

Cancer Association of South Africa (CANSA)



Fact Sheet on Angioimmunoblastic T-Cell Lymphoma

Introduction

Lymphoma is a type of cancer involving cells of the immune system, called lymphocytes. Just as cancer represents many different diseases, lymphoma represents many different cancers of lymphocytes -- about 35 different subtypes, Lymphoma is a group of cancers that affect the cells that play a role in the immune system and primarily represents cells involved in the lymphatic system of the body (eMedicineHealth).

The Lymphatic System

The lymphatic system is an extensive drainage network that helps keep bodily fluid levels in balance and defends the body against infections. It is made up of a network of lymphatic vessels that carry lymph - a clear, watery fluid that contains protein molecules, salts, glucose, urea, and other substances - throughout the body.

The spleen, which is located in the upper left part of the abdomen under the ribcage, works as part of the lymphatic system to protect the body, clearing worn out red blood cells and other foreign bodies from the bloodstream to help fight off infection.

[Picture Credit: Lymphatic System]

One of the lymphatic system's major jobs is to collect extra lymph fluid from body tissues and return it to the blood. This process is crucial because water, proteins, and other substances are continuously leaking out of tiny blood capillaries into the surrounding body tissues. If the lymphatic system didn't drain the excess fluid from the tissues, the lymph fluid would build up in the body's

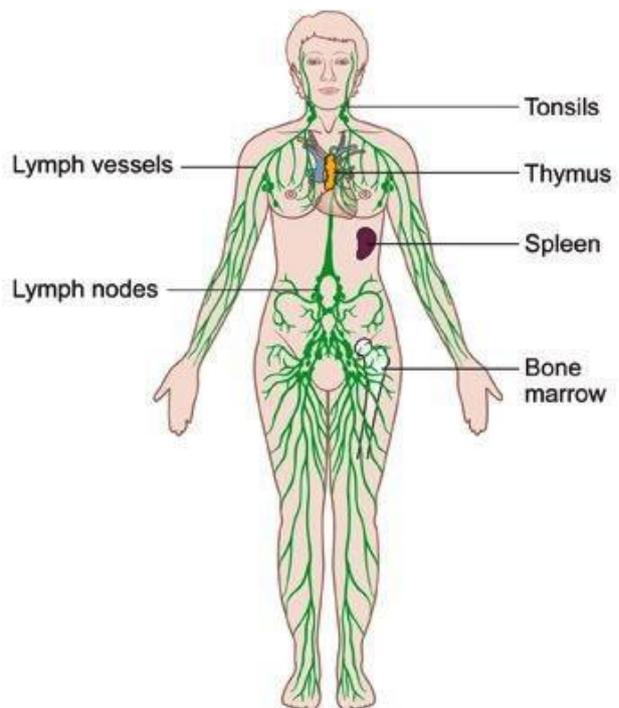
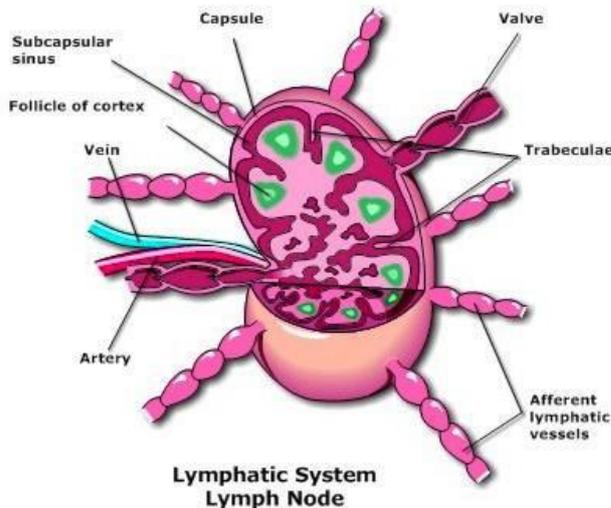


Diagram of the lymphatic system
Copyright © CancerHelp UK

tissues, and they would swell.

The lymphatic system also helps defend the body against germs like viruses, bacteria, and fungi that can cause illnesses. Those germs are filtered out in the lymph nodes, small masses of tissue located along the network of lymph vessels. The nodes house lymphocytes, a type of white blood cell. Some of those lymphocytes make antibodies, special proteins that fight off germs and stop infections from spreading by trapping disease-causing germs and destroying them.

[Picture Credit – Lymph Node]



The spleen also helps the body fight infection. The spleen contains lymphocytes and another kind of white blood cell called macrophages, which engulf and destroy bacteria, dead tissue, and foreign matter and remove them from the blood passing through the spleen (KidsHealth).

Types of Lymphoma

Lymphomas fall into one of two major categories:

- Hodgkin's lymphoma (HL, previously called Hodgkin's disease)
- Non-Hodgkin's Lymphoma (NHL, all other lymphomas)

These two types occur in the same places, may be associated with the same symptoms, and often have similar appearance on physical examination. However, they are readily distinguishable via microscopic examination.

Hodgkin's lymphoma develops from a specific abnormal B lymphocyte lineage. NHL may derive from either abnormal B or T cells and are distinguished by unique genetic markers. There are five subtypes of Hodgkin's lymphoma and about 30 subtypes of non-Hodgkin's lymphoma. Because there are so many different subtypes of lymphoma, the classification of lymphomas is complicated (it includes both the microscopic appearance as well as genetic and molecular markers).

Many of the NHL subtypes look similar, but they are functionally quite different and respond to different therapies with different probabilities of cure. HL subtypes are microscopically distinct, and typing is based upon the microscopic differences as well as extent of disease.

World Health Organization Classification System of Lymphoma Types

Over the years, various classification systems have been used to differentiate lymphoma types including the Rappaport Classification (used until the 70's), the Working Formulation,

the National Cancer Institute Working Formulation, and the Revised European-American Lymphoma Classification (REAL).

The WHO classification has its origins in the 1850s. The first edition, known as the International List of Causes of Death, was adopted by the International Statistical Institute in 1893. The ICD is the international standard diagnostic classification. It is used to classify diseases and other health problems recorded on many types of health and vital records including death certificates and health records. These records also provide the basis for the compilation of national mortality and morbidity statistics by WHO Member States.

The older Rappaport, Working Formulation, and REAL categories are described in a separate section for reference. This might be helpful if a patient's records state some of the classifications of older lymphoma types.

Hodgkin's lymphoma

- Lymphocytic-histiocytic predominance
- Nodular sclerosis
- Mixed cellularity
- Lymphocytic depletion
- Hodgkin's, unspecified

Follicular (nodular) non-Hodgkin's lymphoma

- Small cleaved cell, follicular
- Mixed small cleaved and large cell, follicular
- Large cell, follicular
- Other follicular non-Hodgkin's lymphoma types
- Follicular non-Hodgkin's lymphoma, unspecified
 - Nodular non-Hodgkin's lymphoma NOS

Diffuse non-Hodgkin's lymphoma

- Small cell (diffuse)
- Small cleaved cell (diffuse)
- Mixed small and large cell (diffuse)
- Large cell (diffuse)
 - Reticulum cell sarcoma
- Immunoblastic (diffuse)
- Lymphoblastic (diffuse)
- Undifferentiated (diffuse)
- Burkitt's tumour (Burkitt's lymphoma)
- Other diffuse non-Hodgkin's lymphoma types
- Diffuse non-Hodgkin's lymphoma, unspecified

Peripheral and cutaneous T-cell lymphomas

- Mycosis fungoides

- Sézary's disease
- T-zone lymphoma
- Lymphoepithelioid lymphoma
 - Lennert's lymphoma
- Peripheral T-cell lymphoma
- Other and unspecified T-cell lymphomas

Other and unspecified types of non-Hodgkin's lymphoma

- Lymphosarcoma
- B-cell lymphoma, unspecified
- Other specified types of non-Hodgkin's lymphoma
 - Malignant:
 - reticuloendotheliosis
 - reticulosis
 - Microglioma
- Non-Hodgkin's lymphoma, unspecified type
 - Lymphoma NOS
 - Malignant lymphoma NOS
 - Non-Hodgkin's lymphoma NOS

Malignant immunoproliferative diseases

- Waldenström's macroglobulinaemia
- Alpha heavy chain disease
- Gamma heavy chain disease
 - Franklin's disease
- Immunoproliferative small intestinal disease
 - Mediterranean disease
- Other malignant immunoproliferative diseases
- Malignant immunoproliferative disease, unspecified
 - Immunoproliferative disease NOS

Multiple myeloma and malignant plasma cell neoplasms

- Multiple myeloma
 - Kahler's disease
 - Myelomatosis
 - Excludes: solitary myeloma
- Plasma cell leukemia
- Plasmacytoma, extramedullary
 - Malignant plasma cell tumour NOS
 - Plasmacytoma NOS
 - Solitary myeloma

Lymphoid leukaemia

- Acute lymphoblastic leukaemia

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- Excludes: acute exacerbation of chronic lymphocytic leukaemia
- Chronic lymphocytic leukaemia
- Subacute lymphocytic leukaemia
- Prolymphocytic leukaemia
- Hairy-cell leukaemia
- Leukaemic reticuloendotheliosis
- Adult T-cell leukaemia
- Other lymphoid leukaemia
- Lymphoid leukaemia, unspecified

Myeloid leukaemia

- Includes:
 - granulocytic
 - myelogenous
- Acute myeloid leukaemia
 - Excludes: acute exacerbation of chronic myeloid leukaemia
- Chronic myeloid leukaemia
- Subacute myeloid leukaemia
- Myeloid sarcoma
 - Chloroma
 - Granulocytic sarcoma
- Acute promyelocytic leukaemia
- Acute myelomonocytic leukaemia
- Other myeloid leukaemia
- Myeloid leukaemia, unspecified

Monocytic leukaemia

- Includes: monocytoid leukaemia
- Acute monocytic leukaemia
 - Excludes: acute exacerbation of chronic monocytic leukaemia
- Chronic monocytic leukaemia
- Subacute monocytic leukaemia
- Other monocytic leukaemia
- Monocytic leukaemia , unspecified

Other leukaemias of specified cell type

- Acute erythraemia and erythroleukaemia
 - Acute erythraemic myelosis
 - Di Guglielmo's disease
- Chronic erythraemia
 - Heilmeyer-Schöner disease
- Acute megakaryoblastic leukaemia
 - leukaemia :
 - megakaryoblastic (acute)
 - megakaryocytic (acute)
- Mast cell leukaemia

- Acute panmyelosis
- Acute myelofibrosis
- Other specified leukaemia s
 - Lymphosarcoma cell leukaemia

Leukaemia of unspecified cell type

- Acute leukaemia of unspecified cell type
 - Blast cell leukaemia
 - Stem cell leukaemia
- Chronic leukaemia of unspecified cell type
- Subacute leukaemia of unspecified cell type
- Other leukaemia of unspecified cell type
- leukaemia , unspecified

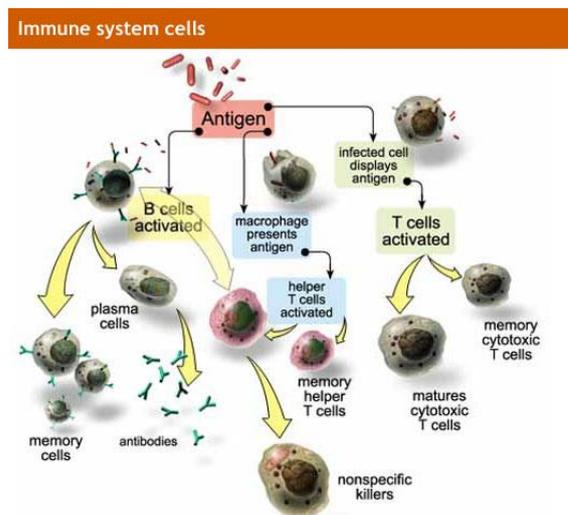
Other and unspecified malignant neoplasms of lymphoid, haematopoietic and related tissue

- Letterer-Siwe disease
 - Nonlipid:
 - reticuloendotheliosis
 - reticulosis
- Malignant histiocytosis
 - Histiocytic medullary reticulosis
- Malignant mast cell tumour
 - Malignant:
 - mastocytoma
 - mastocytosis
 - Mast cell sarcoma
 - Excludes: mast cell leukaemia
 - mastocytosis (cutaneous)
- True histiocytic lymphoma
- Other specified malignant neoplasms of lymphoid, haematopoietic and related tissue
- Malignant neoplasm of lymphoid, haematopoietic and related tissue, unspecified (Lymphomainfo.net)

Angioimmunoblastic T-Cell Lymphoma (AITL)

[Picture Credit: Cells of the Immune System]

Angioimmunoblastic T-cell lymphoma (AITL) is a rare, aggressive (fast-growing) T-cell lymphoma that accounts for approximately one to two percent of all non-Hodgkin Lymphoma cases. Elderly patients are more likely to have AITL, and it occurs more often in men than women. The majority of patients with AITL are diagnosed with advanced-stage disease, either



(Source: the Human Immune Response System www.uta.edu/chagas/images/immunSys.jpg)

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stage III or stage IV disease. In stage III, affected lymph nodes are found both above and below the diaphragm. In stage IV, one or more organs beyond the lymph nodes are affected, such as the bone, bone marrow, skin, or liver. Less-extensive disease, stage I or II, is rare. Patients with stage I have localised disease that has not spread beyond the tumour, and with stage II, if the cancer has spread, it has affected only a nearby lymph node. Angioimmunoblastic T-cell lymphoma is an aggressive peripheral T-cell lymphoma whose natural history is not fully understood. Up to 17% of cases can present histologically with hyperplastic germinal centres (pattern I). The accurate recognition of Angioimmunoblastic T-cell lymphoma with pattern I remains a challenge. T-cell lymphoma may represent histological evolution rather than clinical progression. (Rodriguez-Justo, 2009).

Incidence of Angioimmunoblastic T-Cell Lymphoma in South Africa (AITL)

The National Cancer Registry (2012) does not provide information regarding the incidence of Angioimmunoblastic T-Cell Lymphoma. Because Angioimmunoblastic T-Cell Lymphoma makes up approximately 2% of Non-Hodgkin's Lymphoma, it is included in the statistics of Non-Hodgkin's Lymphoma.

According to the National Cancer Registry (2013) the following number of Non-Hodgkin's Lymphoma cases were histologically diagnosed in South Africa during 2013:

Group - Males 2013	Actual No of Cases	Estimated Lifetime Risk	Percentage of All Cancers
All males	882	1:221	2,45%
Asian males	25	1:241	2,97%
Black males	516	1:316	4,79%
Coloured males	88	1:192	2,12%
White males	254	1:123	1,26%

Group - Females 2013	Actual No of Cases	Estimated Lifetime Risk	Percentage of All Cancers
All females	802	1:327	2,19%
Asian females	21	1:296	1,98%
Black females	471	1:461	3,02%
Coloured females	76	1:267	1,87%
White females	234	1:163	1,47%

The frequency of histologically diagnosed cases of Non-Hodgkin's Lymphoma in South Africa for 2013 was as follows (National Cancer Registry, 2013):

Group - Males 2013	0 – 19 Years	20 – 29 Years	30 – 39 Years	40 – 49 Years	50 – 59 Years	60 – 69 Years	70 – 79 Years	80+ Years
All males	29	46	152	199	172	144	85	40
Asian males	0	0	1	7	7	5	2	1
Black males	25	30	126	142	105	40	18	5
Coloured males	2	4	7	14	18	27	8	4
White males	2	9	15	32	38	67	55	28

Group - Females 2013	0 – 19 Years	20 – 29 Years	30 – 39 Years	40 – 49 Years	50 – 59 Years	60 – 69 Years	70 – 79 Years	80+ Years
All females	24	54	164	165	124	125	81	52
Asian females	1	0	0	3	2	7	4	1
Black females	16	47	140	122	61	39	16	10
Coloured females	2	3	10	12	18	13	11	4
White females	5	2	12	23	38	60	48	36

N.B. In the event that the totals in any of the above tables do not tally, this may be the result of uncertainties as to the age, race or sex of the individual. The totals for 'all males' and 'all females', however, always reflect the correct totals.

Causes of Angioimmunoblastic T-Cell Lymphoma (AITL)

It has been noticed that many people with this lymphoma show signs of having had an infection with a virus called the Epstein–Barr virus (EBV). It is not clear, however, whether this virus is causing the genetic changes in the lymphocytes – which then grow out of control to form a lymphoma – or whether an EBV infection has just been reawakened in the body because the immune system is not working as well as it should because of the lymphoma. Many people in the population who have had an EBV infection, develop lymphoma, so there must be other reasons for the lymphoma developing.

Despite this possible link with EBV infection, it is still not known exactly what causes AITL. What doctors do know is that nothing that was done – or not done – will have caused the lymphoma to develop. AITL is not a disease that one can inherit or pass on to one's children.

Patients with Sjögren syndrome are at increased risk for developing lymphoma. Although most lymphomas in these patients are of the B-cell variety, AITL constitutes the majority of T-cell lymphomas associated with Sjögren syndrome.

Sjögren syndrome (SS) is a chronic autoimmune disease in which the body's white blood cells destroy the exocrine glands, specifically the salivary and lacrimal glands, that produce saliva and tears, respectively.

(Lymphoma Association UK; Medscape).

Signs and Symptoms of Angioimmunoblastic T-Cell Lymphoma (AITL)

Angioimmunoblastic T-Cell Lymphoma (AITL) causes a wide range of possible symptoms:

- Lumps, which are swollen lymph nodes (glands) - these are often in several places, for example in the groin, armpits and neck
- Feeling generally unwell, with symptoms similar to those experienced when one has an infection
- Fever
- Unexplained weight loss
- Night sweats
- Pruritus (itching)
- Lymphadenopathy (lymph nodes that are abnormal in size, number or consistency)
- Oedema
- Abdominal discomfort and sometimes distension (swelling) caused by cancerous lymphocytes in the spleen and/or the liver or by a collection of fluid in the abdomen (this is called 'ascites')

- Difficulty with breathing due to collection of fluid around the lungs (a pleural effusion)
- Maculopapular rashes (these can resemble a viral rash)

[Picture Credit:
Typical Rash Associated with AITL]



- Joint pains
- Tiredness or shortness of breath due to a type of anaemia called 'haemolytic anaemia', which is caused by an autoimmune reaction against red blood cells
- Symptoms of infections – infections are more likely to occur and to be more severe if there is AITL in the bone marrow.

As the disease progresses, symptoms persist (Medscape; Lymphoma Association UK).

Diagnosis of Angioimmunoblastic T-Cell Lymphoma (AITL)

In order to assess which parts of the body are affected by AITL, the patient will have a physical examination and will have some or all of the following tests:

- blood tests – to measure the numbers of different blood cells in the sample (the blood counts), to assess the immune system and to assess how well the liver and kidneys are working
- bone marrow biopsy, a test in which a small sample is taken from the bone marrow in the hip bone using a needle (the skin is numbed with a local anaesthetic first) to see if the lymphoma is affecting the bone marrow
- scans – computed tomography (a CT scan) of the chest, abdomen and pelvis is the most usual scan people with AITL will have – positron-emission tomography (a PET scan) – this type of scan is done in some centres if the specialist feels it would help them to plan their treatment.

Staging of Angioimmunoblastic T-Cell Lymphoma (AITL)

Once the test results of all the tests are back the medical team will be able to tell what stage the lymphoma is at.

AITL is staged as follows:

Stage I

Only one group of lymph nodes is affected

Stage II

Two or more groups of lymph nodes are affected on one side of the diaphragm (a sheet of muscle that separates the chest from the abdomen)

Stage III

Lymph nodes on both sides of the diaphragm are affected

Stage IV

There is lymphoma in the bone marrow or in organs that are not part of the lymphatic system

- If a 'B' is attached to the Stage Number this means that the patient has experienced one or more of the B symptoms, namely:
 - Fever
 - unexplained weight loss
 - night sweats
- If the patient has not experienced any of the B Symptoms, an 'A' will be attached to the Stage Number.
- An 'E' attached to the stage number means that there is lymphoma in extranodal sites.

Stage I and stage II lymphomas are described as 'early stage'. A few people with AITL will be diagnosed at an early stage. Most people will have AITL at a more advanced stage when they are diagnosed, meaning stage III or IV.

Treatment of Angioimmunoblastic T-Cell Lymphoma (AITL)

A few people can be treated with steroid tablets alone, but Angioimmunoblastic T-Cell Lymphoma (AITL) is usually treated with:

Chemotherapy - chemotherapy is treatment with drugs that kill the lymphoma cells or stop them from dividing. Sometimes a patient will be given one chemotherapy drug, but usually will be given two or more drugs. This is called 'combination chemotherapy'. The patient will normally have the drug combination over a period of a few days, then have a few weeks without any drugs (usually about 3 weeks), then have another cycle of treatment.

The most common combination chemotherapy treatment that is used to treat AITL is:

- CHOP – a combination of cyclophosphamide, hydroxydaunorubicin and vincristine (Oncovin®), together with the steroid drug, prednisolone.

Other combination therapies that are given for AITL are:

- FC – fludarabine and cyclophosphamide
- CVP – cyclophosphamide, vincristine and prednisolone.

Some people might afterwards go on to have treatment with low doses of a chemotherapy drug called methotrexate, together with prednisolone. Other chemotherapy drugs that are sometimes given singly to treat AITL are fludarabine, cladribine and gemcitabine. Gemcitabine might be given in combination with prednisolone. A combination of gemcitabine, cisplatin and prednisolone was used as an initial treatment in a clinical trial in the UK (the Chemo-T trial).

There are several chemotherapy options to choose from because this is a rare lymphoma and specialists have not been able to show yet that any one regimen is markedly better than any of the others. Which treatment a patient will have will depend on what the hospital and

doctors prefer to use for people with AITL. It will also depend on whether or not the patient is taking part in a clinical trial.

Other drugs under investigation for treating AITL

There are several other drugs that have been shown to be effective in treating AITL, either on their own or together with chemotherapy. These are usually only available if one is taking part in a clinical trial because they are still being investigated. An antibody treatment is sometimes given together with, or after, chemotherapy. If it is given afterwards this is called 'consolidation therapy'. Antibodies are proteins that attach themselves to the cancerous lymphocytes. This attracts other cells of the body's immune system to come and destroy and remove the 'marked' lymphoma cells.

Antibody treatments that are sometimes given to people with AITL are:

- rituximab (MabThera®)
- alemtuzumab (Campath)
- bevacizumab (Avastin®).

Bevacizumab targets an important molecule that is involved in the formation of new blood vessels (such as the abnormal vessels that form in AITL). Two other drugs that are known to prevent blood vessel formation that are being used to treat AITL are:

- thalidomide
- lenalidomide

Thalidomide, in particular, can be a good option for people who are not well enough to have treatment with an intensive chemotherapy regimen.

Other treatments that are sometimes used to treat AITL are denileukin diftitox (Ontak®), interferon alpha and ciclosporin. Lastly, there are a few drugs that have shown some success in treating other T-cell lymphomas that are occasionally used to treat AITL, such as romidepsin (Istodax®) and vorinostat (Zolinza®).

High-dose chemotherapy and stem cell transplantation

Specialists who treat AITL aim to get the lymphoma into remission with chemotherapy. Remission means that tests show no sign of the lymphoma. If a patient is fit enough and if the lymphoma was sensitive to the chemotherapy drugs, the team might then want to 'consolidate' the remission with high-dose chemotherapy and a stem cell transplant. A stem cell transplant might also be an option if the AITL comes back some time after a patient has gone into remission.

This type of treatment would not be suitable if the AITL did not respond well to the initial chemotherapy, if there is lymphoma in the bone marrow or if the patient has had treatment with fludarabine chemotherapy.

A stem cell transplant is a treatment in which very high doses of anti-lymphoma therapy is given to the patient. Prior to stem cell transplant a patient is given high doses of chemotherapy (and sometimes also radiotherapy). Although this high-dose treatment will kill any lymphoma cells that remain in the body after the initial chemotherapy, it causes so much damage to the bone marrow, that the bone marrow might never recover by itself. Instead it is 'rescued' (helped to recover) by the stem cells that are transplanted.

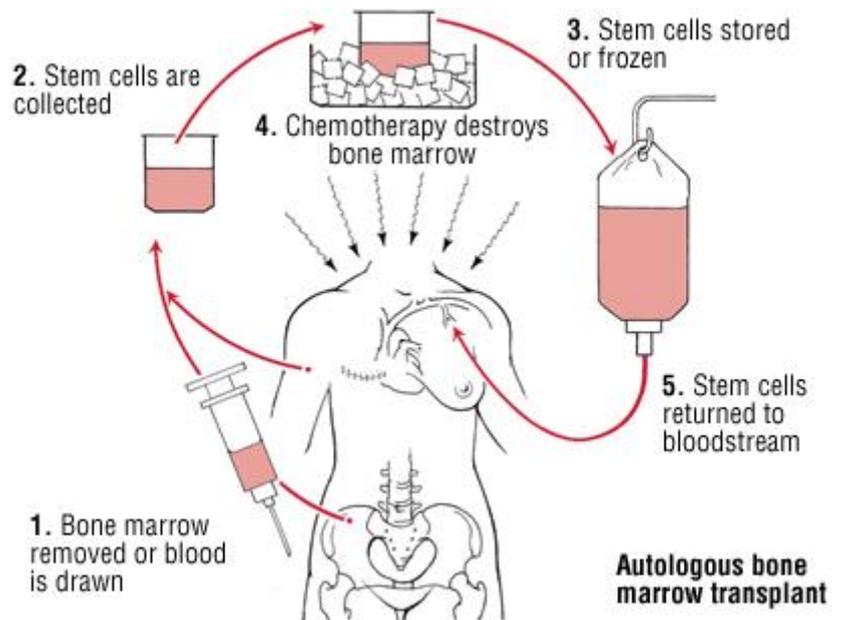
Stem cells are special cells from the bone marrow that can make normal blood cells. The stem cells are put into the bloodstream, just like a blood transfusion. They then settle in the bone marrow where they start growing to make new blood cells.

The stem cells can come from:

- the patient him/herself, collected from blood before high-dose chemotherapy – this is known as an autologous transplant (sometimes called 'stem cell support'); or they can come from
- a donor (a related donor if possible) – this kind of transplant is called an allogeneic or 'donor' transplant and is a much more intense form of treatment.

[Picture Credit: Autologous transplant]

Autologous stem cell transplants are sometimes used to treat people with AITL. Allogeneic transplants are only occasionally used to treat AITL, usually only in people whose general health is good enough to withstand this more intense and risky type of transplant.



Supportive Treatments

Supportive treatments are treatments the patient is given to help with the symptoms of the lymphoma and the side effects of the chemotherapy. For example he/she might be given:

- steroids to help with joint pains, skin rash or abnormalities in blood counts
- blood transfusions to combat anaemia anti-sickness drugs to prevent nausea during chemotherapy
- antibiotics for any infections that develop.

Even though most people with AITL will have advanced disease by the time it is diagnosed, this does not mean that it is too late for treatment. What treatment the patient is given will depend on several factors, including age and general health. It might also depend on whether there is a clinical trial the patient can participate in.

(LymphomaInfo.net; Lymphoma Association UK).

Follow-up Care and Support

Once treatment is completed and AITL is in remission, physicians will continue to monitor the health and status of each patient. Patients in remission should have regular visits (at least 6-monthly in the beginning) with their physician who is familiar with their medical history as well as with the treatments they have received.

Disease relapse and infections are common with this cancer. It is important to seek medical attention for fever or other symptoms related to improper functioning of the immune system.

Some treatments can cause long-term effects or late effects, which can vary based on duration and frequency of treatments, age, gender, and the overall health of each patient at the time of treatment. The doctor will check for these effects during follow-up care. Visits may become less frequent the longer the disease remains in remission.

Survivors and their caregivers are encouraged to keep copies of all medical records and test results as well as information on the types, amounts, and duration of all treatments received. This documentation will be important for keeping track of any effects resulting from treatment or potential disease recurrences.

(Lymphoma Research Foundation).

About Clinical Trials

Clinical trials are research studies that involve people. These studies test new ways to prevent, detect, diagnose, or treat diseases. People who take part in cancer clinical trials have an opportunity to contribute to scientists' knowledge about cancer and to help in the development of improved cancer treatments. They also receive state-of-the-art care from cancer experts.

Types of Clinical Trials

Cancer clinical trials differ according to their primary purpose. They include the following types:

Treatment - these trials test the effectiveness of new treatments or new ways of using current treatments in people who have cancer. The treatments tested may include new drugs or new combinations of currently used drugs, new surgery or radiation therapy techniques, and vaccines or other treatments that stimulate a person's immune system to fight cancer. Combinations of different treatment types may also be tested in these trials.

Prevention - these trials test new interventions that may lower the risk of developing certain types of cancer. Most cancer prevention trials involve healthy people who have not had cancer; however, they often only include people who have a higher than average risk of developing a specific type of cancer. Some cancer prevention trials involve people who have had cancer in the past; these trials test interventions that may help prevent the return (recurrence) of the original cancer or reduce the chance of developing a new type of cancer.

Screening - these trials test new ways of finding cancer early. When cancer is found early, it may be easier to treat and there may be a better chance of long-term survival. Cancer screening trials usually involve people who do not have any signs or symptoms of cancer. However, participation in these trials is often limited to people who have a higher than average risk of developing a certain type of cancer because they have a family history of that type of cancer or they have a history of exposure to cancer-causing substances (e.g., cigarette smoke).

Diagnostic - these trials study new tests or procedures that may help identify, or diagnose, cancer more accurately. Diagnostic trials usually involve people who have some signs or symptoms of cancer.

Quality of life or supportive care - these trials focus on the comfort and quality of life of cancer patients and cancer survivors. New ways to decrease the number or severity of side effects of cancer or its treatment are often studied in these trials. How a specific type of cancer or its treatment affects a person's everyday life may also be studied.

Where Clinical Trials are Conducted

Cancer clinical trials take place in cities and towns in doctors' offices, cancer centres and other medical centres, community hospitals and clinics. A single trial may take place at one or two specialised medical centres only or at hundreds of offices, hospitals, and centres.

Each clinical trial is managed by a research team that can include doctors, nurses, research assistants, data analysts, and other specialists. The research team works closely with other health professionals, including other doctors and nurses, laboratory technicians, pharmacists, dieticians, and social workers, to provide medical and supportive care to people who take part in a clinical trial.

Research Team

The research team closely monitors the health of people taking part in the clinical trial and gives them specific instructions when necessary. To ensure the reliability of the trial's results, it is important for the participants to follow the research team's instructions. The instructions may include keeping logs or answering questionnaires. The research team may also seek to contact the participants regularly after the trial ends to get updates on their health.

Clinical Trial Protocol

Every clinical trial has a protocol, or action plan, that describes what will be done in the trial, how the trial will be conducted, and why each part of the trial is necessary. The protocol also includes guidelines for who can and cannot participate in the trial. These guidelines, called eligibility criteria, describe the characteristics that all interested people must have before they can take part in the trial. Eligibility criteria can include age, sex, medical history, and current health status. Eligibility criteria for cancer treatment trials often include the type and stage of cancer, as well as the type(s) of cancer treatment already received.

Enrolling people who have similar characteristics helps ensure that the outcome of a trial is due to the intervention being tested and not to other factors. In this way, eligibility criteria help researchers obtain the most accurate and meaningful results possible.

National and International Regulations

National and international regulations and policies have been developed to help ensure that research involving people is conducted according to strict scientific and ethical principles. In these regulations and policies, people who participate in research are usually referred to as "human subjects."

Informed Consent

Informed consent is a process through which people learn the important facts about a clinical trial to help them decide whether or not to take part in it, and continue to learn new

information about the trial that helps them decide whether or not to continue participating in it.

During the first part of the informed consent process, people are given detailed information about a trial, including information about the purpose of the trial, the tests and other procedures that will be required, and the possible benefits and harms of taking part in the trial. Besides talking with a doctor or nurse, potential trial participants are given a form, called an informed consent form, that provides information about the trial in writing. People who agree to take part in the trial are asked to sign the form. However, signing this form does not mean that a person must remain in the trial. Anyone can choose to leave a trial at any time—either before it starts or at any time during the trial or during the follow-up period. It is important for people who decide to leave a trial to get information from the research team about how to leave the trial safely.

The informed consent process continues throughout a trial. If new benefits, risks, or side effects are discovered during the course of a trial, the researchers must inform the participants so they can decide whether or not they want to continue to take part in the trial. In some cases, participants who want to continue to take part in a trial may be asked to sign a new informed consent form.

New interventions are often studied in a stepwise fashion, with each step representing a different “phase” in the clinical research process. The following phases are used for cancer treatment trials:

Phases of a Clinical Trial

Phase 0. These trials represent the earliest step in testing new treatments in humans. In a phase 0 trial, a very small dose of a chemical or biologic agent is given to a small number of people (approximately 10-15) to gather preliminary information about how the agent is processed by the body (pharmacokinetics) and how the agent affects the body (pharmacodynamics). Because the agents are given in such small amounts, no information is obtained about their safety or effectiveness in treating cancer. Phase 0 trials are also called micro-dosing studies, exploratory Investigational New Drug (IND) trials, or early phase I trials. The people who take part in these trials usually have advanced disease, and no known, effective treatment options are available to them.

Phase I (also called phase 1). These trials are conducted mainly to evaluate the safety of chemical or biologic agents or other types of interventions (e.g., a new radiation therapy technique). They help determine the maximum dose that can be given safely (also known as the maximum tolerated dose) and whether an intervention causes harmful side effects. Phase I trials enrol small numbers of people (20 or more) who have advanced cancer that cannot be treated effectively with standard (usual) treatments or for which no standard treatment exists. Although evaluating the effectiveness of interventions is not a primary goal of these trials, doctors do look for evidence that the interventions might be useful as treatments.

Phase II (also called phase 2). These trials test the effectiveness of interventions in people who have a specific type of cancer or related cancers. They also continue to look at the safety of interventions. Phase II trials usually enrol fewer than 100 people but may include as many as 300. The people who participate in phase II trials may or may not have been

treated previously with standard therapy for their type of cancer. If a person has been treated previously, their eligibility to participate in a specific trial may depend on the type and amount of prior treatment they received. Although phase II trials can give some indication of whether or not an intervention works, they are almost never designed to show whether an intervention is better than standard therapy.

Phase III (also called phase 3). These trials compare the effectiveness of a new intervention, or new use of an existing intervention, with the current standard of care (usual treatment) for a particular type of cancer. Phase III trials also examine how the side effects of the new intervention compare with those of the usual treatment. If the new intervention is more effective than the usual treatment and/or is easier to tolerate, it may become the new standard of care.

Phase III trials usually involve large groups of people (100 to several thousand), who are randomly assigned to one of two treatment groups, or "trial arms": (1) a control group, in which everyone in the group receives usual treatment for their type of cancer, or 2) an investigational or experimental group, in which everyone in the group receives the new intervention or new use of an existing intervention. The trial participants are assigned to their individual groups by random assignment, or randomisation. Randomisation helps ensure that the groups have similar characteristics. This balance is necessary so the researchers can have confidence that any differences they observe in how the two groups respond to the treatments they receive are due to the treatments and not to other differences between the groups.

Randomisation is usually done by a computer program to ensure that human choices do not influence the assignment to groups. The trial participants cannot request to be in a particular group, and the researchers cannot influence how people are assigned to the groups. Usually, neither the participants nor their doctors know what treatment the participants are receiving.

People who participate in phase III trials may or may not have been treated previously. If they have been treated previously, their eligibility to participate in a specific trial may depend on the type and the amount of prior treatment they received.

In most cases, an intervention will move into phase III testing only after it has shown promise in phase I and phase II trials.

Phase IV (also called phase 4). These trials further evaluate the effectiveness and long-term safety of drugs or other interventions. They usually take place after a drug or intervention has been approved by the medicine regulatory office for standard use. Several hundred to several thousand people may take part in a phase IV trial. These trials are also known as post-marketing surveillance trials. They are generally sponsored by drug companies.

Sometimes clinical trial phases may be combined (e.g., phase I/II or phase II/III trials) to minimize the risks to participants and/or to allow faster development of a new intervention.

Although treatment trials are always assigned a phase, other clinical trials (e.g., screening, prevention, diagnostic, and quality-of-life trials) may not be labelled this way.

Use of Placebos

The use of placebos as comparison or “control” interventions in cancer treatment trials is rare. If a placebo is used by itself, it is because no standard treatment exists. In this case, a trial would compare the effects of a new treatment with the effects of a placebo. More often, however, placebos are given along with a standard treatment. For example, a trial might compare the effects of a standard treatment plus a new treatment with the effects of the same standard treatment plus a placebo.

Possible benefits of taking part in a clinical trial

The benefits of participating in a clinical trial include the following:

- Trial participants have access to promising new interventions that are generally not available outside of a clinical trial.
- The intervention being studied may be more effective than standard therapy. If it is more effective, trial participants may be the first to benefit from it.
- Trial participants receive regular and careful medical attention from a research team that includes doctors, nurses, and other health professionals.
- The results of the trial may help other people who need cancer treatment in the future.
- Trial participants are helping scientists learn more about cancer (e.g., how it grows, how it acts, and what influences its growth and spread).

Potential harms associated with taking part in a clinical trial

The potential harms of participating in a clinical trial include the following:

- The new intervention being studied may not be better than standard therapy, or it may have harmful side effects that doctors do not expect or that are worse than those associated with standard therapy.
- Trial participants may be required to make more visits to the doctor than they would if they were not in a clinical trial and/or may need to travel farther for those visits.

Correlative research studies, and how they are related to clinical trials

In addition to answering questions about the effectiveness of new interventions, clinical trials provide the opportunity for additional research. These additional research studies, called correlative or ancillary studies, may use blood, tumour, or other tissue specimens (also known as ‘biospecimens’) obtained from trial participants before, during, or after treatment. For example, the molecular characteristics of tumour specimens collected during a trial might be analysed to see if there is a relationship between the presence of a certain gene mutation or the amount of a specific protein and how trial participants responded to the treatment they received. Information obtained from these types of studies could lead to more accurate predictions about how individual patients will respond to certain cancer treatments, improved ways of finding cancer earlier, new methods of identifying people who have an increased risk of cancer, and new approaches to try to prevent cancer.

Clinical trial participants must give their permission before biospecimens obtained from them can be used for research purposes.

When a clinical trial is over

After a clinical trial is completed, the researchers look carefully at the data collected during the trial to understand the meaning of the findings and to plan further research. After a phase I or phase II trial, the researchers decide whether or not to move on to the next phase or stop testing the intervention because it was not safe or effective. When a phase III trial is completed, the researchers analyse the data to determine whether the results have medical importance and, if so, whether the tested intervention could become the new standard of care.

The results of clinical trials are often published in peer-reviewed scientific journals. Peer review is a process by which cancer research experts not associated with a trial review the study report before it is published to make sure that the data are sound, the data analysis was performed correctly, and the conclusions are appropriate. If the results are particularly important, they may be reported by the media and discussed at a scientific meeting and by patient advocacy groups before they are published in a journal. Once a new intervention has proven safe and effective in a clinical trial, it may become a new standard of care. (National Cancer Institute).

Medical Disclaimer

This Fact Sheet is intended to provide general information only and, as such, should not be considered as a substitute for advice, medically or otherwise, covering any specific situation. Users should seek appropriate advice before taking or refraining from taking any action in reliance on any information contained in this Fact Sheet. So far as permissible by law, the Cancer Association of South Africa (CANSA) does not accept any liability to any person (or his/her dependants/estate/heirs) relating to the use of any information contained in this Fact Sheet.

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Sources and References

American Cancer Society

<http://www.cancer.org/Cancer/Non-HodgkinLymphoma/DetailedGuide/non-hodgkin-lymphoma-risk-factors>

Autologous Transplant

<http://multiple-sclerosis-research.blogspot.com/p/grand-challenges-in-ms.html>

Boston Children's Hospital

<http://childrenshospital.org/az/Site2182/mainpageS2182P1.html>

Cancer Research UK

<http://www.cancerresearchuk.org/cancer-info/cancerstats/types/hodgkinslymphoma/riskfactors/hodgkins-lymphoma-risk-factors#genetics>

Cells of the Immune System

http://www.alohamedicinals.com/how-your-immune-system-works.html#.VBvpG_mSySo

eMedicineHealth. Lymphoma. http://www.emedicinehealth.com/lymphoma/article_em.htm

Hodgkin's Lymphoma

https://www.google.co.za/search?q=hodgkin%27s+lymphoma&source=lnms&tbm=isch&sa=X&ei=KI-ZU_bUJaev7Ab_q4CwCA&sqj=2&ved=0CAYQ_AUoAQ&biw=1517&bih=714&dpr=0.9#facrc=_&imgdii=wrUKxr_raB8ehM%3A%3B3MTF6fAZjSVIEM%3BwrUKxr_raB8ehM%3A&imgrc=wrUKxr_raB8ehM%253A%3ByWB-1qzXMW4rDM%3Bhttp%253A%252F%252Fs2.hubimg.com%252Fu%252F6438913_f260.jpg%3Bhttp%253A%252F%252Fkimhdimino.blogspot.com%252F2013%252F03%252Fhodgkins-disease-overview.html%3B260%3B195

KidsHealth. The Lymphatic System.

http://kidshealth.org/parent/general/body_basics/spleen_lymphatic.html

Lymphatic System

[http://www.google.co.za/imgres?start=83&hl=en&sa=X&rlz=1T4LENN_enZA490ZA490&biw=1366&bih=613&tbm=isch&prmd=imvns&tbnid=-flgwTmsqqhLNM:&imgrefurl=http://cancerhelp.cancerresearchuk.org/type/hodgkins-lymphoma/about/what-is-hodgkins-lymphoma&docid=sUkIP6oPMYlj-M&imgurl=http://cancerhelp.cancerresearchuk.org/prod_consump/groups/cr_common/%2540cah/%2540gen/documents/image/crukimg_1000img-12066.jpg&w=350&h=431&ei=YdRSUOCpMOSx0QXWr4DABQ&zoom=1&iact=hc&vpx=1106&vpy=249&dur=2671&hovh=249&hovw=202&tx=127&ty=114&sig=107310304455409594391&page=4&tbnh=129&tbnw=105&ndsp=30&ved=1t:429,r:29,s:83,i:96\]](http://www.google.co.za/imgres?start=83&hl=en&sa=X&rlz=1T4LENN_enZA490ZA490&biw=1366&bih=613&tbm=isch&prmd=imvns&tbnid=-flgwTmsqqhLNM:&imgrefurl=http://cancerhelp.cancerresearchuk.org/type/hodgkins-lymphoma/about/what-is-hodgkins-lymphoma&docid=sUkIP6oPMYlj-M&imgurl=http://cancerhelp.cancerresearchuk.org/prod_consump/groups/cr_common/%2540cah/%2540gen/documents/image/crukimg_1000img-12066.jpg&w=350&h=431&ei=YdRSUOCpMOSx0QXWr4DABQ&zoom=1&iact=hc&vpx=1106&vpy=249&dur=2671&hovh=249&hovw=202&tx=127&ty=114&sig=107310304455409594391&page=4&tbnh=129&tbnw=105&ndsp=30&ved=1t:429,r:29,s:83,i:96)

Lymph Node

http://www.google.co.za/imgres?hl=en&sa=X&rlz=1T4LENN_enZA490ZA490&biw=1366&bih=613&tbm=isch&prmd=imvns&tbnid=y5UPisMY6d3v2M:&imgrefurl=http://www.smartdraw.com/examples/view/non-hodgkin%2Blymphoma%2B-%2Bcell/&docid=r4nBtXE1dXFreM&imgurl=http://wc1.smartdraw.com/examples/content/Examples/10_Healthcare/Cancer_Illustrations/Non-Hodgkin_Lymphoma_-

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_Cell_L.jpg&w=842&h=627&ei=RNRSUM_6O9DY0QX1vYDABQ&zoom=1&iact=rc&dur=527&sig=107310304455409594391&page=2&tbnh=131&tbnw=175&start=23&ndsp=29&ved=1t:429,r:19,s:23,i:206&tx=110&ty=82]

Lymphoma Association UK

<http://www.lymphomas.org.uk/sites/default/files/pdfs/Angioimmunoblastic-T-cell-lymphoma.pdf>

Lymphomainfo.net

<http://www.lymphomainfo.net/nhl/classify.html>
<http://www.lymphomainfo.net/nhl/types/t-ail.html>

Lymphoma Research Foundation

<http://www.lymphoma.org/site/pp.asp?c=bkLTKaOQLmK8E&b=6300145>

MacMillan Cancer support

<http://www.macmillan.org.uk/Cancerinformation/Cancertypes/Lymphomanon-Hodgkin/TypesofNHL/Burkitt.aspx>

Medscape

<http://emedicine.medscape.com/article/1099386-overview#aw2aab6b4>

Merseyside & Cheshire Cancer Network

<http://www.mccn.nhs.uk/userfiles/documents/Guidelines%20for%20treatment%20of%20Burkitts%20Lymphoma%20DEC%202010.pdf>

Mayo Clinic

<http://www.mayoclinic.com/health/hodgkins-disease/DS00186/DSECTION=risk-factors>

Medline Plus

<http://www.nlm.nih.gov/medlineplus/ency/article/001308.htm>

National Cancer Institute

<http://www.training.seer.cancer.gov/lymphoma/abstract-code-stage/>
<http://www.cancer.gov/clinicaltrials/learningabout/what-are-clinical-trials>

Non-Hodgkin's Lymphoma

https://www.google.co.za/search?q=non-hodgkin%27s+lymphoma&source=lnms&tbm=isch&sa=X&ei=AGCZU8q1KsLD7Aax9IH4Aw&sqi=2&ved=0CAYQ_AUoAQ&biw=1517&bih=714&dpr=0.9#facrc=_&imgdii=kKB9P4GyA_Fu3M%3A%3B2h1pJ-GD7YW-PM%3BkKB9P4GyA_Fu3M%3A&imgrc=kKB9P4GyA_Fu3M%253A%3BNDhAy5EHR6ijXM%3Bhttp%253A%252F%252Fwww.cixip.com%252FPublic%252Fkindeditor%252Fattached%252Fimage%252F20120925%252F20120925100954_31690.jpg%3Bhttp%253A%252F%252Fwww.cixip.com%252Findex.php%252Fpage%252Fcontent%252Fid%252F613%3B537%3B600

PubMed Health. Hodgkin's Lymphoma.

<http://www.ncbi.nlm.nih.gov/pubmedhealth/PMH0001606/>
<http://www.ncbi.nlm.nih.gov/pubmedhealth/PMH0001607/>
<http://www.ncbi.nlm.nih.gov/pubmedhealth/PMH0002285/>

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Rodriguez-Justo, M., Attygalle, A.D., Munson, P., Roncador, G, Maragioti, T. & Pirisw, M.A. 2009. Antioimmunoblastic T-Cell lymphoma with hyperplastic germinal centres: a neoplasia with origin in the outer zone of the germinal centre? Clinicopathological and immunohistochemical study of 10 cases with follicular T-cell markers. *Modern Pathology*, 22:753-761. doi:10.1038/modpathol.2009.12; published online 27 March 2009

The Burkitt's Lymphoma Society

<http://burkittslymphomasociety.com/>

The Immune System

<http://www.humanvitaminhealth.com/yourimmunesystem.html>

University of Maryland Medical Center

http://www.umm.edu/patiented/articles/what_risk_factors_non-hodgkins_lymphomas_000084_2.htm

WebMD

<http://www.webmd.com/cancer/burkitt-lymphoma-prognosis-diagnosis-treatments>