Understanding chronic myeloid leukemia (CML)

Chronic myeloid leukemia (CML) is a type of cancer that starts in the blood-forming cells of the bone marrow and invades the blood[1].

There are three phases of CML: chronic-phase, accelerated-phase, and blast-phase. In most patients, CML is diagnosed in the early, chronic phase, and if properly treated may remain in this phase without progressing to a more advanced phase[2].

CML statistics

1.2 to **1.5** million people are currently living with **CML** worldwide[3]

About **15%** of all leukemia cases are **CML**[4]

The average age at diagnosis for **CML** is **64** years; it is rarely seen in children[4]

CML is slightly more common in men[5]

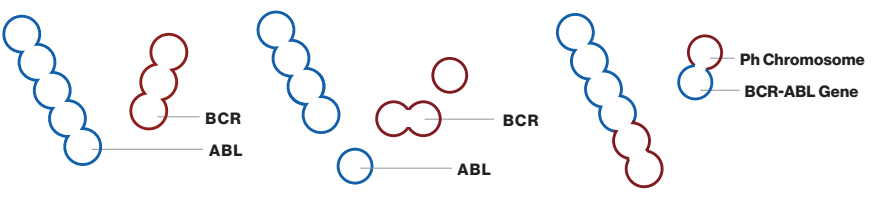
The Ph chromosome

CML is caused by a genetic mutation called the Philadelphia (Ph) chromosome – a rearrangement in the genetic material between chromosomes 9 and 22[6].

The Ph chromosome carries a defective gene called *BCR-ABL*, which produces a protein of the same name. The protein triggers bone marrow to keep making abnormal white blood cells. When the Ph chromosome is present, CML is classified as Philadelphia chromosome-positive (Ph+)[6].

95% of CML cases are classified as **Ph+ CML**[7].

Chromosomal rearrangement



Symptoms of CML

Many patients with CML do not show symptoms when diagnosed, and the disease is often found when a doctor orders a blood test for unrelated health problems, or during a routine checkup[8].

When symptoms of CML do develop, they may include[9]:

- ☑ **Fatigue**
- ☑ **Weight loss**
- ☑ **Bone pain**
- ☑ **Fever**
- ☑ **Pain below the ribs from an enlarged spleen**

Monitoring, management, and milestones

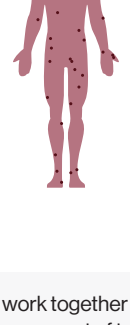
Routine monitoring of *BCR-ABL* levels through a sensitive blood polymerase chain reaction (PCR) test can detect early and deep response to treatment and is fundamental to the management of Ph+ CML[10].

This is a simplified way to understand CML treatment milestones. Think of the dots shown in the body as the amount of leukemic cells in the blood. With each treatment milestone, the amount of leukemia in the body is reduced.

AT DIAGNOSIS
The level of *BCR-ABL* in the body is different for every patient at diagnosis. The values are reported on the International Scale (IS) so that they can be compared with other patients[11]

EARLY MOLECULAR RESPONSE (EMR)
The level of *BCR-ABL* in the body is **≤10%** on the IS[11]

COMPLETE CYTOGENETIC RESPONSE (CCYR)
The level of *BCR-ABL* in the body is expected to correspond with **≤1%** on the IS[11]*



MAJOR MOLECULAR RESPONSE (MMR)
The level of *BCR-ABL* in the body is **≤0.1%** on the IS[11]*

Patients and their health care providers should work together to establish proper treatment goals; with regular monitoring and assessment of tolerability, treatment may need to be adjusted.

Treatment and management of CML

The introduction of tyrosine kinase inhibitor (TKI) therapy more than 20 years ago helped transform CML into a chronic disease for many patients, opening possibilities to achieve deeper and stable responses[12,13].

Most TKIs target the ATP binding site of the *BCR-ABL* gene, blocking this gene's ability to send signals to produce the leukemic cells[14].

Need for additional advances

Despite the significant advancements in CML care over the last few decades, many patients remain at risk of disease progression, and the sequential use of currently available TKIs is associated with treatment resistance and/or intolerance, resulting in increased failure rates in later lines[15-19].

Some patients with CML develop mutations that cause resistance to TKI therapy, including the T315I mutation, which confers resistance to most available TKIs. As a result, patients harboring this mutation have limited treatment options[20,21].

In patients with later-line (≥ third-line) CML, approximately 55% reported intolerance to a previous TKI*[22].

There remains a significant unmet need for novel treatment options for patients with Ph+ CML who do not respond adequately to available therapies.

**Data from an analysis of studies where patients were treated with 2 prior TKIs*

References:

1. American Cancer Society. What Is Chronic Myeloid Leukemia? 2021. Available at https://www.cancer.org/cancer/chronic-myeloid-leukemia/about/what-is-cml.html. **2.** American Cancer Society. Phases of Chronic Myeloid Leukemia. 2021. Available at https://www.cancer.org/cancer/chronic-myeloid-leukemia/detection-diagnosis-staging/staging.html. **3.** Experts in Chronic Myeloid Leukemia. The price of drugs for chronic myeloid leukemia (CML) is a reflection of the unsustainable prices of cancer drugs: from the perspective of a large group of CML experts. Blood. 2013;121(22):4439-4442. doi:10.1182/blood-2013-03-490003 **4.** American Cancer Society. Key Statistics for Chronic Myeloid Leukemia. 2021. https://www.cancer.org/cancer/chronic-myeloid-leukemia/about/statistics.html. **5.** American Cancer Society. Risk Factors for Chronic Myeloid Leukemia. 2021. https://www.cancer.org/cancer/chronic-myeloid-leukemia/causes-risks-prevention/risk-factors.html **6.** National Cancer Institute. Chronic Myelogenous Leukemia Treatment (PDQ®)–Patient Version. 2021. Available at https://www.cancer.gov/types/leukemia/patient/cml-treatment-pdq. **7.** Kang ZJ, Liu YF, Xu LZ, et al. The Philadelphia chromosome in leukemogenesis. Chin J Cancer. 2016;35:48. Published 2016 May 27. doi:10.1186/s40880-016-0108-0 **8.** American Cancer Society. Tests for Chronic Myeloid Leukemia. 2021. Available at https://www.cancer.org/cancer/chronic-myeloid-leukemia/detection-diagnosis-staging/how-diagnosed.html. **9.** American Cancer Society. Signs and Symptoms of Chronic Myeloid Leukemia. 2021. Available at https://www.cancer.org/cancer/chronic-myeloid-leukemia/detection-diagnosis-staging/signs-symptoms.html. **10.** Soverini S, De Benedittis C, Mancini M, Martinelli G. Best Practices in Chronic Myeloid Leukemia Monitoring and Management. Oncologist. 2016;21(5):626-633. doi:10.1634/theoncologist.2015-0337 **11.** Hehlmann R, Müller MC, Lauseker M, et al. Journal of Clinical Oncology : Official Journal of the American Society of Clinical Oncology. 2014 Feb;32(5):415-423. DOI: 10.1200/jco.2013.49.9020. **12.** National Institutes of Health. Fighting Cancer: Ushering in a new era of molecular medicine. Available at https://www.nih.gov/sites/default/files/about-nih/impact/fighting-cancer-case-study.pdf. **13.** Rossari, F., Minutolo, F. & Orciuolo, E. Past, present, and future of Bcr-Abl inhibitors: from chemical development to clinical efficacy. J Hematol Oncol 11, 84 (2018). https://doi.org/10.1186/s13045-018-0624-2. **14.** Garg RJ, et al. Blood. 2009;114(20):4361-4368. **15.** Ibrahim AR, et al. Efficacy of tyrosine kinase inhibitors (TKIs) as third-line therapy in patients with chronic myeloid leukemia in chronic phase who have failed 2 prior lines of TKI therapy. Blood. 2010 Dec 16;116(25):5497-500. doi: 10.1182/blood-2010-06-291922. Epub 2010 Sep 10. PMID: 20833982; PMCID: PMC6143154. **16.** Gambacorti-Passerini C, et al. Am J Hematol. 2014 Jul;89(7):732-42. doi: 10.1002/ajh.23728. Epub 2014 Apr 28. PMID: 24711212; PMCID: PMC4173127. **17.** Shah NP, et al. Haematologica. 2010 Feb;95(2):232-40. doi: 10.3324/haematol.2009.011452. PMID: 20139391; PMCID: PMC2817025. **18.** Kantarjian HM, et al. Blood. 2010;117(4):1141-1145. doi:10.1182/blood-2010-03-277152. **19.** Hochhaus A, et al. European LeukemiaNet 2020 recommendations for treating chronic myeloid leukemia. Leukemia. 2020;34:966-984 **20.** Jabbour E, Kantarjian H. Chronic myeloid leukemia: 2018 update on diagnosis, therapy and monitoring. Am J Hematol. 2018 Mar;93(3):442-459. doi: 10.1002/ajh.25011. PMID: 29411417. **21.** Fabian MA, Biggs WH III, Treiber DK, et al. Nat Biotechnol. 2005;23(3):329-336. **22.** Giles FJ, et al. Leukemia. 2010; 24(7):1299–1301.

NOVARTIS

Novartis Pharma AG
CH-4002 Basel Switzerland

1/22
133396-1
Novartis Pharmaceuticals Corporation
East Hanover, New Jersey 07936-1080