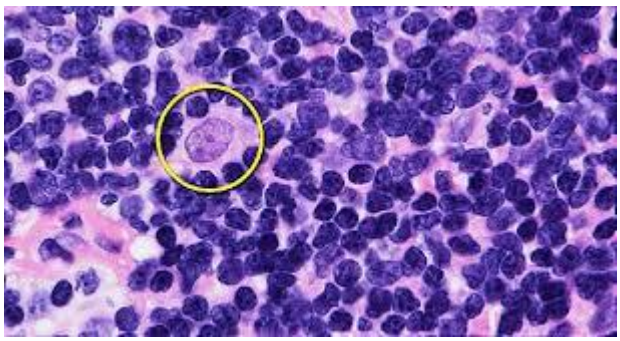
Cancer Association of South Africa (CANSA)

Research • Educate • Support

Fact Sheet on Mantle Cell Lymphoma

Introduction

Lymphoma is the most common blood cancer. The main forms of lymphoma are classified as Hodgkin lymphoma (HL) or non-Hodgkin lymphoma (NHL), which includes several B-cell lymphomas and T-cell lymphomas.



[Picture Credit: Mantle Cell Lymphoma]

Lymphoma occurs when cells of the immune system called lymphocytes, a type of white blood cell, grow and multiply uncontrollably. Cancerous lymphocytes can travel to many parts of the body, including the lymph nodes, spleen, bone marrow, blood, or other organs, and form a mass called a tumour.

The body has two main types of lymphocytes that can develop into lymphomas: B lymphocytes (B cells) and T lymphocytes (T cells).

For most individuals with Mantle Cell Lymphoma, the prognosis is only fair to poor.

Mantle Cell Lymphoma Facts

- Mantle Cell Lymphoma (MCL) is a relatively rare cancer of the lymphoid cells that arises from the outer rim or mantle lymphoid follicle.
- The cause of MCL is unknown, although around 85% of patients have a genetic abnormality known as a translocation, resulting in the overproduction of cyclin D1, a protein that drives cell growth.
- The risk factors for MCL are not clear and may be related to environmental or genetic factors.

Mantle Cell Lymphoma (MCL)

Mantle cell lymphoma (MCL) is an aggressive, rare, form of non-Hodgkin lymphoma (NHL). It develops when the body makes abnormal B-cells – the lymphoma cells. B-cells are white blood cells that fight infection. The

Researched and Authored by Prof Michael C Herbst
[D Litt et Phil (Health Studies); D N Ed; M Art et Scien; B A Cur; Dip Occupational Health; Dip Genetic Counselling; Dip Audiometry and Noise Measurement; Diagnostic Radiographer; Medical Ethicist]
Approved by Ms Elize Joubert, Chief Executive Officer [BA Social Work (cum laude); MA Social Work]

lymphoma cells build up in lymph nodes, which makes them bigger. Sometimes lymphoma cells begin in other parts of the body. This is called extranodal disease.

In Mantle Cell Lymphoma, some of the "Be-cell" lymphocytes change into cancer cells. This causes them to multiply rapidly and out of control. These cancer cells start to form tumours in lymph nodes. They may enter the bloodstream or lymphatic system and spread to other lymph nodes, as well as to the bone marrow, digestive tract, spleen, and liver.

Often, Mantle Cell Lymphoma has already spread to other parts of the body by the time of diagnosis. Although in most cases it cannot be cured, treatment and support can help patients live longer and better.

Navarro, A., Beà, S., Jares, P. & Campo, E. 2020.
"Mantle cell lymphoma (MCL) is a mature B-cell neoplasm with heterogeneous clinical behavior molecularly characterized by the constitutive overexpression of cyclin D1 and deregulation of different signaling pathways. SOX11 expression determines an aggressive phenotype associated with accumulation of many chromosomal alterations and somatic gene mutations. A subset of patients with the SOX11-negative leukemic non-nodal MCL subtype follows an initial indolent clinical evolution and may not require treatment at diagnosis, although eventually may progress to an aggressive disease. We discuss the genetic and molecular alterations with impact on the cancer hallmarks that characterize the lymphomagenesis of the 2 MCL subtypes."

Lynch, D.T. & Acharya, U. 2020.
"Mantle cell lymphoma (MCL) is a rare subtype of B-cell non-Hodgkin lymphomas (NHLs) defined by a confirmatory translocation of the *CCND1* gene. The variety of morphologic variants may make this a challenging diagnosis, although most cases are uncomplicated. It typically follows an aggressive clinical course, although an indolent leukemia variant has been described."

Cortelazzo, S., Ponzoni, M., Ferreri, A.J.M. & Dreyling, M. 2020.
"MCL is a well-characterized generally aggressive lymphoma with a poor prognosis. However, patients with a more indolent disease have been reported in whom the initiation of therapy can be delayed without any consequence for the survival. In 2017 the World Health Organization updated the classification of MCL describing two main subtypes with specific molecular characteristics and clinical features, classical and indolent leukaemic nonnodal MCL. Recent research results suggested an improving outcome of this neoplasm. The addition of rituximab to conventional chemotherapy has increased overall response rates, but it did not improve overall survival compared to chemotherapy alone. The use of intensive frontline therapies including rituximab and consolidation with autologous stem cell transplantation ameliorated response rate and prolonged progression-free survival in young fit patients, but any impact on survival remains to be proven. Furthermore, the optimal timing, cytoreductive regimen and conditioning regimen, and the clinical implications of achieving a disease remission even at molecular level remain to be elucidated. The development of targeted therapies as the consequence of better understanding of pathogenetic pathways in MCL might improve the outcome of conventional chemotherapy and spare the toxicity of intense therapy in most patients. Cases not eligible for intensive regimens, may be considered for less demanding therapies, such as the combination of rituximab either with CHOP or with purine analogues, or bendamustine. Allogeneic SCT can be an effective option for relapsed disease in patients who are fit enough and have a compatible donor. Maintenance rituximab may be considered after response to immunochemotherapy as the first-line strategy in a wide range of patients. Finally, since the optimal approach to the management of MCL is still evolving, it is critical that these patients are enrolled in clinical trials to identify the better treatment options."

Incidence of Mantle Cell Lymphoma
The incidence of Mantle Cell Lymphoma in South Africa is not known.

Signs and Symptoms of Mantle Cell Lymphoma
The most common symptom is a painless swelling in the neck, armpit or groin. Other symptoms may include:

- Tiredness
- Weight loss
- Night sweats
- High temperatures (fevers)
- Unexplained itching
- Enlarged lymph nodes in neck, armpit or groin
- Enlarged spleen (splenomegaly)
- Enlarged Liver (hepatomegaly)
- Abdominal bloating
- Nausea
- Worsening diarrhoea

Causes and Risk Factors for Mantle Cell Lymphoma
About 85 percent of patients with MCL have a characteristic genetic lesion that involves chromosome 11 and chromosome 14. This is called a "reciprocal translocation," and is abbreviated as t(11;14).

This translocation results in short segments of chromosome 11 and chromosome 14 exchanging places. The exchange occurs at the site of the cyclin D1 gene on chromosome 11 and the site of a gene that controls the formation of antibody molecules on chromosome 14. The t(11;14) triggers an overproduction of cyclin D1, a protein that causes tumour cell division and growth. The overproduction of the cyclin D1 protein leads to accumulation of large numbers of MCL cells. This translocation can be thought of as a driver in the behaviour of the disease, which likely complements other genetic defects leading to MCL development.

In a small proportion of patients t(11;14) is not present. In most of these patients, other genetic changes cause excess production of cyclin D1. Rarely, MCL arises from overexpression of other cyclin genes (e.g., cyclin D2 and cyclin D3).

Mantle Cell Lymphoma (MCL) affects males about four times as commonly as females. Blacks and Asians are less likely than whites to develop MCL.

Age is a risk factor - the median age of MCL onset is 60 years of age with an age range of 35-85 years.

It is not possible to prevent Mantle Cell Lymphoma.

Diagnosis of Mantle Cell Lymphoma
To diagnose Mantle Cell Lymphoma, a doctor removes an enlarged lymph node and forwards it to a pathology laboratory where a pathologist checks it under a microscope for lymphoma cells.

Overproduction of a protein called cyclin D1 in the lymphoma cells is found in more than 90 percent of patients with MCL. Identification of excess cyclin D1 from a biopsy is considered a very sensitive tool for diagnosing MCL. One-quarter to one-half of patients with MCL also have higher-than-normal levels of certain proteins that circulate in the blood, such as lactate dehydrogenase (LDH) and beta-2 microglobulin. Measuring these and other proteins can help physicians determine how aggressive an individual patient's MCL is and may guide therapy decisions.

The treating physician may also request additional tests and scans to find out how many groups of lymph nodes are affected and whether the lymphoma has spread. This is called staging.

A patient who has a potential diagnosis of lymphoma needs to make sure that his or her subtype has been correctly identified. Treatment depends on knowing the specific subtype. Each patient should be evaluated by a haematologist/oncologist, a doctor who specializes in treating patients who have NHL.

Albano, D., Laudicella, R., Ferro, P., Allocca, M., Abenavoli, E., Buschiazzo, A., Castellino, A., Chiaravalloti, A., Cuccaro, A., Cuppari, L., Durmo, R., Evangelista, L., Frantellizzi, V., Kovalchuk, S., Linguanti, F., Santo, G., Bauckneht, M., Annunziata, S. & Young Italian Association of Nuclear Medicine. 2019.
"Mantle cell lymphoma (MCL) is an aggressive lymphoma subtype with poor prognosis in which 18F-FDG-PET/CT role in treatment response evaluation and prediction of outcome is still unclear. The aim of this multicentric study was to investigate the role of 18F-FDG-PET/CT in staging MCL and the prognostic role of Deauville criteria (DC) in terms of progression-free survival (PFS) and overall survival (OS). We retrospectively enrolled 229 patients who underwent baseline and end-of-treatment (eot) 18F-FDG-PET/CT after first-line therapy. EotPET/CT scans were visually interpreted according to DC. The sensitivity, specificity, positive predictive value, negative predictive value and accuracy of PET/CT for evaluation of bone marrow (BM) were 27%, 100%, 100%, 48% and 57%, respectively. The sensitivity, specificity, positive predictive value, negative predictive value and accuracy of PET/CT for evaluation of the gastrointestinal (GI) tract were 60%, 99%, 93%, 90% and 91%, respectively. At a median follow-up of 40 months, relapse occurred in 104 cases and death in 49. EotPET/CT results using DC significantly correlated with PFS, not with OS. Instead, considering OS, only MIPI score was significantly correlated. In conclusion, we demonstrated that MCL is an FDG-avid lymphoma and 18F-FDG-PET/CT is a useful tool for staging purpose, showing good specificity for BM and GI evaluation, but suboptimal sensitivity. EotPET/CT result was the only independent significant prognostic factor that correlated with PFS."

Treatment of Mantle Cell Lymphoma
The type of treatment selected for a patient with MCL depends on multiple factors, including the stage of disease, the age of the patient, and the patient's overall health.

Mantle Cell Lymphoma is usually treated with chemotherapy, targeted therapy, radiotherapy, or a combination of two or more of the mentioned forms of treatment. Another form of treatment may include stem cell treatment.

Other new therapy may include immunotherapy.

Some treatments can cause long-term side effects or late side 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. A physician will check for these effects during follow-up care.

Patients with any form of lymphoma should have regular visits with their treating physician. Medical tests (such as blood tests, CT scans, and PET scans) may be required at various times to evaluate the need for additional treatment.

Hanel, W. & Epperla, N. 2020.
"Mantle cell lymphoma (MCL) is a rare, B cell non-Hodgkin's lymphoma with highly heterogeneous clinical presentation and aggressiveness. First-line treatment consists of intensive chemotherapy with autologous stem cell transplant for the fit, transplant eligible patients, or less intensive chemotherapy for the less fit (and transplant-ineligible) patients. Patients eventually relapse with a progressive clinical course. Numerous therapeutic approaches have emerged over the last few years which have significantly changed the treatment landscape of MCL. These therapies consist of targeted approaches such as BTK and BCL2 inhibitors that provide durable therapeutic responses. However, the optimum combination and sequencing of these therapies is unclear and is currently investigated in several ongoing studies. Furthermore, cellular therapies such as chimeric antigen receptor (CAR) T cells and bispecific T cell engager (BiTe) antibodies have shown impressive results and will likely shape treatment approaches in relapsed MCL, especially after failure with BTK inhibitors. Herein, we provide a comprehensive review of past and ongoing studies that will likely significantly impact our approach to MCL treatment in both the frontline (for transplant eligible and ineligible patients) as well as in the relapsed setting. We present the most up to date results from these studies as well as perspectives on future studies in MCL."

Roué, G. & Sola, B. 2020.
"Mantle cell lymphoma (MCL) is a rare but aggressive B-cell hemopathy characterized by the translocation t(11;14)(q13;q32) that leads to the overexpression of the cell cycle regulatory protein cyclin D1. This translocation is the initial event of the lymphomagenesis, but tumor cells can acquire additional alterations allowing the progression of the disease with a more aggressive phenotype and a tight dependency on microenvironment signaling. To date, the chemotherapeutic-based standard care is largely inefficient and despite the recent advent of different targeted therapies including proteasome inhibitors, immunomodulatory drugs, tyrosine kinase inhibitors, relapses are frequent and are generally related to a dismal prognosis. As a result, MCL remains an incurable disease. In this review, we will present the molecular mechanisms of drug resistance learned from both preclinical and clinical experiences in MCL, detailing the main tumor intrinsic processes and signaling pathways associated to therapeutic drug escape. We will also discuss the possibility to counteract the acquisition of drug refractoriness through the design of more efficient strategies, with an emphasis on the most recent combination approaches."

About Clinical Trials
Clinical trials are research studies that involve people. They are conducted under controlled conditions. Only about 10% of all drugs started in human clinical trials become an approved drug.

Clinical trials include:

- Trials to test effectiveness of new treatments
- Trials to test new ways of using current treatments

- Tests new interventions that may lower the risk of developing certain types of cancers
- Tests to find new ways of screening for cancer

The **South African National Clinical Trials Register** provides the public with updated information on clinical trials on human participants being conducted in South Africa. The Register provides information on the purpose of the clinical trial; who can participate, where the trial is located, and contact details.

Wang, M., Munoz, J., Goy, A., Locke, F.L., Jacobson, C.A., Hill, B.T., Timmerman, J.M., Holmes, H., Jaglowski, S., Flinn, I.W., McSweeney, P.A., Miklos, D.B., Pagel, J.M., Kersten, M.J., Milpied, N., Fung, H., Topp, M.S., Houot, R., Beitinjaneh, A., Peng, W., Zheng, L., Rossi, J.M., Jain, R.K., Rao, A.V. & Reagan, P.M. 2020.
Background: Patients with relapsed or refractory mantle-cell lymphoma who have disease progression during or after the receipt of Bruton's tyrosine kinase (BTK) inhibitor therapy have a poor prognosis. KTE-X19, an anti-CD19 chimeric antigen receptor (CAR) T-cell therapy, may have benefit in patients with relapsed or refractory mantle-cell lymphoma.
Methods: In a multicenter, phase 2 trial, we evaluated KTE-X19 in patients with relapsed or refractory mantle-cell lymphoma. Patients had disease that had relapsed or was refractory after the receipt of up to five previous therapies; all patients had to have received BTK inhibitor therapy previously. Patients underwent leukapheresis and optional bridging therapy, followed by conditioning chemotherapy and a single infusion of KTE-X19 at a dose of 2×10^6 CAR T cells per kilogram of body weight. The primary end point was the percentage of patients with an objective response (complete or partial response) as assessed by an independent radiologic review committee according to the Lugano classification. Per the protocol, the primary efficacy analysis was to be conducted after 60 patients had been treated and followed for 7 months.
Results: A total of 74 patients were enrolled. KTE-X19 was manufactured for 71 patients and administered to 68. The primary efficacy analysis showed that 93% (95% confidence interval [CI], 84 to 98) of the 60 patients in the primary efficacy analysis had an objective response; 67% (95% CI, 53 to 78) had a complete response. In an intention-to-treat analysis involving all 74 patients, 85% had an objective response; 59% had a complete response. At a median follow-up of 12.3 months (range, 7.0 to 32.3), 57% of the 60 patients in the primary efficacy analysis were in remission. At 12 months, the estimated progression-free survival and overall survival were 61% and 83%, respectively. Common adverse events of grade 3 or higher were cytopenias (in 94% of the patients) and infections (in 32%). Grade 3 or higher cytokine release syndrome and neurologic events occurred in 15% and 31% of patients, respectively; none were fatal. Two grade 5 infectious adverse events occurred.
Conclusions: KTE-X19 induced durable remissions in a majority of patients with relapsed or refractory mantle-cell lymphoma. The therapy led to serious and life-threatening toxic effects that were consistent with those reported with other CAR T-cell therapies. (Funded by Kite, a Gilead company; ZUMA-2 ClinicalTrials.gov number, NCT02601313.).

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.

Whilst the Cancer Association of South Africa (CANSA) has taken every precaution in compiling this Fact Sheet, neither it, nor any contributor(s) to this Fact Sheet can be held responsible for any action (or the lack thereof)

taken by any person or organisation wherever they shall be based, as a result, direct or otherwise, of information contained in, or accessed through, this Fact Sheet.

Sources and References Consulted and/or Utilised

Albano, D., Laudicella, R., Ferro, P., Allocca, M., Abenavoli, E., Buschiazzo, A., Castellino, A., Chiaravalloti, A., Cuccaro, A., Cuppari, L., Durmo, R., Evangelista, L., Frantellizzi, V., Kovalchuk, S., Linguanti, F., Santo, G., Bauckneht, M., Annunziata, S. & Young Italian Association of Nuclear Medicine. 2019. The Role of 18F-FDG PET/CT in Staging and Prognostication of Mantle Cell Lymphoma: An Italian Multicentric Study. Cancers (Basel). 2019 Nov 21;11(12). pii: E1831. doi: 10.3390/cancers11121831.

Cortelazzo, S., Ponzoni, M., Ferreri, A.J.M. & Dreyling, M. 2020. Mantle cell lymphoma. *Crit Rev Oncol Hematol*. 2020 Sep;153:103038.

Glimelius, I., Semdby, K.E., Eloranta, S., Jerkeman, M. & Weibull, C.E. 2019. Comorbidities and sex differences in causes of death among manatl cell lymphoma patients – a nationwide population-based cohort study. *Br J Haematol*. 2019 Nov 13. doi: 10.1111/bjh.16317. [Epub ahead of print]

Hanel, W. & Epperla, N. 2020. Emerging therapies in mantle cell lymphoma. *J Hematol Oncol*. 2020 Jun 17;13(1):79.

Jain, A.G., Chang, C.C., Ahmad, S. & Mori, S. 2019. Leukemic non-nodal mantle cell lymphoma: diagnosis and treatment. *Curr Treat Options Oncol*. 2019 Nov 27;20(12):85. doi: 10.1007/s11864-019-0684-8.

Lynch, D.T. & Acharya, U. 2020. Mantle cell lymphoma. ***In***: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2021 Jan. 2020 Aug 12.

Mantle Cell Lymphoma
https://www.macmillan.org.uk/information-and-support/lymphoma/lymphoma-non-hodgkin/understanding-cancer/types-of-non-hodgkin-lymphoma/mantle-cell-lymphoma.html
https://www.webmd.com/cancer/lymphoma/mantle-cell-lymphoma#1
https://lymphoma.org/aboutlymphoma/nhl/mcl/
https://lymphoma.org/wp-content/uploads/2019/08/LRF1702-MantleCellLymphomaFS_D3V4.pdf
https://www.lls.org/sites/default/files/file_assets/mantlecelllymphoma.pdf
https://www.medicinenet.com/mantle_cell_lymphoma_mcl/article.htm
https://www.mdedge.com/hematology-oncology/article/136262/mantle-cell-lymphoma/newly-diagnosed-mantle-cell-lymphoma-one
https://rarediseases.info.nih.gov/diseases/6969/mantle-cell-lymphoma
https://www.cancerresearchuk.org/about-cancer/non-hodgkin-lymphoma/types/mantle-cell
https://www.leukaemia.org.au/disease-information/lymphomas/non-hodgkin-lymphoma/other-non-hodgkin-lymphomas/mantle-cell-lymphoma/
https://www.cancer.ca/en/cancer-information/cancer-type/non-hodgkin-lymphoma/non-hodgkin-lymphoma/mantle-cell-lymphoma/?region=on
https://lymphoma-action.org.uk/types-lymphoma-non-hodgkin-lymphoma/mantle-cell-lymphoma
https://rarediseases.org/rare-diseases/mantle-cell-lymphoma/
https://www.cancertherapyadvisor.com/home/decision-support-in-medicine/hematology/mantle-cell-lymphoma/
https://www.healthline.com/health/mantle-cell-lymphoma

Mantle Cell Lymphoma Picture
https://www.webmd.com/cancer/lymphoma/mantle-cell-lymphoma#1

Morabito, F., Recchia, A.G., Vigna, E., Botta, C., Skafi, M., Abu-Rayyan, M., Atrash, M., Galimberti, S., Morabito, L., Al-Janazreh, H., Martino, M., Cutrona, G. & Gentile, M. 2019. An in-depth evaluation of acalabrutinib for the treatment of mantle-cell lymphoma. *Expert Opin Pharmacother*. 2019 Nov 18:1-10. doi: 10.1080/14656566.2019.1689959. [Epub ahead of print]

Navarro, A., Beà, S., Jares, P. & Campo, E. 2020. Molecular pathogenesis of mantle cell lymphoma. *Hematol Oncol Clin North Am*. 2020 Oct;34(5):795-807.

Okay, M., Meletli, O., Kelkitli, E., Malkan, U.Y., ATurgut, M., Buyukasik, Y., Tekin, F., Demitoglu, H. & Goker, H. 2019. Mantle cell lymphoma: a ATurkish Multi-Center study. *J BUON*. 2019 Sep-Oct;24(5):2084-2089.

Ratnasingam, S., Casan, J., Shortt, J., Hawkes, E., Gilbertson, M., McQuilten, Z., Grigoriadis, G., Htun, K.T., Htet, S.M., Campbell, P., Chai, K.L., Quach, H., Patil, S. & Opat, S. 2019. Cytarabaine-based inducdtion immunochemotherapy in the front-line treatment of older patients with mantle cell lymphoma. *Sci Rep*. 2019 Sep 19;9(1):13544. doi: 10.1038/s41598-019-49776-9.

Roué, G. & Sola, B. 2020. Management of drug resistance in mantle cell lymphoma. *Cancers (Basel)*. 2020 Jun 12;12(6):1565.

Wang, M., Munoz, J., Goy, A., Locke, F.L., Jacobson, C.A., Hill, B.T., Timmerman, J.M., Holmes, H., Jaglowski, S., Flinn, I.W., McSweeney, P.A., Miklos, D.B., Pagel, J.M., Kersten, M.J., Milpied, N., Fung, H., Topp, M.S., Houot, R., Beitinjaneh, A., Peng, W., Zheng, L., Rossi, J.M., Jain, R.K., Rao, A.V. & Reagan, P.M. 2020. KTE-X19 CAR T-Cell Therapy in Relapsed or Refractory Mantle-Cell Lymphoma. *N Engl J Med*. 2020 Apr 2;382(14):1331-1342.