Cancer Association of South Africa (CANSA)

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Fact Sheet on Adult Chronic Myelomonocytic Leukaemia

Introduction

Chronic Myelomonocytic Leukaemia (CMML) is a form of chronic leukaemia characterised by high numbers of white blood cells called monocytes in the blood and bone marrow.

[Picture Credit: Blood Cells]

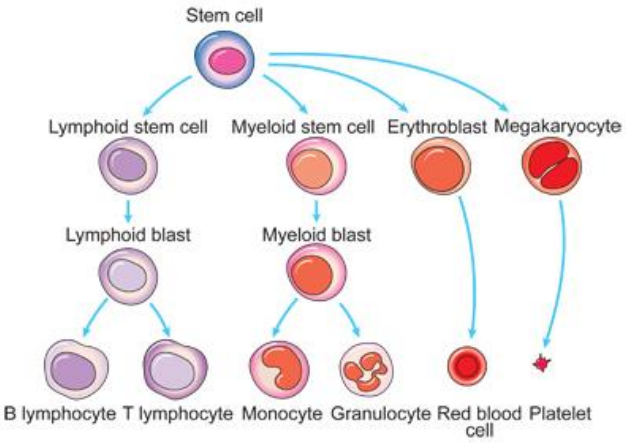

Diagram showing how blood cells are made
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About half of all patients with CMML have a form in which there is a high white cell count at diagnosis and the condition behaves most like a myeloproliferative neoplasm (MPN). The other half of patients have a normal or reduced white cell count at diagnosis and the disease behaves more like a Meyelodysplastic syndrome (MDS). Men are more often affected than women.

It is mainly a disease of later life with the median age at onset being about 70 years. There is also a juvenile form known as Juvenile Myelomonocytic Leukaemia (JMML).

Espinoza, V.E. & Emmady, P.D. 2020.

"Monocytes are white blood cells that derive from the bone marrow. A monocyte is part of the innate immune response and functions to regulate cellular homeostasis, especially in the setting of infection and inflammation. They account for approximately 5% of circulating nucleated cells in normal adult blood. The half-life of circulating monocytes is approximately one to three days. Monocytopenia, a decrease in circulating monocytes, is a common finding in myelodysplastic syndromes. While monocytosis, an increase in circulating monocytes, is a common finding in the peripheral blood, especially in association with infection, trauma, medications, autoimmune disease, and some malignancies. When monocytosis is persistent and unexplained, the diagnosis of chronic myelomonocytic leukemia merits investigation."

Elbæk, M.V., Sørensen, A.L. & Hasselbalch, H.C. 2019.

"Patients with chronic myelomonocytic leukemia (CMML) have monocytosis and likely a state of chronic inflammation. Both have been associated with an increased risk of atherosclerosis. The

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aim of the study was to test the hypothesis that CMML patients are at increased risk of developing cardiovascular disease (CVD) due to persistent monocytosis and sustained chronic inflammation. In a retrospective cohort study, we assessed hazards for cardiovascular events after diagnosis in 112 CMML patients and 231 chronic lymphocytic leukemia (CLL) patients. Analyses were carried out on restricted cohorts (CMML = 84, CLL = 186), excluding patients with a prior history of CVD, as well as on unrestricted cohorts. In the restricted cohorts, a significant effect of cardiovascular event occurrence did not remain after adjustment (HR 2.49, 95% CI 0.94-6.60). In unrestricted cohorts, we found a more than twofold increased rate of cardiovascular events in CMML (HR 2.34, 95% CI 1.05-5.20). Our results indicate an increased risk of CVD after the diagnosis in CMML patients."

Incidence of Adult Chronic Myelomonocytic Leukaemia (CMML)

In providing the incidence figures of Leukaemia in South Africa, the outdated National Cancer Registry (2017) does not make provision for the reporting of the different types of Leukaemia – it also does not differentiate between acute and chronic Leukaemia - neither does it provide for different statistics for cases of adult and childhood Leukaemia - except in the 'Frequency of Histologically Diagnosed Cancer in South Africa' Section of the Registry .

According to the National Cancer Registry (2017) the following number of Leukaemia cases was histologically diagnosed in South Africa during 2017:

Group - Males 2017	Actual No of Cases	Estimated Lifetime Risk	Percentage of All Cancers
All males	338	1:634	0,85%
Asian males	7	1:1 000	1,72%
Black males	151	1:1 357	1,12%
Coloured males	29	1:862	0,58%
White males	151	1:209	0,72%

Group - Females 2017	Actual No of Cases	Estimated Lifetime Risk	Percentage of All Cancers
All females	230	1:1 289	0,55%
Asian females	8	1:1 010	0,62%
Black females	106	1:2 410	0,56%
Coloured females	25	1:1 074	0,53%
White females	91	1:455	0,52%

The frequency of histologically diagnosed cases of Leukaemia in South Africa for 2017 was as follows (National Cancer Registry, 2017):

Group - Males 2017	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	82	21	29	33	54	61	42	16
Asian males	0	0	3	1	1	1	1	0
Black males	66	10	19	16	16	19	4	1
Coloured males	7	2	1	4	8	3	6	1
White males	9	9	6	12	31	38	3	14

Group - Females 2017	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	40	17	20	28	31	39	37	18
Asian females	1	1	0	6	2	3	1	0
Black females	32	10	17	12	15	14	2	4
Coloured females	1	3	0	5	4	6	5	1
White females	6	3	3	11	10	16	29	13

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 Adult Chronic Myelomonocytic Leukaemia (CMML)

The cause of CMML is not known.

Clinical features of CMML may include the following:

- Fever
- Fatigue
- Sweat at night
- Weight loss without trying to lose weight
- Regular infections
- Bleeding
- Enlargement of the liver (in some patients)
- Enlargement of the spleen (in some patients)

Diagnosis of Adult Chronic Myelomonocytic Leukaemia (CMML)

The most important features in confirming the diagnosis usually include blood count and bone marrow results. The disease is characterised by increased numbers of monocytes in the blood (greater than 1×10^9/L) and in the marrow. Also, there are fewer than 20% blasts (primitive leukaemic cells) in the marrow and an absence of the BCR/ABL genetic abnormality. There are often chromosome abnormalities, and one rare abnormality may be associated with a response to a specific drug called Glivec.

Patnaik, M.M. & Tefferi, A. 2020.

Disease overview: Chronic myelomonocytic leukemia (CMML) is a clonal hematopoietic stem cell disorder with overlapping features of myelodysplastic syndromes and myeloproliferative neoplasms, with an inherent risk for leukemic transformation (~15% over 3-5 years).

Diagnosis: Diagnosis is based on the presence of sustained (>3 months) peripheral blood monocytosis (≥1×10^9 /L; monocytes ≥10%), along with bone marrow dysplasia. Clonal cytogenetic abnormalities occur in ~ 30% of patients, while >90% have gene mutations. Mutations involving TET2 (~60%), SRSF2 (~50%), ASXL1 (~40%) and the oncogenic RAS pathway (~30%) are frequent; while the presence of ASXL1 and DNMT3A mutations and the absence of TET2 mutations negatively impact over-all survival.

Risk stratification: Molecularly integrated prognostic models include; the Groupe Français des Myélodysplasies (GFM), Mayo Molecular Model (MMM) and the CMML specific prognostic model (CPSS-Mol). Risk factors incorporated into the MMM include presence of nonsense or frameshift ASXL1 mutations, absolute monocyte count>10×10^9 /L, hemoglobin <10 g/dL, platelet count <100×10^9 /L and the presence of circulating immature myeloid cells. The MMM stratifies CMML patients

into four groups; high (≥3 risk factors), intermediate-2 (2 risk factors), intermediate-1 (1 risk factor) and low (no risk factors), with median survivals of 16, 31, 59 and 97 months, respectively.
Risk-adapted therapy: Hypomethylating agents such as 5-azacitidine and decitabine are commonly used, with overall response rates of ~40%-50% and complete remission rates of ~7%-17%; with no impact on mutational allele burdens. Allogeneic stem cell transplant is the only potentially curative option, but is associated with significant morbidity and mortality.

Coltro, G., Mangaonkar, A.A., Lasho, T.L., Finke, C.M., Pophali, P., Carr, R., Gangat, N., Binder, M., Pardanani, A., Fernandez-Zapico, M., Robertson, K.D., Bosi, A., Droin, N., Vannucchi, A.M., Tefferi, A., Hunter, A., Padron, E., Solary, E., Patnaik, M.M. 2020.
"Loss-of-function TET2 mutations ($TET2^{MT}$) are frequent early clonal events in myeloid neoplasms and are thought to confer a fitness advantage to hematopoietic precursors. This large, multi-institutional study (n = 1084), investigated the TET2 mutational landscape and prognostic implications of the number, type, and location of $TET2^{MT}$ and the epistatic relationship with other somatic events in chronic myelomonocytic leukemia (CMML). Nine hundred and forty-two $TET2^{MT}$ were identified in 604 (56%) patients, of which 710 (75%) were predicted to be truncating (involving the catalytic domain). Three hundred and sixteen (29%) patients had ≥1 $TET2^{MT}$, with 28%, 1%, and 0.2% harboring 2, 3, and 5 mutations, respectively. In comparison to $TET2^{WT}$, $TET2^{MT}$ patients were older in age, more likely to have dysplastic CMML, a higher number of co-occurring mutations, and lower-risk stratification. Importantly, $TET2^{MT}$ were associated with a survival advantage (49 vs. 30 months, $p < 0.0001$), especially in the context of multiple $TET2^{MT}$ (≥2; 57 months, $p < 0.001$), and truncating $TET2^{MT}$ (51 months, $p < 0.001$). In addition, the adverse prognostic impact of $ASXL1^{MT}$ was partially mitigated by concurrent $TET2^{MT}$, with the $ASXL1^{WT}/TET2^{MT}$ genotype having better outcomes and resulting in further risk stratification of ASXL1 inclusive CMML prognostic models, in comparison to $ASXL1^{MT}$ alone."

Staging of Adult Chronic Myelomonocytic Leukaemia (CMML)
Doctors often group cancers into different stages. The stage of a cancer can help predict the outlook for a cancer. Often, the stage of a cancer is used to decide which treatment is needed.

Khan, M., Muzzafar, T., Kantarjian, H., Badar, I., Short, N., Wang, X., Chamoun, K., Jain, P., DiNardo, C., Pemmaraju, N., Bose, P., Borthakur, G., Cortes, J., Verstovsek, S., Garcia-Manero, G. & Estrov, Z. 2018.
The impact of bone marrow fibrosis grade on the prognosis of patients with chronic myelomonocytic leukemia (CMML) remains controversial. Therefore, we examined the records of 82 patients diagnosed with CMML at our institution and summarized baseline characteristics and molecular profiles by subgroups of absent or mild (grades 0/1) and moderate (grade 2) fibrosis. Cox proportional hazards models were constructed to assess the prognostic significance of fibrosis grade. Grade 2 fibrosis was identified in 63 patients (76.8%), grade 1 in 16 patients (19.5%), and grade 0 in 3 patients (3.7%). Grade 2 fibrosis was associated with reduced hemoglobin levels (median 9.75 vs 11.0 g/dL in grade 0/1; p = 0.04) and increased percentages of ringed sideroblasts (7.5 vs 0%; p = 0.008). In multivariable analysis, grade 2 fibrosis was an independent predictor of poor overall survival (OS; 95% CI 1.32-6.35; HR 2.90; p = 0.008), but not event-free survival (EFS; 95% CI 0.62-2.67; HR 1.28; p = 0.50). Absolute neutrophil count (ANC) was found to impact OS (95% CI 1.01-1.09; HR 1.05; p = 0.009), while both ANC (95% CI 1.00-1.07; HR 1.04; p = 0.04) and peripheral blood blast percentage (95% CI 1.02-1.32; HR 1.16; p = 0.02) impacted EFS. These results implicate fibrosis grade is an important indicator of prognosis, with high-grade fibrosis predicting inferior survival. Given the

prevalence of marrow fibrosis in CMML, fibrosis grading should be incorporated into prognostic assessment and therapeutic decision-making.

Treatment of Adult Chronic Myelomonocytic Leukaemia (CMML)
If one has no or few symptoms one may possibly not need treatment at first. Instead the patient may have regular check-ups including blood tests.

The type of treatment needed depends on

- The type of CMML he/she has
- Whether they have symptoms
- Their age
- Whether they have any other medical conditions

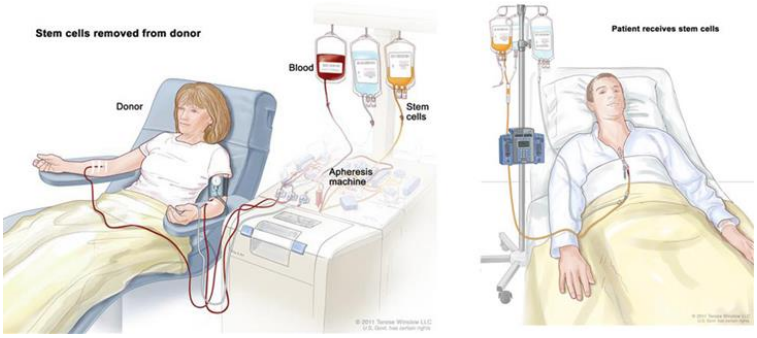
Supportive treatment - this treatment aims to help control the symptoms of CMML. Most people need this type of treatment at some point.

Blood transfusion - one may have blood transfusions if the red blood cell count is low. And if the platelets are low the patient will have a drip of a clear fluid containing platelets.

Prescribing of growth factors - drugs that encourage the bone marrow to make more blood cells.

Chemotherapy - chemotherapy is the main treatment for most people with CMML. It uses cell killing (cytotoxic) drugs to destroy the immature monocyte cells.

Donor stem cell transplant - in a donor stem cell transplant the patient has a very high dose of chemotherapy. He/she may also have total body irradiation (TBI). These treatments destroy the cells in the bone marrow. This treatment is very intensive and may get rid of the CMML completely but it is not suitable for everyone.



[Picture Credit: Donor Stem Cell Transplant]

Liu, H.D., Ahn, K.W.,Hu, Z.H., Hamandani, M., Nishihori, T., Wirk, B., Beitinjaneh, A., Rizzieri, D., Grunwald, M.R., Sabloff, M., Olsson, R.F., Baiel, A., Bredeson, C., Daly, A., Inamoto, Y. Majhail, N., Saad, A., Gupta, V., Gerds, A., Malone, A., Tallman, M., Reshef, R., Marks, D.O., Copelan, E., Gergis, U., Savoie, M.L., Ustun, C., Litzow, M.R., Cahn, J.Y., Kindwall-Keller, T., Akpek, G., Savani, B.N., Aliurf,M., Rowe, J.M., Wiernik, P.H., Hsu, J.W., Cortes, J., Kalavcio, M., Maziarz, R., Sobecks, R., Popat, U., Alvea, E. & Saber, W. 2017.

"Allogeneic hematopoietic cell transplantation (HCT) is potentially curative for patients with chronic myelomonocytic leukemia (CMML); however, few data exist regarding prognostic factors and transplantation outcomes. We performed this retrospective study to identify prognostic factors for post-transplantation outcomes. The CMML-specific prognostic scoring system (CPSS) has been validated in subjects receiving nontransplantation therapy and was included in our study. From 2001 to 2012, 209 adult subjects who received HCT for CMML were reported to the Center for International Blood and Marrow Transplant Research. The median age at transplantation was 57 years (range, 23 to 74). Median follow-up was 51 months (range, 3 to 122). On multivariate analyses, CPSS scores, Karnofsky performance status (KPS), and graft source were significant predictors of survival (P = .004, P = .01, P = .01, respectively). Higher CPSS scores were not associated with disease-free survival, relapse, or transplantation-related mortality. In a restricted analysis of subjects with relapse after HCT, those with intermediate-2/high risk had a nearly 2-fold increased risk of death after relapse compared to those with low/intermediate-1 CPSS scores. Respective 1-year, 3-year, and 5-year survival rates for low/intermediate-1 risk subjects were 61% (95% confidence interval [CI], 52% to 72%), 48% (95% CI, 37% to 59%), and 44% (95% CI, 33% to 55%), and for intermediate-2/high risk subjects were 38% (95% CI, 28% to 49%), 32% (95% CI, 21% to 42%), and 19% (95% CI, 8% to 29%). We conclude that higher CPSS score at time of transplantation, lower KPS, and a bone marrow graft are associated with inferior survival after HCT. Further investigation of CMML disease-related biology may provide insights into other risk factors predictive of post-transplantation outcomes."

Solary, E. & Itzykson, R. 2017. How I treat chronic myelomonocytic leukemia.
"Chronic myelomonocytic leukemia (CMML) is a clonal hematopoietic malignancy that may deserve specific management. Defined by a persistent peripheral blood monocytosis ≥1 × 10^9/L and monocytes accounting for ≥10% of the white blood cells, this aging-associated disease combines cell proliferation as a consequence of myeloid progenitor hypersensitivity to granulocyte-macrophage colony-stimulating factor with myeloid cell dysplasia and ineffective hematopoiesis. The only curative option for CMML remains allogeneic stem cell transplantation. When transplantation is excluded, CMML is stratified into myelodysplastic (white blood cell count <13 × 10^9/L) and proliferative (white blood cell count ≥13 × 10^9/L) CMML. In the absence of poor prognostic factors, the management of myelodysplastic CMML is largely inspired from myelodysplastic syndromes, relying on erythropoiesis-stimulating agents to cope with anemia, and careful monitoring and supportive care, whereas the management of proliferative CMML usually relies on cytoreductive agents such as hydroxyurea, although ongoing studies will help delineate the role of hypomethylating agents in this patient population. In the presence of excessive blasts and other poor prognostic factors, hypomethylating agents are the preferred option, even though their impact on leukemic transformation and survival has not been proved. The therapeutic choice is illustrated by 4 clinical situations among the most commonly seen. Although current therapeutic options can improve patient's quality of life, they barely modify disease evolution. Improved understanding of CMML pathophysiology will hopefully lead to the exploration of novel targets that potentially would be curative."

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.

For additional information, please visit: www.sanctr.gov.za/

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