The introduction of the BCR-ABL inhibitor imatinib revolutionized the treatment of patients with chronic myeloid leukemia (CML). However, resistance to imatinib has become a clinically significant issue, limiting its long-term efficacy. Numerous mechanisms have been associated with imatinib resistance, including mutations to the BCR-ABL gene, increased production of BCR-ABL, and activation of BCR-ABL–independent pathways (e.g., SRC-family kinases [SFKs]). Resistance to imatinib has driven the development of second-line therapies, such as dasatinib, a dual BCR-ABL/SFK inhibitor more potent than imatinib at targeting BCR-ABL. Dasatinib is approved for the treatment of patients with imatinib-resistant and -intolerant CML and Philadelphia chromosome–positive acute lymphoblastic leukemia. Nilotinib, an analog of imatinib, more potent than its parent compound, is another approved agent for patients with imatinib-resistant or -intolerant CML in the chronic or accelerated phase. Nurses must be aware of what constitutes a requirement for treatment change and the mechanisms of resistance that inform the choice of second-line agents. Oncology nurses also must ensure that patients have been educated appropriately to understand imatinib resistance and available second-line treatment options. This article explores the mechanisms and identification of resistance and treatment options for when resistance occurs, as well as nursing implications.