Cancer Association of South Africa (CANSA)

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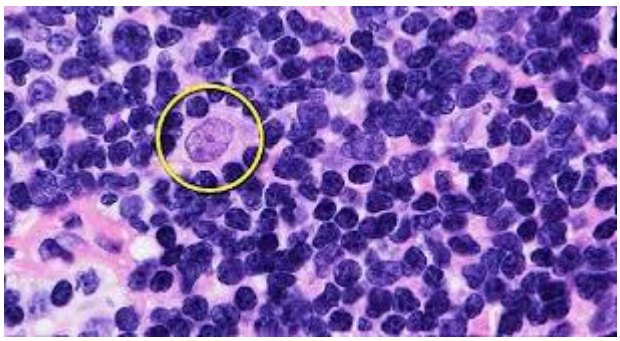
Fact Sheet on Mantle Cell Lymphoma

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

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.

Okay, M., Meletli, O., Kelkitli, E., Malkan, U.Y., ATurgut, M., Buyukasik, Y., Tekin, F., Demitoglu, H. & Goker, H. 2019.
PURPOSE: Mantle Cell Lymphoma (MCL) is a B-cell neoplasm with CCND1 [t(11;14)(q13;q32), cyclin D1] translocation. The guidelines recommend various treatment options based on age, performance status and comorbidities. Our purpose was to analyze the clinical features and evaluate prognostic factors for survival of 78 MCL patients.
METHODS: We retrospectively analyzed all MCL patients in two reference Hematology Departments between January 2001 and September 2018.
RESULTS: The patient median age was 62 years (34-86) and 78.2% of them were male. The treatment regimens were R−CHOP in 42.3%, R−Bendamustine in 26.9%, HyperCVAD in 9% and R−CHOP/R−DHAP alternating in 7.7%. Only 13 patients underwent autologous stem cell transplantation. Median overall survival (OS) was 77.8 months (53.8−101.8) and median disease-free survival (DFS) was 20.6 months (14.2−26.9), all patients included. Univariate analysis showed that MCL International Prognostic Index and neutrophil count effected OS in all groups (p=0.047 and p=0.001). Multivariate analysis showed that the neutrophil count at diagnosis was independent prognostic risk factor (HR=0.209, 95% confidence interval 0.069-0.629, p=0.005) for OS. The median OS was 77.8 months in absolute neutrophil count (ANC) less than 7.5×103/µL and 14.8 months in ANC more than 7.5×103/µL (p=0.001).
CONCLUSIONS: Median OS is somewhat prolonged in the last years with new treatment approaches but MCL is still an incurable disease. The first choice of treatment in MCL patients was R-CHOP. Higher neutrophil count at the time of diagnosis has a detrimental effect on OS.

Glimelius, I., Semdby, K.E., Eloranta, S., Jerkeman, M. & Weibull, C.E. 2019.
"The prognosis for mantle cell lymphoma (MCL) remains poor. Our aim was to assess the impact of comorbidities on survival and causes of death. For 1,385 MCL patients (1,009 males, 376 females) diagnosed in 2000-2014 (median age 71 years, range 22-96) comorbidities ≤ 10 years of diagnosis were classified according to the Charlson comorbidity index (CCI; 0, 1, 2+). Hazard ratios (HRs) with 95% confidence intervals (CIs) were estimated to compare lymphoma-specific and all-cause mortality rates. Model-based predictions were used to obtain probabilities of death. Overall, 44% had any comorbidity (CCI 1+) and 28% severe comorbidity (CCI 2+). Over a median follow-up of 3·7 years (range 0-16), 633 (46%) died, the majority (76%) from lymphoma. Severe comorbidity was independently associated with higher all-cause [hazard ratio (HR) = 1·52; 95% CI: 1·24-1·85) and lymphoma-specific mortality (HR = 1·31; 95% CI: 1·04-1·65). Particularly among patients with connective tissue, renal and psychiatric diseases, and dementia. Among females with any comorbidity, non-lymphoma deaths represented a larger proportion of all deaths, compared to males with any comorbidity. In general, more efficient lymphoma treatments need to be considered also for patients with severe comorbidity. However, among females with any comorbidity, the likelihood of non-lymphoma death was still considerable, perhaps favouring a more liberal use of a "wait and watch" approach."

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.

Jain, A.G., Chang, C.C., Ahmad, S. & Mori, S. 2019.
"Mantle cell lymphoma (MCL) encompasses nearly 6% of all the non-Hodgkin lymphomas. It is considered an incurable neoplastic process arising from B cells. The cytogenetic abnormality t(11;14) (q13; q32) leading to cyclin D1 overexpression is the sentinel genetic event and provides an exceptional marker for diagnosis. MCL is generally considered to have an aggressive course as compared with other indolent lymphomas with traditionally reported median survival of 3-5 years. According to the 2016 WHO classification, there are two major known variants of MCL: classical which affects the lymph nodes and extra nodal sites and leukemic non-nodal MCL (L-NN-MCL) which characteristically involves the bone marrow, peripheral blood, and the spleen. It is important to distinguish between classical and leukemic non-nodal MCL since the latter variant of MCL follows a rather indolent course with a wait and watch approach in order to avoid overtreatment. However, a subset of patients with L-NN-MCL can transform into a more aggressive course requiring treatment. Current evidence suggests those patients with alteration in TP53 gene do not respond to standard chemotherapy agents and may need targeted therapy. In this review, we describe the characteristics of L-NN-MCL, its diagnosis, and management."

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.
Introduction: Regimens involving intensive immuno-chemotherapy, followed by high-dose therapy and autologous stem cell transplant represent the standard treatment for younger fit patients with mantle cell lymphoma (MCL). Targeted approaches (i.e. ibrutinib, bortezomib, and lenalidomide) represent the backbone of therapy for relapsed cases.
Areas covered: Acalabrutinib is a novel small molecule with a butynamide moiety specifically designed to irreversibly inhibit Bruton tyrosine kinase (BTK), which is more potent and selective than ibrutinib. Relevant publications have been identified through literature searches using the terms 'mantle cell lymphoma' and 'acalabrutinib'
Expert opinion: Acalabrutinib has been approved for the treatment of relapsed/refractory (RR) MCL patients. To date, clinical trials have reported some adverse effects such as cardiac toxicity or atrial fibrillation. Acalabrutinib in combination with other drugs, either in chemo-containing or chemo-free schedules, represent a valid option for MCL. However, none of the treatment schedules containing BTK inhibitors have been shown to be curative in MCL. Acalabrutinib may ultimately represent an option for patients who are 'fit' and exhibit well-controlled disease, which often characterizes only a limited 'niche' among MCL patients.

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.
"The role of cytarabine-based induction and autologous stem cell transplantation (ASCT) in front-line treatment of younger patients with mantle cell lymphoma (MCL) is well established, however the utility of

intensive approaches in older patients remains unclear. This retrospective study compared first line treatment outcomes in patients aged 60 years or more, treated at six tertiary centres between 2000-2015. 70 patients included had a median age of 69 (60-91) and most (94%) demonstrated advanced stage disease. Treatment regimens included: R-CHOP-like (n = 39), alternating R-CHOP/R-DHAC (n = 10), R-HyperCVAD/R-MA (n = 7), R-CHOP/Cytarabine (Nordic Protocol) (n = 10) and other (n = 4). 16 patients underwent an ASCT. The median follow-up for surviving patients was 37 months. Compared to R-CHOP-like therapies, cytarabine-based regimens were associated with an improved overall response rate (ORR) of 70% vs 33% ($p < 0.001$) and overall survival (OS) (HR 0.541, [0.292-1.001], $p = 0.05$). No difference in efficacy between different cytarabine-based regimens was detected, but R-HyperCVAD/R-MA was associated with increased hospitalisation and transfusion requirements. Patients undergoing ASCT demonstrated an improved median OS (HR 0.108 [0.015-0.796], $p = 0.029$) but were significantly younger. These results reaffirm the use of cytarabine in MCL for selected patients aged over 60. Such regimens should be strongly considered for this population in frontline therapy."

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.

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Mantle Cell Lymphoma
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Mantle Cell Lymphoma Picture
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