BCR-ABL1 Testing for Chronic Myeloid Leukemia

Introduction

BCR-ABL1 chronic myeloid leukemia (CML) testing is addressed by this guideline.

Procedures addressed

The inclusion of any procedure code in this table does not imply that the code is under management or requires prior authorization. Refer to the specific Health Plan's procedure code list for management requirements.

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What is chronic myeloid leukemia

Definition

Chronic myeloid leukemia (CML) is a hematopoietic stem cell disease that results in overgrowth of white blood cells in the bone marrow. It is defined by the presence of the Philadelphia chromosome (Ph), a reciprocal translocation between chromosomes 9 and 22 that results in fusion of BCR and ABL1 genes. There are two major protein forms of the fusion gene, p210 (major breakpoint) which is the most common in CML and p190 (minor breakpoint) which is more common in acute lymphoblastic leukemia.

CML phases

The three phases of CML are chronic, accelerated, and blast. In the chronic phase, there are few symptoms other than splenomegaly, and most people are diagnosed after a routine blood test reveals the characteristic blood count and differential. If not treated, the disease will progress to the accelerated and blast phases, signs and symptoms of which include:
• fever
• bone pain
• splenomegaly

Diagnosis

Diagnosis of CML is usually made with peripheral blood and bone marrow evaluations. Detection of the BCR-ABL1 fusion gene is diagnostic for CML and Ph+ acute lymphoblastic leukemia (ALL) and can be established by metaphase karyotype (cytogenetics), fluorescent in situ hybridization (FISH), or quantitative real-time reverse transcriptase polymerase chain reaction (qPCR). At diagnosis, a broader qPCR may help distinguish which fusion product (p210 vs p190 vs other) is present in the patient to narrow the testing for future follow-up qPCRs.

Acute lymphoblastic leukemia (ALL) is a different form of leukemia, but may also be positive for the chromosome (Ph+), accounting for 2-4% of pediatric ALL and 25% of adult ALL.

Treatment

First-line treatment for CML is with a class of drugs called tyrosine kinase inhibitors (TKIs), which block the production of the BCR-ABL1 fusion gene protein product. Several TKI therapies are available as first-line therapies, including:

• imatinib (Gleevec®)
• nilotinib (Tasigna®)
• dasatinib (Sprycel®)
• bosutinib (BOSULIF®)

TKI therapies have all demonstrated proven benefit, with decreased rates of progression of disease, and increased rates of major molecular responses. With treatment, median survival is expected to approach normal life expectancy for most patients with CML.

Treatment response

Monitoring of patients for treatment response to TKIs includes routine measurement of the BCR-ABL1 fusion gene protein product via qPCR prior to initiation of treatment and during treatment every 3 months. Once the BCR-ABL1 transcript is <1%, monitoring occurs every 3 months for 2 years, and then every 3-6 months thereafter. If there is a 1-log increase in BCR-ABL1 transcript with the major molecular response (MMR), qPCR should be repeated in 1-3 months.
Treatment resistance

Treatment resistance is defined as the failure to reach response milestones, loss of TKI response, 1-log increase in BCR-ABL1 transcript levels and loss of MMR, or those with disease progression to accelerated phase or blast phase. For individuals who display apparent treatment resistance, consideration of alternative treatment options may be appropriate. Treatment resistance in both CML and ALL can be caused by point mutations in the BCR-ABL1 kinase domain. Some tyrosine kinase inhibitors are still active with certain mutations that may cause resistance to other TKIs.

Treatment discontinuation

Discontinuation of TKI therapy in carefully selected patients who have maintained deep molecular responses for more than 2 years has been evaluated in studies. These patients still need to be carefully monitored by qPCR due to risk of recurrence. Recommendations are for molecular monitoring monthly for the first year, then every 6 weeks for the second year, and then every 12 weeks thereafter (indefinitely). Prompt resumption of TKI is recommended if there is loss of the major molecular response.

Test information

Introduction

Testing for chronic myeloid leukemia (CML) may include qPCR for BCR-ABL1 transcript levels or FISH for t(9;22) BCR-ABL1.

qPCR for BCR-ABL1 transcript levels

Bone marrow cytogenetics and measurement of BCR-ABL1 transcript levels by quantitative polymerase chain reaction (qPCR) is recommended before initiation of treatment as well as for assessing response to therapy.

FISH for t(9;22) BCR-ABL1

If collection of bone marrow is not feasible, fluorescence in situ hybridization (FISH) on peripheral blood specimen using dual probes for the BCR and ABL1 genes is an acceptable method of confirming the diagnosis of CML.

BCR-ABL1 kinase domain sequencing

Sequencing of BCR-ABL1 kinase domain is recommended when there is treatment resistance or progression of disease on therapy. Identification of such mutations can help guide in selection of subsequent tyrosine kinase inhibitor therapy. For this assay, PCR followed by Sanger DNA sequencing of peripheral blood or bone marrow is employed to identify resistant mutations in the kinase domain.
Guidelines and evidence

Introduction

This section includes relevant guidelines and evidence pertaining to BCR-ABL1 testing for chronic myeloid leukemia.

National Comprehensive Cancer Network

The National Comprehensive Cancer Network (NCCN, 2019) recommends bone marrow cytogenetics to confirm a diagnosis of CML. If bone marrow is not available, FISH on a peripheral blood specimen using dual probes for BCR and ABL1 genes can confirm the diagnosis.2

The NCCN recommends BCR-ABL1 transcript levels be obtained by quantitative RT-PCR (qPCR) in the following scenarios:2

- At diagnosis
- Every three months after initiating treatment. After a patient reaches BCR-ABL1 transcript levels <1% IS (international scale), every 3 months for two years, and every 3-6 months thereafter
- If a patient has a rising level of BCR-ABL1 transcripts (1 log increase), repeat testing in 1–3 months

The NCCN also recommended BCR-ABL1 kinase domain sequencing in the following scenarios:2

- Failure to reach response milestones as defined by the NCCN guidelines
- Any sign of loss of response
- 1-log increase in BCR-ABL1 transcript levels and loss of major molecular response
- Disease progression to accelerated or blast phase

These recommendations are category 2A which is “Based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate.”

Criteria

BCR-ABL1 transcript level testing

BCR-ABL1 transcript level testing is indicated in individuals at the initiation of treatment and at regular intervals (ranges from every month to once every 3-6 months) during treatment with ANY of the following drug therapies:

- Imatinib (Gleevec®)
• Nilotinib (Tasigna® )
• Dasatinib (Sprycel® )
• Bosutinib (BOSULIF®)

BCR-ABL1 kinase domain targeted sequencing

BCR-ABL1 kinase domain targeted sequencing is indicated in individuals with chronic myeloid leukemia who:

• Are on TKI inhibitor therapy, AND
• Are in chronic phase of the disease, and
  o Have failed to reach treatment milestones, or
  o Experience loss of response to TKI inhibitor therapy (hematologic or cytogenetic relapse), or
  o Experience a 1-log increase in BCR-ABL1 transcript levels and loss of major molecular response, OR
• Experience progression of disease from chronic phase to accelerated phase or blast phase, AND
• Rendering laboratory is a qualified provider of service per the Health Plan policy.

References

Introduction

These references are cited in this guideline.


4. Jones D, Kamel-reid S, Bahler Dong H, et al. (ABL Mutation Working Group of the Association for Molecular Pathology, Clinical Practice Committee). Laboratory practice guidelines for detecting and reporting BCR-ABL drug resistance mutations