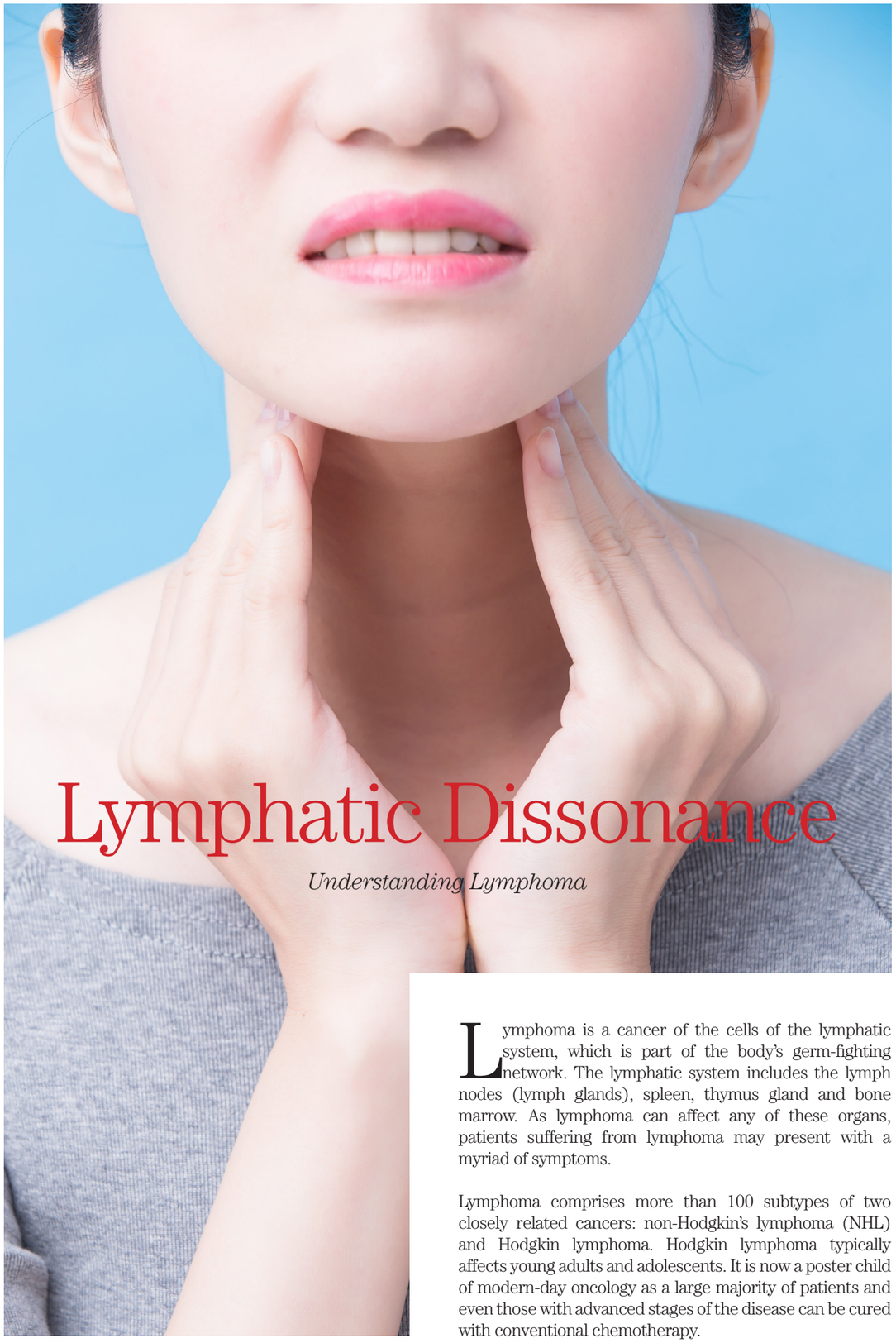


Lymphatic Dissonance

Understanding Lymphoma

Lymphoma is a cancer of the cells of the lymphatic system, which is part of the body's germ-fighting network. The lymphatic system includes the lymph nodes (lymph glands), spleen, thymus gland and bone marrow. As lymphoma can affect any of these organs, patients suffering from lymphoma may present with a myriad of symptoms.

Lymphoma comprises more than 100 subtypes of two closely related cancers: non-Hodgkin's lymphoma (NHL) and Hodgkin lymphoma. Hodgkin lymphoma typically affects young adults and adolescents. It is now a poster child of modern-day oncology as a large majority of patients and even those with advanced stages of the disease can be cured with conventional chemotherapy.

Non-Hodgkin's lymphoma, on the other hand, is far more common and by itself, constitutes numerous other subtypes. These subtypes are based largely on whether the lymphoma cancer cells originate from the B or T-lymphocyte. These are the basic components of the lymphatic system and they serve different functions in maintaining our immunity. B-cell lymphomas constitute about 85% of non-Hodgkin's lymphoma, while T-cell lymphomas comprises only about 15%. Non-Hodgkin's lymphoma ranges from indolent (slow growing) to highly aggressive (fast growing).

Of late, with the acceleration of new drug discoveries and introduction of targeted drugs into the lymphoma therapeutic armamentarium, the prognosis of B-cell lymphomas has improved tremendously. The cure rates of aggressive B-cell lymphomas have improved remarkably. While indolent B-cell lymphomas are still considered incurable, survival is now significantly prolonged, such that these lymphomas are more akin to chronic diseases than terminal cancers. This is predicated on the improved understanding of the biology and the underlying mechanisms that drive B-cell lymphomas.

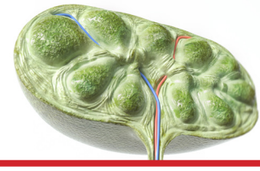
The possibility of expediently conducting clinical trials through international collaborations leads to rapid drug approvals worldwide. On the other hand, due to the rarity of T-cell lymphomas and the paucity of clinical trials investigating effective drug combinations in the diseases, the prognosis of many patients with T-cell lymphoma still remains poor and this certainly represents an unmet need in the lymphoma space.

RISK FACTORS AND SYMPTOMS

Lymphoma is the fifth and sixth most common cancer for males and females respectively in Singapore, with about 800 new cases in total diagnosed per year (according to the Singapore Cancer Registry Annual Report 2018: Singapore Cancer Registry 50th Anniversary Monograph 1968-2017). Little is known about the causes of lymphoma. Almost all types of lymphoma contain mutations within the DNA, and risk factors include old age, exposure to certain chemicals, immune deficiency (due to immunosuppressive drugs, HIV/AIDS or congenital immune deficiency), certain infections (*H. pylori* of the stomach and human T-lymphotropic virus), radiation exposure, and possibly some viruses such as Epstein-Barr virus and hepatitis C virus.

Common signs and symptoms of lymphoma include enlarged lymph nodes, lethargy, fever, night sweats, poor appetite, weight loss, pain, profound fatigue, itching and abnormal routine blood tests. Certain observations may raise the suspicion of lymphoma. The doctor or physician may feel enlarged lymph nodes during a routine clinical examination, or a computed tomography (CT) or positron emission tomography (PET) scan may show an enlarged liver, spleen or lymph nodes. The most accurate way to diagnose lymphoma is by obtaining a biopsy of the enlarged or abnormal tissue. A biopsy involves surgically removing a small tissue sample and looking at the specimen under a microscope by the pathologist.

> Historically, the mainstay of treatment for lymphoma has been conventional chemotherapy. Being a type blood cancer, lymphoma cells are most "druggable" as chemotherapy can be easily carried by the blood stream to the lymphoma cells.



As we begin to know more about the biology of lymphoma, the nomenclature and sub-classification are also evolving to be more complex. Hence, histological interpretation by an experienced haemato-pathologist is important, especially if we are dealing with the rarer entities. Lymphoma can also present in bone marrow, and in some instances, the diagnosis is made by bone marrow biopsy

MODERN TREATMENT OPTIONS FOR LYMPHOMA

Treatment of lymphoma has evolved a great deal over the past few years and is tailored to the specific subtype of lymphoma. Some lymphomas require immediate treatment (aggressive) while others can be watched and treatment administered only at the time of disease progression (indolent).

Recent advances have focused on increasing the precision of medicines and activating the body's immune system to enhance the destruction of lymphoma cells. As a result, the survival of patients with the two most frequent lymphomas (i.e. diffuse large B-cell lymphoma and follicular lymphoma) have improved remarkably with the incorporation of rituximab (the first form of immunotherapic agent) as a standard treatment regimen. New insights into the biology of lymphomas provided by studying patterns of the mutational landscape in the cancer cell has further helped improve our ability to target lymphoma-driving abnormalities in the cancer's genome or biomarker targets on lymphoma cells.

Although we can now cure most patients with Hodgkin lymphoma, the past decade has seen advances in our ability to identify patients who are most likely to be cured with less toxic treatment approaches. Unfortunately, our ability to improve the treatment of patients with T-cell lymphoma has not kept pace with the management of those suffering from B-cell lymphomas and Hodgkin lymphoma. Hopefully, with the ongoing efforts in studying the various mutations driving T-cell lymphoma, we can begin to improve treatment results over the next decade.

Historically, the mainstay of treatment for lymphoma has been conventional chemotherapy. Being a type blood cancer, lymphoma cells are most "druggable" as chemotherapy can be easily carried by the blood stream to the lymphoma cells. However, the pet peeve with chemotherapy is that the cell killing is indiscriminate. Bystander healthy cells are also affected and this accounts for the notorious side effects of traditional chemotherapy like hair loss, nausea, diarrhoea, bleeding and infections. As there is a limit to how much chemotherapy the body can receive, autologous stem cell transplantation was developed to allow the body to receive a way higher dose of chemotherapy without permanently damaging the bone marrow. This procedure has remained a standard treatment for patients with relapsed aggressive lymphomas. Precision cancer medicine, on the other hand, uses targeted drugs and immunotherapy engineered to directly attack lymphoma cells with specific abnormalities, with the goal of leaving normal cells largely unharmed. Here are some therapies that exemplify the advances being made:

Monoclonal antibodies - Rituximab is the prototype, while obinutuzumab is a bio-engineered and improved version. These man-made antibodies are designed to attach to CD20, a protein found on many types of B-cells. It is thought to work by attacking targeted cells both directly and together with the body's immune system.

Antibody drug conjugate (ADC) - A type of precision cancer agent that targets specific proteins on the lymphoma cell surface with an antibody. The antibody is in turn attached to a cancer cell killing agent that is then internalized following attachment of the antibody to the cancer cell and this causes the cancer cell to die when the toxic effect of this "smart bomb" is unleashed. Important examples in this class includes bretuximab vedotin and polatuzumab vedotin

Checkpoint inhibitors – This is a new class of medicines that help the immune system recognize and attack cancer. These drugs block PD-1, a protein that inhibits certain types of immune responses. Their application releases the brakes on the immune system, thereby allowing the body to unleash its own army upon the cancer. Pembrolizumab and nivolumab are now standards of care for relapsed cases of Hodgkin lymphoma.

BCL-2 inhibitors - The BCL-2 protein is over-expressed in some lymphoma cells, and it contributes to a cancer cell's survival and resistance to standard chemotherapy. Venetoclax is an agent that binds to the BCL-2 protein, thereby disabling its ability to keep cancer cells alive.

Bruton tyrosine kinase (BTK) inhibitors - These are targeted agents that work by inhibiting the enzyme BTK which is needed by the cancer to multiply and spread. BTK inhibitors like ibrutinib and acalbrutinib have now been moved to the frontline standard of care for certain lymphomas that rely on BTK for growth.

Bispecific antibodies - This treatment represents an innovative precision immunotherapy approach that helps the body's immune system target lymphoma cells. These antibodies have two arms; one arm of the drug attaches to a specific protein on the lymphoma cell, while the other arm activates immune cells in the patient to kill the lymphoma cell.

Chimeric Antigen Receptor (CAR) T-cell therapy - CAR-T therapy is a new type of treatment that utilizes a patient's own T immune cells to fight certain types of lymphoma. The T-cells are removed from the patient and engineered to recognize specific proteins found on the surface of cancer cells. The T-cells are then infused back into the patient to fight the lymphoma in the body. Tisagenlecleucal is the first CAR-T therapy to be approved by the Health Sciences Authority of Singapore. An ongoing clinical trial now directly compares CAR-T therapy to the standard autologous stem cell transplantation, and this may eventually inform if autologous stem cell transplantation will become an obsolete procedure in the future.

PRECISION MEDICINE AS THE FUTURE

With the above-mentioned innovations and many more other treatment options on the horizon in the fight against lymphoma, the prognosis of patients will continue to get better and conventional chemotherapy will eventually become obsolete as it gets replaced by precision medicine. PRIME

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Dr Tan is a consultant haematologist at Mount Elizabeth Novena Hospital in Singapore. He graduated from National University of Singapore in 1997 and obtained his membership with the Royal College of Physicians (United Kingdom) in 2002. Dr Tan had served as the clinical lead for the lymphoma and myeloma services at the Singapore General Hospital. He integrated research with clinical practice, availing novel therapeutics for cancer patients failing standards of care. Dr Tan is an elected member of the International Myeloma Working Group and also sits on the advisory panel of the International Myeloma Foundation's Asia Myeloma Network.