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Molecular Predisposition and Environmental Factors in Development of Diffuse Large B Cell Lymphoma

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ABSTRACT

Due to increased amounts of industrial and food related carcinogens, rising rates of cancers such as Diffuse Large B Cell Lymphoma pose a serious threat to the wellbeing of people. Although cases of Diffuse Large B Cell Lymphoma (DLBCL) are found globally, a staggering majority of the cases are found in developed nations, such as the United States and United Kingdom. Current research on DLBCL mostly focuses on potential cures rather than on preventative measures individuals can take. Additionally, DLBCL, a type of non-Hodgkin's Lymphoma, is a diffused cancer. This means the cancerous cells travel all over the body through the lymphatic system. DLBCL has one of the highest rates of metastasis because the lymphatic system is connected to all organs in the body. After in-depth research into the impacts of genetic predisposition, environmental causation, and lifestyle habits on DLBCL lymphatogenesis, a research-backed map was created to help guide individuals with DLBCL genetic predisposition, who are exposed to certain carcinogens through food and drink, and the average inhabitant of developed countries to living lives that are preventative to DLBCL. This paper concludes that factors such as genetic testing, dietary changes including reduced consumption of bovine milk and edible dyes, and limited exposure to certain environmental carcinogens such as benzene all allow individuals to be proactive about their health. This research allows individuals who are concerned about their chances of developing cancer to understand and employ preventative measures into their lives, effectively preventing, stabilizing, or halting the development of any DLBCL.

Introduction

This research paper provides a comprehensive analysis of the effects of molecular/genetic predispositions and environmental factors on the development of Diffuse Large B Cell Lymphoma (DLBCL). Drawing upon statistical research, the paper examines both the genetic predispositions of individuals through gene sequencing and the environmental factors (eg. diet, exercise, pollutants…etc) that formulate higher chances of DLBCL and non-Hodgkin's Lymphoma subdiagnoses.

Diffuse Large Cell-B Lymphoma is a type of non-Hodgkin's lymphoma that grows quickly (high grade), which often happens to be caught in later stages (3 or 4). B cells are a type of lymphocytes, or white blood cells, that travel across the body to fight infection. B cells work with T cells, which are another type of lymphocyte that is unaffected in DLBCL. The lymphocytes travel throughout the lymphatic system, which encompasses the lymph glands, vessels, and spleen, a system of tubes carrying lymph (a clear, straw colored fluid that contains lymphocytes). In DLBCL, the cancerous B cells also spread through the lymphatic system. The cancer is not localized and it shows up throughout the lymphatic organs. It will only affect other non-lymphatic organs in later stages. Symptoms of DLBCL can include swelling in the neck, armpits, or groin (swollen lymph nodes) that expedites quickly. Symptoms of this lymphoma include drenching sweats at night,

high fevers without a cause, and losing a large amount of weight (10% of body weight). To diagnose, doctors perform biopsies, PET-CT scans, and lumbar punctures to detect blood abnormalities or locate tumor growths. It is important to research this type of cancer because its causes of cancer in general are often overlooked and can be prevented.

Additionally, this paper investigates the lifestyles that may encourage DLCBL's growth, with a focus on how certain processed food and drink can create genetic alterations/mutations in the DNA framework, impacting gene regulation and creating abnormal cell reproductive cycles that lead to cancerous B-cells produced by the lymphatic system for immune response.

Globally, DLBCL makes up ⅓ of every type of NHL (Non Hodgkin Lymphoma), ranging from 20% to 50% of cases in different countries (Wang, 2023). While the global death rate from DLBCL is 17%, the death rate in more developed nations, such as the United States, rises significantly to 21%.

As the most common type of NHL, oncologists and scientists have been searching for potential treatments to try and combat the disease, especially considering its prevalence. It is also important to note that developed countries, such as the United States and England, have higher DLBCL incidence rates compared to less developed countries in Asia and Africa. This significant difference shows that there are environmental, lifestyle, and genetic factors that control the development of malignant B-cells in adult humans. The global occurrence rate for DLBCL is expected to rise significantly in the next 50 years, for the amount of carcinogenic chemicals being released into the atmosphere and environment as industrial composition practices increase. This paper provides insight into the many different factors that may be influencing these trends globally.

The American Cancer Society reports cancer cases to be trending upward in the United States, from 1.9 million in 2022 to over 2 million in 2023 (ACS, 2024). DLBCL makes up 40% of all NHL cases in the US. Interestingly, a clear age trend has been established with DLBCL, showing that over half of the diagnosed cases range in age between 65 to 84. (Wang, 2023) This trend could be explained by the numerous carcinogenic civilian infrastructural exposures during the 1940-1980. Additionally, variations in rates across different racial and ethnic groups suggest the influence of genetic predispositions, environmental exposures, and socioeconomic factors in the risk of developing DLBCL. The United States has allowed the use of common carcinogens in various products, such as BPA (found in food/toy plastics), aspartame (an artificial sweetener), and phthalates (found in many beauty care products). These chemicals, often banned in other (mostly European) countries, have been shown to have detrimental effects on the health of humans, and damage genetic coding, allowing cancers like DLBCL to form. As civil and government advocates against endocrine disruptors and common carcinogens gain more traction, the US consumer market can become a healthier and safer industry for growing populations in the States.

By evaluating the genetic predisposition of patients with certain genetic traits and markers as well as environmental exposures leading to DLBCL, this paper provides insight into the effects of disposition and exposure on the development of DLBCL. It is important to research this type of cancer because its causes of cancer in general are often overlooked and can be prevented. Additionally, this paper investigates the lifestyles that may encourage DLCBL's growth, with a focus on how certain processed food and drink can create genetic alterations/mutations in the DNA framework, impacting gene regulation and creating abnormal cell reproductive cycles that lead to cancerous B-cells produced by the lymphatic system for immune response.

It highlights the importance of preventative treatment through gene therapy, early detection systems, and informed knowledge on how certain everyday products such as food containers, cosmetics, and infrastructural equipment around homes create chances for DLBCL lymphoma and its subtypes to form. The information presented in this paper may eventually lead to the increase in the lifespan of those with a higher probability of development, and minimize the preventable environmental causes of this disease.

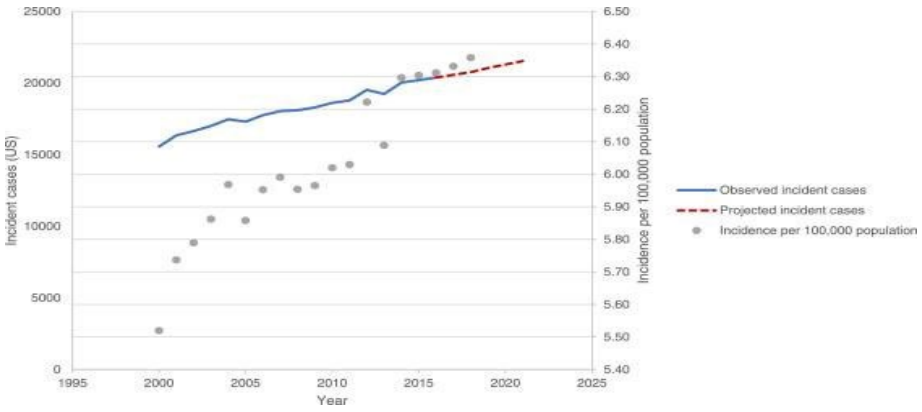

Figure 1. Estimate of people living with DLBCL worldwide, as well as projected incidence cases
Source: Chihara, 2022

Methodology

The goal of this research paper was to identify and establish potential causes for the most common type of NHL, DLBCL. This study utilized a literature review, examining a variety of informative sources of information. Case studies and clinical trials were essential for the comprehensive analysis of potential treatments, additionally. To pursue qualitative data analysis and present information accordingly, this paper was sectioned into different subcategories to better address the issues with environmental and genetic causes. Firstly, the genetic abnormalities leading to lymphatogenesis were examined to determine potential genetic anomalies that leave a person susceptible to DLBCL development, and overviews potential genetic treatments. Second, chemical/environmental exposure was discussed, shedding light on chemicals such as pollutants that mutate genetic code and cause cancer cells to form. Third, dietary lifestyle leading to alterations in genes was overviewed, exposing bovine milk as a potential precursor to DLBCL. Lastly, potential future treatments were talked about, creating hope for the future of DLBCL treatment. This research utilized online sources including existing research papers and clinical trials. This study has significantly reduced research biases by analyzing a variety of sources with differing research objectives, researchers, and time periods to guarantee that a variety of perspectives were taken into consideration.

Genetic Abnormalities Leading to DLBCL Lymphatogenesis

DNA and alternate forms of genetic coding create the framework in which life can develop. However, mutations and alterations in the genetic code provide an opportunity for the development of cancers, such as DLBCL (Yanguas-Casás, 2021). Mistakes in the chromatin remodeling process (going from condensed chromatin to unpacked chromosomes in anticipation for DNA replication) as well as mutations in the p53 enzyme (a tumor suppressor gene) create opportunities for lymphoma cells to be produced. DLBCL has been tracked to have several emerging subtypes of cancers and has brought awareness to the increasing importance for personalized treatment based on specific causes for DLBCL.

Targeted treatments are specific types of cancer fighting agents that are “personalized” towards a certain individual's treatment. Because of the complex nature of DLBCL, targeted treatments provide more effective therapies for treatment. By locating the exact cause of the cancer, medical professionals and scientists can effectively treat the patient at the source of the mutation instead of having to affect the entire body’s normal functioning with systemic chemotherapy and distressing medications that are notorious for causing intense side

effects. One of the most common genetic mutations that cause DLBCL is a non-silent point mutation. (Pasqualucci, 2018) A point mutation is a type of mutation that causes a change (such as a deletion or substitution) of a single nucleotide base within the DNA sequence.

This change can occur during DNA replication or due to other factors such as exposure to mutation-causing elements. This in turn alters the reading of the codons on the mRNA strand by tRNA complexes and results in incorrect amino acids being translated from the erroneous sequence. The protein that was meant to be coded for is now missing, (either a protein is not coded for at all or the protein is incorrect), and the incorrect protein can cause many issues, especially with cancer predisposition. This simple change can cause catastrophic effects on the tumor regulation cycle (See Figure 1).

Chromosomal translocations also play a large role in altering genetic code to create lymphatic tumors. Chromosomal translocations occur when a fragment of a chromosome breaks off and reattaches itself to another chromosome. These chromosomes are homologous, meaning they code for the same gene, however house different phenotypic traits. The most common chromosomal abnormality in DLBCL is BCL6 translocations, which occur at 3q27 and can involve many immunoglobulin (Ig) and non-Ig genes as partners (Zhou, 2018). Ig/BCL6 fusions are common in high BCL6 gene expression, while non-Ig/BCL6 fusions can have low BCL6 mRNA levels. These chromosomal changes in DLBCL do not create new proteins in the chromosomes directly but disrupt the normal control of existing genes, leading to uncontrolled cell growth and cancer development. When a chromosome controlling cell division (such as the gene that codes for p53) is disrupted, cell division can occur without restriction, which is detrimental to the health of the person.

The rate of BCL6 translocation in DLBCL patients has been found to be 20-40%, a staggeringly high statistic. Not only does this translocation impact one of the 3 Immunoglobulin genes (Ig), this also has a potential to impact some forms of non-Ig partner genes (Ohno, 2004). When this involves the non-Ig gene, the BCL6 gene can become controlled by different and more diverse promoter sequences, leading to unregulated gene expression. This gene normally helps control the growth of B cells, which are the cells that turn cancerous in DLBCL. When a translocation occurs, the BCL6 gene ends up in a new location where it gets turned on unnecessarily and very often. This overactive BCL6 causes B cells to grow uncontrollably, leading to DLBCL lymphatogenesis. The cancerous B cells then can metastasize to other areas of the body, including vital organs. Because DLBCL is one of the most aggressive and high grade cancers identified in humans, it is a very challenging cancer to treat.

Changes in promoter regions due to chromosomal translocations can lead to significant alterations in gene expression. When a gene is relocated to a new chromosomal environment during crossing over, it may come under the influence of different regulatory sequences that eventually change the way that gene is expressed. A proto-oncogene is a type of normal somatic cell that turns cancerous. Proto-oncogenes are often what tumors are made of. For example, if a proto-oncogene is moved next to a highly active promoter sequence (usually located in the 5' location of the gene) , it can become overexpressed, driving the uncontrolled replication of cells. In DLBCL, translocations involving the BCL6 gene often place it near promoters that are abnormally active in B cells, leading to the excessive production of the BCL6 protein. This disrupts the normal regulation of cell growth, contributing to the development and progression of cancers. Such changes in promoter regions are an extremely critical factor in the molecular buildup of many cancers.

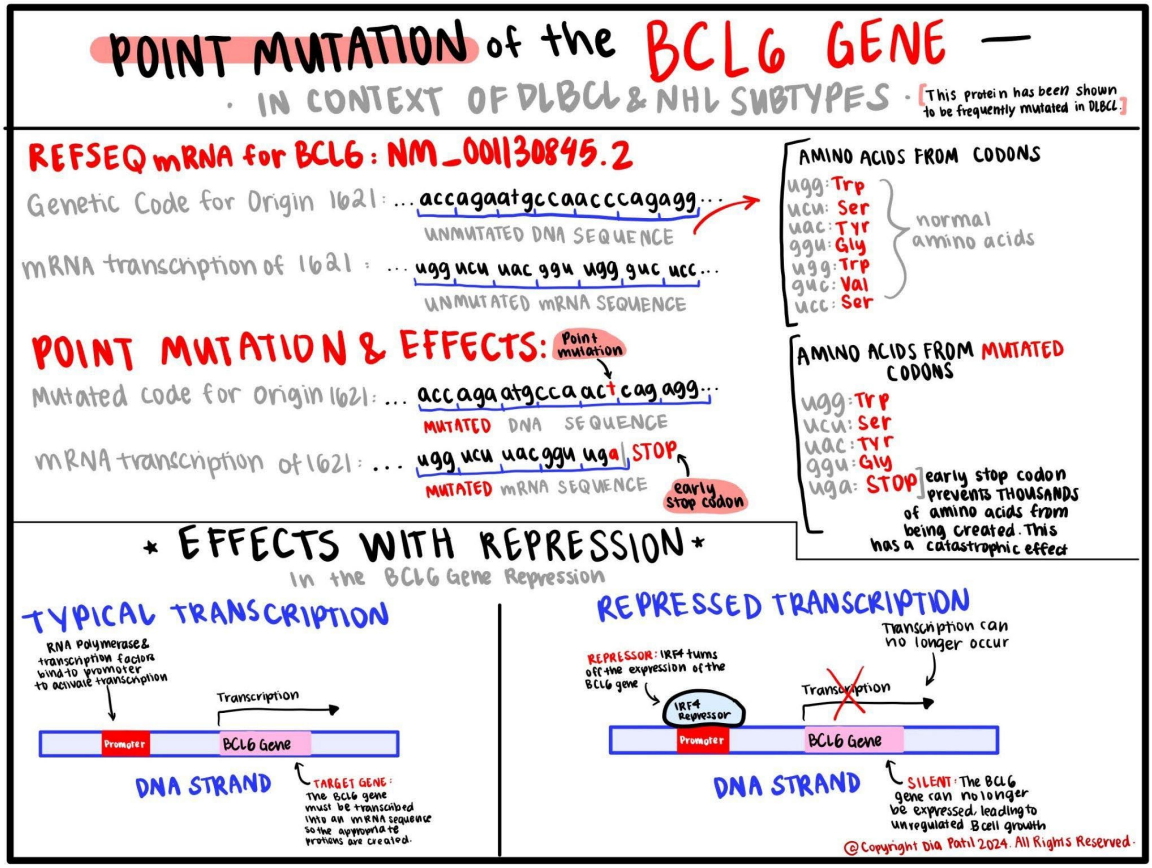

Figure 2. Mutations in the BCL6 Gene leading to DLBCL Lymphatogenesis. Repressor IRF4 in conjunction with the promoter region is also discussed in relation to transcription of BCL6. Diagram created by Dia Patil, Copyright 2024

Chemical Exposure and Environmental Causations in Relation to DLBCL

It is necessary to identify the environmental and lifestyle risk factors in order to investigate rare exposures and NHL subtype-specific associations. While only a few extremely consistent risk factors for NHL aside from immunosuppression and certain infectious agents have been shown so far, associations with several lifestyle and environmental factors have been shown to have a probable cause in cancer development in epidemiologic studies, showing a need for further study (Bassig, 2012).

Certain chemicals, such as polychlorinated biphenyls (PCBs). PCBs are often found in pre 1979 paint products, as they are now banned in the United States. PCBs are absorbed into body fats, as they are lipid soluble. They do not leave the body through excrement or urine, meaning they accumulate over time (a phenomenon known as bioaccumulation) and cause carcinogenic environments within the body (Moubadder, 2020). Certain medications, viral infections, and autoimmune disorders have also been flagged as NHL specific causation agents.

Further correlations between farming product and fertilizer in relation to NHL and NHL subtype diagnoses have also been identified. Various popular pesticides, herbicides, and Volatile Organic Compounds (VOCs) that are used in agricultural (and sometimes industrial) settings have been linked to NHL (Wu, 2019). In further study, it was found that organochlorine insecticides, often used as agricultural aids and previously as in home pest control, has been shown to act as an endocrine disruptor. Endocrine disruptors are chemicals that

interfere with the natural function of the endocrine system. Organochlorine insecticides (OCIs) alter hormonal release in the body, leading to liver damage and increased rate of liver tumors/cancer.

DDT, a well-known banned pesticide in the United States, was widely used in the 80s as an effective pest control, however, later led to a catastrophic array of biological complications in all that were exposed. DDT DMRs in three genes, CCDC85A, CYP1A1 and ZFPM2, which have been linked to pubertal development and breast cancer susceptibility, were genetically mutated by DDT exposure to the mother during prenatal development. The findings suggest prenatal DDT exposure may have life-long consequences due to alteration of genes, majorly in those that regulate breast cancer in affected females. (Emeh, 2023)

In a study comprising 29,605 cancer cases, NHL subtypes were the only cancer that consistently demonstrated significant association between external exposure to dioxins and cancer mortality. Dioxins are a form of chemical environmental pollutant that creates respiratory irritation and alteration of genetic code. Bioaerosols, such as organic dust from agricultural produce, contain pesticide residue laced with dioxins. If produce is not washed correctly, the dioxins can be ingested and create DLBCL NHL-subtype development.

Additionally, the most common type of agricultural herbicide, Roundup, was studied by IARC after concerns were raised regarding the potential association of the herbicide as NHL and NHL subtypes. Results showed an ingredient in Roundup called glyphosate was “probably carcinogenic to humans”. The manufacturing company, Monsanto, was sued by many individuals and organizations. Glyphosate exposure creates a 41% greater chance of chromosomal mutation, (Grayson, 2021) leading to the development of NHL and its subtypes, including DLBCL.

When carcinogens interact with DNA, it can lead to mutations in specific genes like BCL6. These carcinogens can cause chemical modifications in the DNA bases. Carcinogens cause DNA adducts, which are abnormal chemical structures formed when the reactive byproducts covalently bond to specific areas on the DNA strand (Pasqualucci, 2018). These adducts can mutate the normal DNA structure and interfere with its replication and repair processes. In the BCL6 gene, these mutations can occur within coding sequences that produce proteins, altering its expression or function. This disruption in BCL6 function impacts its ability to regulate cell growth and differentiate between healthy and cancer cells. Therefore, cells lose their normal growth control mechanisms and begin to replicate uncontrollably, leading to the formation of tumors that are attributed to DLBCL.

One specific chemical, benzene, found in products like gasoline and other petroleum products, can cause mutations in the BCL6 gene, contributing to the development of DLBCL. Benzene exposure in industries like chemical manufacturing and petroleum refining leads to higher risk in individuals frequently exposed (Liu, 2022). Metabolic activation in the liver to rid the body of benzene toxins forms reactive byproducts that bind to DNA, disrupting its structure and promoting uncontrolled cell growth (leading to cancerous tumors).

Throughout the world, humans are exposed to many carcinogens from varying sources. These carcinogens have been proven time and time again to cause cancer and genetic mutation. Strict regulations and safety measures in workplaces and public awareness campaigns are crucial to push the effort to reduce exposure and lower the incidence of DLBCL.

Dietary Components and Lymphatic Interference: Alterations in Genetic Code

The food that an individual ingests has more than just a nutritional effect. In a more specific dietary sense, studies have tied dairy and dairy products to the development of DLBCL through milk-related agents, such as milk-derived exosomes (MDEs) and microRNAs (miRs) in lymphomagenesis. MDE miRs from cow's milk might affect B cell proliferation and the expression of key genes involved in DLBCL, potentially contributing

to lymphomagenesis (Melnik, 2023). The authors suggest that bovine MDEs and their miRs should be considered potential human pathogens and should be removed from the dairy market for consumption. A positive association between total dairy product, milk, and cheese consumption and the risk of NHL was found, particularly in DLBCL. The risk of NHL increased with each 200 g/day increment in total dairy product and milk consumption (Wang et al.2016). In other studies conducted by the European Prospective Investigation into Cancer and Nutrition as well as the China Kadoorie Biobank found similar findings, strengthening the theory that bovine products creates mutated B lymphocytes.

On a molecular level, the studies identified a hormone called IGF-1, present in cow's milk that activates the IGF-1 receptor (IGF1R). IGF1R, a well known cancer regulation transcription factor, controls the rate at which DNA is replicated in the cell mitotic process, also regulating the growth of DLBCL cancer cells (Melnik, 2023). The pathway encourages mitogenesis (induction of mitosis or cell proliferation) but prevents the apoptotic processes from occurring (preventing cell death). IGF1R significantly decreases a protein called Hippo-yes-associated protein (YAP). However, when IGF-1 is introduced into the body from dairy products and into the IGF1R receptor, YAP increases, causing unregulated cell replication and the ultimate spread of DLBCL cells. Infectious agents such as bovine leukemia virus (BLV) which creates cancer cells that reside in B lymphocytes specifically, cause the development of DLBCL.

Additionally, food dyes, often used to enhance the color of processed foods and beverages, have raised concerns about their potential detrimental health effects, including their link to certain types of cancer like DLBCL. These dyes, such as common colorants Red 40, Yellow 5, and Blue 1, which are added to food products to make them visually appealing to consumers. However, studies have suggested that prolonged consumption and exposure to these artificial dyes may increase the risk of developing cancer, including DLBCL (Dwivedi, 2015).

The process in which food dyes contribute to DLBCL is because of their ability to become carcinogens. These dyes undergo metabolic reactions in the body when being digested, forming byproducts that damage cellular DNA. For example, Red 40, one of the most commonly used food dyes, has been shown to generate reactive oxygen species (ROS) in cells, which can cause damage to DNA. ROS are chemicals formed by oxygen gas, water, and hydrogen peroxide (Dwivedi, 2015). This damage can lead to mutations in critical genes like BCL6 , which plays a key role in regulating cell growth and differentiation. When BCL6 is mutated, its normal function is disrupted, making cells grow and divide uncontrollably. This eventually leads to DLBCL cancers.

Furthermore, food dyes may also have indirect effects on cancer development by creating inflammation and stress in the body. These processes make the body more susceptible to tumor growth and progression. Additionally, some studies have suggested that certain food dyes may interfere with the normal function of the immune system, compromising its ability to identify and eliminate cancerous cells.

Overall, while more research is needed to fully understand the connection between food dyes and DLBCL, limiting exposure to these food dyes by avoiding certain foods. Highly processed, brightly colored, or synthetic food items should have a limited overall part of the diet. This can limit the amount of exposure to these carcinogenic dyes in foods.

Current Treatments and Efficiency of Cancer Eradication

Currently, oncologists and healthcare providers have standard treatments for their patients with DLBCL. These treatments are generalized, meaning they will impact the entire body. Oftentimes, traditional methods such as chemotherapy will result in painful side effects, such as mouth sores, joint deterioration, and hairfall (ACS, 2020)

The standard chemotherapy for DLBCL is the R-CHOP treatment, which comprises a series of drugs taken in combination. This treatment includes rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone. For a long time, adding other drugs to R-CHOP didn't have significant effects on how well patients did. However, the results of a recent study called the POLARIX trial are promising.

Doctors replaced vincristine with a drug called polatuzumab-vedotin in the R-CHOP regimen, creating a new combination called R-CHP (Frontzek, 2022). This new combination improved the time patients lived without their disease getting worse, especially for those with a higher risk of the disease progressing quickly. Because of these positive results, R-CHP plus polatuzumab-vedotin might soon become the recommended first treatment for these high-risk DLBCL patients, awaiting approval from health authorities.

One pivotal approach is immunotherapy, which utilizes the body's immune system to recognize and attack cancer cells. Monoclonal antibodies, such as rituximab, are commonly used in DLBCL treatment (Basel, 2021). Rituximab targets CD20, a protein found on the surface of B-cells, encouraging their destruction by the immune system's healthy T cells. This targeted therapy has helped improve outcomes for many DLBCL patients, particularly when combined with traditional chemotherapy.

Another treatment that is as a later option is the use of targeted therapies that focus on correcting specific molecular abnormalities that encourage cancer growth. The BCL2 inhibitor venetoclax has been used in certain DLBCL cases with BCL2 overexpression, leading to programmed cell death inhibition (Matulis, 2020). This means the BCL2 is abundant in the body and causes cells to continue to survive, meaning it prevents cell death (apoptosis). Additionally, small molecule inhibitors (SMIs) such as lenalidomide and ibrutinib target signaling pathways involved in cancer cell development, offering alternative treatment options for DLBCL patients.

Lastly, another common treatment is radiation therapy. Radiation therapy uses high-energy beams of light to target and destroy cancer cells in specific areas of the body. It is often used to shrink tumors or remove any residual cancer cells after primary treatment (eg. R-CHOP). By delivering radiation in a precise area to affected lymph nodes or other sites of cancer spread, radiation therapy can help control the spread of the cancer cells and increase survival rates in patients with DLBCL. (Choi, 2023) Additionally, advancements in radiation technology, such as intensity-modulated radiation therapy (IMRT) and image-guided radiation therapy (IGRT), have further advanced precise removal of tumor tissue while leaving the healthy organs untouched. Radiation therapy remains a helpful tool in treatment for DLBCL.

Developing Therapeutic Treatments for DLBCL

In this modern age, many types of cancer treatments have been established, ranging from chemotherapy to oral pills. However, non-conventional treatments are on the rise, especially those that are meant to be specifically targeted to a specific type of cancer (Ritter, 2019). To even start identifying potential treatments for DLBCL, scientists must have an advanced understanding of the organs and body systems' responses to the specific cancer. In these cases, the use of 3D organoids has been employed.

3D organoid models are lab-grown miniature versions of organs that scientists use to study cancer's effects on the body in a smaller scale. By administering potential medicines and chemical treatments (chemotherapy) to the organoids, labs can study the effects of the medicine on a smaller and safer scale without testing on patients and lab trial volunteers (Frontzek, 2022). The organoids would react the same way human organs would under the same conditions. DLBCL is an extremely complex disease that needs to be studied more to identify the complex natures of the development of this specific cancer. (Yanguas-Casás et al, 2021)

Using these organoids, certain types of therapies in development have been put through clinical trials and tested in these models. A type of therapy called CAR-T cell, or Chimeric Antigen Receptor T Cell therapy, has been introduced and, in the future, may be commonly being used as a 3rd line of defense in DLBCL treatment.

Studies show that if targeted treatments do not prove effective on the cancerous B cells, gene alteration serves as an excellent alternative. By employing the use of CRISPR, a restriction enzyme based tool that can find and alter specific sets of genetic code, genetic mutations and removing certain genes. In patients with DLBCL, mutations in the p53 cancer-regulating enzyme can be targeted and fixed by CRISPR CAS-9 in CAR-T.

CAR-T cells are genetically engineered T cells structured to recognize cancer antigens (proteins) in its native form without the need for presentation within the MHC class I molecule. A CAR T-cell is made up of multiple components: a part that targets specific protein on cancer cells, a connector section, and a part that activates T-cells to fight cancer and helps the CAR T-cells last longer in the body. The T cells identify DLBCL antigens and can destroy the cancer cells. All the CAR T-cells approved for use right now focus on 'cluster of differentiation 19' (CD19), an antigen found on cancer cells, a common antigen in DLBCL treatment.

However, collecting enough T-cells from patients to make this treatment can be difficult, especially if the patient has already had previous immune diminishing treatments. The generation of CAR-T cells can also take a while, which is risky for patients with high grade cancers. Because of these issues, scientists are looking into creating CAR T-cells from donors that can be ready to use anytime, bypassing these delays.

In a clinical trial conducted in 2022 by the National Cancer Institute, the effect of CAR-T cell immunotherapy was tested on patients with B-Cell lymphoma. White blood cells (T cells) were taken from the patients, genetically altered with a retrovirus, and then infused back into the patient (Rosenberg, 2022). This therapy, also known as a gene transfer, contains the gene for anti-CD19 in the retrovirus. The drugs Cyclophosphamide and Fludarabine were also incorporated into the treatment to assist with the study. At the end of the study, the treatment was proven to be effective, providing 37% of patients with total remission, 40% with stable growth, and 21% with no change. CAR-T has proven to be a helpful tool, and with more research and changes, patients can receive better outcomes from these developing treatments.

Although new treatments for DLBCL are being studied and released, doctors are still figuring out the best way to use these treatments together and in what order. Also, it's not yet clear why some patients respond well to certain treatments while others do not, or which patients will benefit most from different types of therapy. More research into the biology of DLBCL and how these new treatments affect the disease is needed to answer these questions. Understanding these aspects better could lead to more effective treatment combinations and strategies that could potentially cure more patients with DLBCL.

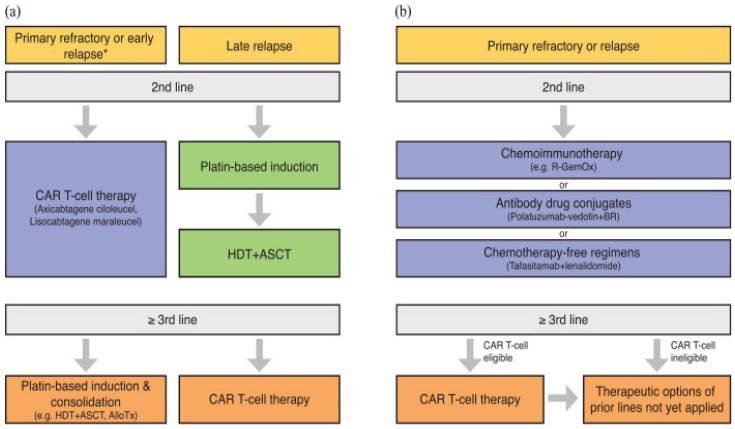

Figure 3. Therapeutic algorithm for patients with R/R DLBCL. Source: Frontzek, 2022

Description: For transplant-eligible patients, depending on the time point of relapse, either an anti-CD19 CAR T-cell therapy (using axicabtagene ciloleucel or lisocabtagene maraleucel) or platin-based induction followed by high-dose therapy (HDT) and autologous stem cell transplantation (ASCT) represent the

standard approach (*within 12 months after completion of first-line therapy). (b) For transplant-ineligible patients, chemoimmunotherapy, antibody drug conjugates, as well as chemotherapy-free regimens represent potential therapeutic options in the second line. Third-line therapy using anti-CD19–directed CAR T-cells represents a potentially curative option for eligible patients.

Results/Conclusions

The purpose of this study was to identify and discuss potential anthropogenic, dietary, and genetic causes in human development for DLBCL, a high-grade NHL subtype. Although some of the identified causes of DLBCL can be unavoidable, the research has determined preventable causes of DLBCL that people can actively work to avoid in their lifestyle.

Firstly, concerning genetic abnormalities, Individuals should actively identify risk factors for DLBCL in their family, such as past familial history of NHL and NHL subtypes or autoimmune disorders, such as hepatitis B and HIV. By actively identifying these risk factors, individuals can consult with their primary care physicians to get NHL identifying genetic tests regularly to prevent high-grade cancers. By being proactive about this disease, the rate of development can lower significantly. Additionally, dietary habits have been shown to cause changes in the body, specifically bovine dairy altering genetic code and signal transduction. When signaling pathways are disrupted by bovine dairy consumption, the risk of genetic mutations in DNA and p53 enzymatic code increases significantly. p53, a tumor suppressor gene, being affected would have catastrophic effects in causing DLBCL.

The government must also recognize and play a role in decreasing chemical/environmental exposure in communities, such as old water pipes containing the cancer-causing chemical Polychlorinated biphenyls (PCBs).

Although following these recommendations to prevent DLBCL can prove to be a challenge because of the widespread influence of carcinogens in modern society and lack of economically friendly genetic testing, these recommendations are crucial to preventing potential causes of DLBCL.

Limitations

This study aimed to examine and discuss data that shows correlation with the increased chances of developing DLBCL cancer. As a secondary literature review, this research paper uses several primary sources, including research studies, other reviews, and clinical trials to make connections and discuss potential effects of certain changes in the body and their relation to cancer development. In an effort to consider many varying perspectives from different sources around the world, the researcher attempted to ensure all of the sources used were diverse and could be accurately applied to the paper. Considering DLBCL and cancer in general are very complex diseases, it is important to ensure that the sources are complex as well. This research also took sources from a variety of different perspectives and outcomes in treatment, in an effort to reduce writer bias. However, DLBCL is not a very well studied cancer, and there was some difficulty finding specific details relating to its causation.

It is important to note that rates of DLBCL are staggeringly higher in developed nations like the United States and the United Kingdom. Therefore, one limitation may be a lack of worldwide studies done on patients globally. Some of the results may not be generalizable, and may only represent these specific countries. For example, the clinical trial used in this study regarding CAR-T was completed in the United States, and most of all the studies the researcher viewed were also conducted in the States.

Secondly, many of the sample sizes in studies utilized were small, consisting of 50-75 people. Although the rates of DLBCL active cases in the States is several thousand, these studies were unable to gain a sufficient

amount of participants (appx. 200-330 minimum). This does not discredit the results of the patients individually, however the studies on certain treatments may not reflect accurate percentages.

Lastly, the results of this study rely on the idea that individuals would have the financial and physical means to pay for certain treatment and live in a preventative lifestyle. Socioeconomic conditions have a significant impact in people's ability to find treatment or adopt preventative measures for DLBCL, which is a factor that must be considered in future research. In summary, this research took great efforts to have unbiased and generalizable perspectives, but there were still some limitations on the sources used.

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