Despite improvements in treatment, the outcome for some adult patients with acute or chronic leukemias remains poor. Clofarabine, a second-generation purine nucleoside analog, received U.S. Food and Drug Administration approval in 2004 for the treatment of pediatric patients with relapsed or refractory acute lymphocytic leukemia after at least two previous regimens. In addition, clinical studies have shown encouraging safety and efficacy results with clofarabine in the treatment of adult patients with various hematologic malignancies. Although most adult patients with leukemia receive the first course of clofarabine while hospitalized, many can be subsequently treated as outpatients with proper monitoring, support, and education. The most frequent side effects associated with clofarabine are gastrointestinal-related, myelosuppression, hepatotoxicity, renal dysfunction, and anorexia. Careful patient monitoring is essential to ensure early identification and prompt intervention. Younger patients and those of any age with no comorbid health issues, good performance status, and an adequate support network are more likely to tolerate outpatient clofarabine administration. Early identification and proactive pharmacologic and nonpharmacologic interventions may reduce the severity of these toxicities and prevent their progression. Patient education about strategies for prevention and management of symptoms also is essential.