015: Elsevier.
69. MacConaill LE, Garraway LA. Clinical implications of the cancer genome. Journal of Clinical Oncology. 2010;28(35):5219.

