

## FEATURE ARTICLE

# Overview of Second-Generation Tyrosine Kinase Inhibitors for Patients With Imatinib-Resistant Chronic Myelogenous Leukemia

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Imatinib mesylate (Gleevec<sup>®</sup>, Novartis Pharmaceuticals Corporation, East Hanover, NJ) has revolutionized the treatment of chronic myelogenous leukemia (CML) with marked improvement in survival in all three phases—chronic, accelerated, and blast. Most patients with CML now receive imatinib, which produces complete cytogenetic response in more than 80% of patients. About 10% of patients who initially respond to imatinib subsequently develop resistance. Mechanisms of imatinib resistance in CML include amplification, mutations, and additional chromosomal aberration. To date, more than 30 mutations have been identified in imatinib-resistant CML. Dasatinib and AMN107, second-generation tyrosine kinase inhibitors, are highly effective therapies for patients with CML experiencing imatinib resistance and mutation and offer new options for patients who do not achieve an optimal response to imatinib therapy. Studies found that dasatinib and AMN107 form tighter bonds, overcoming imatinib resistance and producing complete hematologic and cytogenetic remissions. Long-term observations are needed to determine the effectiveness of the treatment. Primary care providers need to follow patients receiving first- or second-generation tyrosine kinase inhibitors because unforeseen toxicity may surface, requiring accurate assessment, evaluation, and management. Oncology nurses will be actively involved in the symptom management of patients. Providing guidelines for symptom management and advanced knowledge of specific test results for monitoring CML may increase positive outcomes.

**C**hronic myelogenous leukemia (CML) is a clonal hematopoietic stem cell disorder accounting for 15%–20% of all cases of adult leukemia (Faderl et al., 1999). The first human malignancy, CML is associated with an acquired genetic abnormality known as the Philadelphia chromosome (see Figure 1), which is a balanced reciprocal translocation between the long arms of chromosomes 9 and 22 (t[9;22][q34;q11]) (Nowell & Hungerford, 1961). Translocation of chromosomes produces BCR-ABL pathways activated by tyrosine kinase (Senechal & Sawyers, 1996).

Since the 1960s, a series of landmark discoveries have laid the groundwork to develop effective treatment for CML (Rendu et al., 1992). Understanding tyrosine kinase activity at the molecular level has been essential in drug development. Now standard therapy for CML, imatinib mesylate has revolutionized treatment, resulting in complete cytogenetic response in more than 80% of patients (Kantarjian et al., 2003). Some patients, however, develop resistance to imatinib, and although several mechanisms of resistance have been identified, including mutations (30%–50%), their frequency is unclear (Hochhaus & La Rosee, 2004).

### At a Glance

- ◆ Imatinib mesylate for patients with chronic myelogenous leukemia is available commercially; second-generation inhibitors are rapidly approaching the same status.
- ◆ Oncology nurses should be actively involved in medication administration and familiar with side-effect management.
- ◆ New molecular targeted therapies require vigilant observations and long-term, ongoing evaluation.

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