

## FACT SHEET

# High-Grade B-Cell Lymphoma: Double Hit Lymphoma (DHL) & Triple Hit Lymphoma (THL)



## OVERVIEW

Lymphoma is the 6<sup>th</sup> most common cancer in Australia in adult men and women. It can affect people of all ages and is the most common blood cancer. Lymphoma is a cancer of the immune system and affects lymphocytes which are a type of white blood cell. When lymphocytes gain DNA mutations they divide and grow uncontrollably resulting in lymphoma.

There are two main types of lymphocytes called B lymphocytes (B-cells) and T lymphocytes (T-cells). Lymphomas caused by B-cells are more common and account for around 85% of lymphoma cases and lymphomas caused by T-cells account for around 15% of lymphoma cases. The first lymphoma to be discovered was called "Hodgkin lymphoma" (around 15% of all B-cell lymphomas), after Thomas Hodgkin, who described it. All subsequent lymphomas discovered were called "non-Hodgkin lymphoma" (around 90% of all lymphomas, both B-cell & T-cell lymphomas).

There are over 80 different subtypes of lymphoma, which can be classified according to clinical behaviour. "Aggressive" (high-grade or fast growing) lymphomas are those that grow quickly, usually weeks to months and need treatment immediately. "Indolent" (low-grade or slow growing) lymphomas usually develop over years and often are not treated straight away but are monitored. It is important to know your subtype of lymphoma. Lymphoma cells can travel to any part of the body and be found in lymph nodes, the bone marrow, the spleen, blood, bone, skin and almost any organ or tissue.

Double Hit Lymphoma (DHL) is a type of B-cell lymphoma formally called "High Grade B-cell lymphoma with rearrangements of MYC and BCL2 and/or BCL6". Many consider it a subtype of DLBCL because it presents in a similar way and is characterized by rearrangements of two genes that result in a more resistant type of lymphoma. These changes are usually detected **only if the pathologist is asked to check, using a specialist test called FISH (fluorescence *in situ* hybridisation).**

The first rearrangement involves the MYC gene and the second rearrangement involves the BCL2 gene or less commonly the BCL6 gene. An even rarer subtype of lymphoma is seen when three gene rearrangements are seen in MYC, BCL2 and BCL6 and this is referred to as Triple Hit Lymphoma (THL). Note that DHLs

are different from the so called "double expressor" lymphomas (DEL) where increased protein expression of MYC and BCL2 occurs, as detected by routine staining by a pathologist. This does not necessarily imply that a patient has DHL and these DELs generally are thought to have better prognosis. Some DELs are also DHL, but it is the detection of rearrangements of the genes by FISH which defines DHL as we currently understand it. Around 5% of cases of DLBCL have rearrangements of the MYC, BCL2 or BCL6 genes and are therefore diagnosed as DHL.

**MYC gene** regulates approximately 15% of human genes and has a role in the progression of the cell cycle, apoptosis (programmed cell death) and cellular result in rapid growth of lymphoma cells.

**BCL2 gene** regulates cell death (apoptosis) by either inducing it or inhibiting it. In DHL, changes in this gene result in an anti-apoptotic effect in lymphoma cells, leading to their prolonged survival.

**BCL6 gene** has a role in regulating activation, survival, DNA damage response and cell cycle arrest.

## DIAGNOSIS AND STAGING

A biopsy is always required for a diagnosis of DHL (or THL). A biopsy is a surgical procedure to remove part of or all of an affected lymph node or other abnormal tissue to look at it under the microscope. The biopsy can be done under local or general anaesthetic depending on what part of the body is being biopsied.

Once a diagnosis of DHL is made there are further tests that need to be performed to see where else in the body the lymphoma may be and is referred as staging. Because DHL is a blood cancer the lymphoma can travel all over the body, so it is important that a check of the entire body is done looking for the lymphoma. Staging tests may include:

- Positron emission tomography (PET) /CT scan
- Computed tomography (CT) scan
- Bone marrow biopsy
- Lumbar puncture (if lymphoma suspected in the brain or spinal cord or if there is a future risk of developing that complication)
- Molecular tests of biopsy tissue and blood to check for gene rearrangements

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- Baseline tests prior to starting treatment to check organ function that may include; heart scan kidney scan, breathing test and blood tests

## TREATMENT OPTIONS

DHL is an aggressive, fast growing lymphoma with signs and symptoms close to those of DLBCL and BL which require immediate diagnosis and treatment. There is no certainty in the medical community on whether DHL should be treated like other forms of DLBCL. Some centres elect to use standard intensity regimens (such as R-CHOP), others elect to use more intensified regimens such as the following, in an attempt to improve outcomes. The treatment plan will depend on the stage of the DHL, age, general health & fitness of the patient:

- DA-EPOCH-R (dose adjusted etoposide, prednisolone, vincristine, cyclophosphamide, doxorubicin and rituximab)
- R-Hyper CVAD (rituximab, hyper-fractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone alternating with high dose methotrexate and cytarabine)
- R-CODOX-M (rituximab, cyclophosphamide, vincristine, doxorubicin, methotrexate alternating with rituximab, ifosfamide, etoposide and cytarabine)
- Autologous stem cell transplant may be offered to patients in first remission to consolidate the response to the initial chemotherapy and aim to increase the chance of making the lymphoma go away for good
- In patients with limited stage disease, radiotherapy is typically included.
- DHL is thought to more commonly relapse in the central nervous system (CNS) than other lymphomas, so patients may receive a medication to help prevent this called CNS prophylaxis. This involves chemotherapy such as methotrexate and/or cytarabine administered by a lumbar puncture directly into the spinal fluid.

DHL usually responds well to treatment but in some people the lymphoma comes back (relapses) and further treatment is needed. This may include:

- Salvage chemotherapy with ICE-R, ifosfamide, cyclophosphamide and rituximab)
- Autologous stem cell transplant

## TREATMENTS UNDER INVESTIGATION

Many new individual and combination medicines are currently being tested in clinical trials around the world for both newly diagnosed and relapsed or refractory DHL including:

- Chimeric antigen receptor T-cell therapy (CAR T-cell therapy)

- Bi-specific antibody therapy

## CLINICAL TRIALS

Clinical trials are essential in identifying effective medicines and determining optimal doses of these medicines for people diagnosed with lymphoma. People who are interested in participating in a clinical trial can find one using the following methods:

- Speak to their specialist to see what options are available
- See '[Understanding Clinical Trials](#)' fact sheet

## RESOURCES AND SUPPORT

Organisation	How can they help?
Lymphoma Australia	<ul style="list-style-type: none"><li>• Lymphoma Australia offers a wide variety of resources and support for people with lymphoma or CLL and their carers. Please visit our website for further information: <a href="http://lymphoma.org.au">lymphoma.org.au</a></li><li>• Lymphoma Australia Fact sheets &amp; booklets including:<ul style="list-style-type: none"><li>• Booklet: What you need to know about lymphoma</li><li>• Emotional impact of a lymphoma diagnosis &amp; treatment</li></ul></li><li>• <a href="http://lymphoma.org.au/page/1218/fact-sheets">lymphoma.org.au/page/1218/fact-sheets</a></li><li>• Lymphoma Australia YouTube Channel: Presentations and interviews on lymphoma subtypes, management and supportive care.</li><li>• <a href="https://www.youtube.com/user/LymphomaAustralia">youtube.com/user/LymphomaAustralia</a></li><li>• Lymphoma Nurse Support Line: 1800 953 081 or email: <a href="mailto:nurse@lymphoma.org.au">nurse@lymphoma.org.au</a></li><li>• Online private Facebook group: '<b>Lymphoma Down Under</b>' <a href="http://bit.ly/2mrPA1k">http://bit.ly/2mrPA1k</a></li></ul>

## SOME QUESTIONS TO ASK YOUR DOCTOR

- If you think my lymphoma has transformed, will you do another tissue biopsy to confirm this?
- What treatment options are available for my transformed lymphoma?
- Are there any treatment options that are better but are yet to be funded by the PBS in Australia?
- Are there any clinical trials currently available to me?