Clinical intolerance occurs when the toxicity of a medication outweighs its clinical benefit. Early recognition of clinical intolerance to BCR-ABL inhibitors used for chronic myeloid leukemia (CML) is important for maximizing patient benefit. In CML, most side effects associated with BCR-ABL inhibitor therapy are mild and easily managed, so recognizing, monitoring, and addressing serious side effects may ensure optimal outcome. However, a subset of patients will be intolerant to first-line imatinib. Patients who experience unresponsive grade 3 or any grade 4 nonhematologic side effects to imatinib may require discontinuation and switching to second-line therapies, such as dasatinib or nilotinib, after identification of intolerance. The most common side effects associated with dasatinib and nilotinib are hematologic and generally are reversible with dose adjustment. Pleural effusions are more common with dasatinib use and may be managed by dose interruption and reduction. Both drugs possess warnings regarding QT prolongation, but nilotinib carries a black box warning for QT prolongation and sudden death.