ABL Tyrosine Kinase Sequencing for Chronic Myeloid Leukemia

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Introduction

ABL tyrosine kinase sequencing for chronic myeloid leukemia 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.

<table>
<thead>
<tr>
<th>Procedures addressed by this guideline</th>
<th>Procedure codes</th>
</tr>
</thead>
<tbody>
<tr>
<td>ABL1 Targeted Mutation Analysis</td>
<td>81401</td>
</tr>
<tr>
<td>ABL1 Tyrosine Kinase Domain Sequencing</td>
<td>81170</td>
</tr>
</tbody>
</table>

What are CML and BCR-ABL

Definition

Chronic myelogenous 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 translocation between chromosomes 9 and 22 that results in the fusion of two genes known as BCR and ABL. Acute lymphoblastic leukemia (ALL) is a different form of leukemia, but may also be positive for the Philadelphia chromosome (Ph+). About 3% of pediatric ALL and 25% of adult ALL is Ph+.

Diagnosis

Detection of the BCR-ABL fusion gene is diagnostic for CML and Ph+ ALL and can be established by fluorescent in situ hybridization (FISH) or quantitative real-time polymerase chain reaction (qPCR).

Symptoms

The three phases of CML are chronic, accelerated and blastic. In the chronic phase, there are few symptoms 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 blastic phases, symptoms of which include fever, bone pain, splenomegaly, fatigue and weakness.¹

Treatment

First-line treatment for CML and some Ph+ ALL is with a class of drugs called tyrosine kinase inhibitors (TKIs), which block the activity of the BCR-ABL fusion gene protein product. Three TKI therapies are available as first-line therapies: imatinib (Gleevec®), nilotinib (Tasigna®), and dasatinib (Sprycel®). These TKI therapies have all demonstrated proven benefit, and median survival is expected to approach normal life expectancy for most patients with CML.¹ ²

Monitoring

Monitoring of patients for treatment response to TKIs includes routine measurement of the BCR-ABL fusion gene protein product via qPCR prior to initiation of treatment and during treatment every 3 months. After BCR-ABL1 (IS) less than or equal to 1% has been achieved, measurement of the BCR-ABL fusion gene product is recommended every 3 months for 2 years and every 3 to 6 months thereafter.²

Treatment resistance

For individuals who display apparent treatment resistance, consideration of alternative treatment options (or enrollment in a clinical trial) may be appropriate.² Treatment resistance in both CML and ALL can be caused by mutations in the BCR-ABL kinase domain.² ³

Test information

Introduction

Testing for CML ABL1 tyrosine kinase domain may include targeted mutation analysis or sequence analysis.

Genetic testing

ABL1 tyrosine kinase domain mutation analysis is performed on a blood or bone marrow aspirate sample. Testing is performed by either
- targeted mutation analysis for specific resistance variants, such as T315I, or
- sequencing of the entire ABL1 tyrosine kinase domain.
Guidelines and evidence

Introduction

This section includes relevant guidelines and evidence pertaining to when BCR-ABL kinase domain analysis should be performed.

National Comprehensive Cancer Network

The National Comprehensive Cancer Network (NCCN, 2019)\(^2\) for CML states:

- BCR-ABL kinase domain analysis should be performed when:
  - "Chronic phase:
    - Failure to reach response milestones
    - Any sign of loss of response (defined as hematologic or cytogenetic relapse)
    - 1-log increase in BCR-ABL1 transcript levels and loss of MMR
  - Disease progression to accelerated or blast phase."

- "Mutational analysis is helpful in the selection of subsequent TKI therapy for patients with inadequate initial response to first-line or second-line TKI therapy. Mutational analysis would also be helpful to identify a subgroup of patients who demand careful monitoring (as these patients are at a higher risk of progression) and the subset of patients who will be eligible for allogeneic HSCT."

- These recommendations are category 2A: “based on lower-level evidence and there is non-uniform NCCN consensus (but no major disagreement)"

The National Comprehensive Cancer Network (NCCN, 2018)\(^3\) for ALL states:

- ABL gene mutation testing should be considered for all Ph+ ALL in adolescents, young adults, and adults (AYA).

- These recommendations are category 2A: “based on lower-level evidence and there is non-uniform NCCN consensus (but no major disagreement)"

Criteria

Introduction

Requests for ABL Tyrosine Kinase analysis will be reviewed using these criteria.

Criteria

BCR-ABL kinase domain mutation analysis is indicated in:
• Individuals with CML who have:
  o Inadequate initial response to TKI therapy (lack of PCyR or BCR-ABL1 > 10% (IS) at 3 and 6 months or less than a CCyR or BCR-ABL1 > 1% (IS) at 12 months), or
  o Any sign of loss of response (hematologic or cytogenetic relapse), or
  o A 1-log increase in BCR-ABL1 transcript levels and loss of MMR, or
  o Disease progression to accelerated or blast phase, OR
• Individuals with Ph+ ALL.

**Note** BCR-ABL kinase domain mutation analysis is not indicated in other cancer types for which tyrosine kinase inhibitor therapy may be considered.

**References**

**Introduction**

These references are cited in this guideline.