

Chronic myelogenous leukemia - survival has significantly improved

What underwriters should know

- New targeted tyrosine kinase inhibitor (TKI) therapy for chronic myelogenous leukemia (CML) demonstrates promising results.
- Survival experience appears to be especially good for individuals maintaining a durable response into the fifth year of therapy.
- These improvements in CML survival must be viewed with some caution since sufficiently long follow up studies are not yet available to confirm recent optimistic findings.

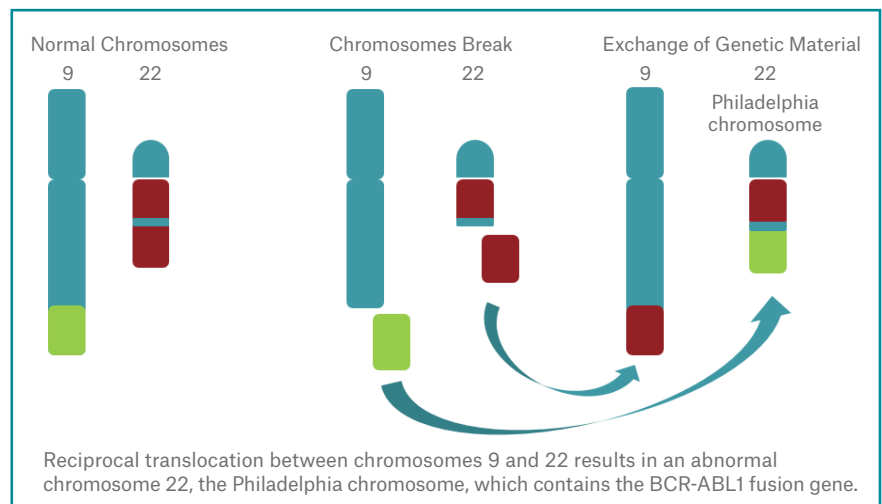
Advances in the treatment of chronic myelogenous leukemia (CML) since 2001 have resulted in greatly improved survival for this hematologic neoplasm, which earlier was treatable only with palliative measures or through a highly risky hematopoietic cell transplantation. Improved survival means that the prevalence of this illness will be steadily increasing in North America. It is estimated that by 2050 there will be over 180,000 individuals in the U.S. living with CML.¹ Trends in improving survival suggest that we may be able to expand insurability to include many individuals with CML in the not too distant future.

Chronic myelogenous leukemia is a hematologic neoplasm characterized by deregulation and uncontrolled proliferation of mature and maturing white blood cells, mainly the granulocyte type.

Initially characterized by a relatively indolent course, at some point proliferation of granulocytes accelerates, with more immature forms being produced. Finally, there is deterioration into acute myelogenous leukemia with early granulocyte precursors such as myeloblasts appearing in the peripheral blood. These three phases of CML are termed the **chronic stable phase**, the **accelerated phase** and the **blast crisis**.

Chronic myelogenous leukemia develops when genetic material is exchanged via translocation between chromosomes 9 and 22, resulting in an abnormal chromosome, called the Philadelphia chromosome.

The Philadelphia chromosome contains a fusion gene called BCR-ABL1 which produces a unique protein product that has activity similar to the activity of tyrosine kinase, but the level of the kinase activity associated with BCR-ABL1 is elevated and deregulated. This has been implicated as the cause of CML and has become the primary therapeutic target.



Traditional, well-established, anti-cancer chemotherapeutic regimens have targeted more rapidly dividing tissues – both normal cells and abnormal cancerous cells. This is usually associated with some degree of adverse side effects. Development of the study of tumor genetics has enabled more target-specific anti-cancer treatments to be produced, which avoid many of the adverse side effects associated with traditional anti-cancer therapies. New treatment of CML is reflective of this target-specific approach. A number of compounds capable of inhibiting tyrosine kinase have been developed, including one found to inhibit growth of BCR-ABL1-positive cells. The first tyrosine kinase inhibitor (TKI) found effective in treating CML was imatinib (commercially known as Gleevec®). Several second generation TKI drugs have subsequently become available (dasatinib and nilotinib). Second generation TKI agents tend to be somewhat more efficacious in treating CML than first generation imatinib, but seem to have worse toxic side effects. Several third generation TKIs are also now available for use in less responsive cases of CML. Therapeutic results with TKIs are best achieved in the chronic stable phase of CML with very few relapses occurring after three to four years of treatment.²

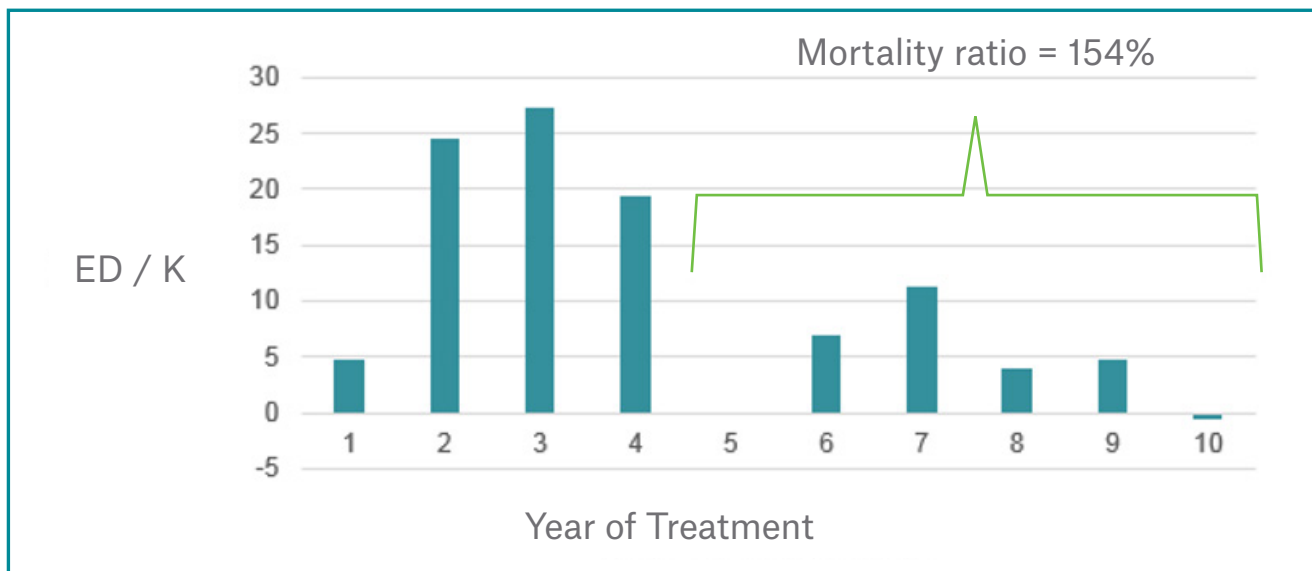
Since tyrosine kinase inhibitor therapy for CML is relatively new, questions concerning durability remain. One of the longest follow up studies appeared in the New England Journal of Medicine in March of 2017.³ This study demonstrated that imatinib treatment for CML remained effective for a period of nearly eleven years with minimal problems due to adverse side effects. Overall survival was 83.3 percent after ten years, resulting in a mortality ratio of 229 percent (determined

by accepted mortality methodology).^{4,5} This study also reproduced earlier findings suggesting that relapse rates significantly decrease after three to four years of treatment³, as shown in the graph, which demonstrates the decrease in excess death rates beginning at year five.

Considering survival of individuals in the chronic stable phase of CML who are being treated with TKI therapy, those demonstrating a continued durable response after four years appear to have an improved mortality experience (mortality ratio = 154 percent beginning with year five in the Hochhaus study³).

Since TKI treatment does not correct the causative genetic defect of CML, treatment must be continued indefinitely in most cases (a small number of individuals have been able to remain completely free of any evidence of disease for up to several years, even after TKI treatment has been discontinued).³ Efficacy of treatment may now be determined by quantitative PCR testing measuring BCR-ABL1 transcripts (products of the abnormal BCR-ABL1 gene) in the peripheral blood, an improvement over the earlier necessity of bone marrow evaluation to assess the progress of therapy.

In summary, earlier forms of treatment for CML were either palliative (chemotherapeutic) or entailed high risk hematopoietic cell transplantation. Targeted tyrosine kinase inhibitor therapy was initiated in 2001 with the introduction of imatinib. Subsequently several additional generations of TKI agents have been developed. Tyrosine kinase therapy has produced encouraging results with significantly improved survival being demonstrated in those individuals beginning treatment while in the



chronic stable phase of CML. Survival appears to be particularly favorable if a durable response can be maintained into year five. However, much remains to be understood concerning long term likely outcome in individuals with CML who are treated with TKI therapy.

References

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Key summary points

- Tyrosine kinase inhibitor therapy (TKI) for CML suppresses the activity of the abnormal BCR-ABL1 fusion gene but is not curative. In most cases it will need to be continued indefinitely.
- The efficacy of TKI therapy is determined by quantitative PCR testing for products of the abnormal BCR-ABL1 gene in the peripheral blood.
- Some cases of CML demonstrate relative resistance to first generation TKI therapy in which case a second (or even third) generation TKI agents may be employed.