Primary central nervous system lymphoma (PCNSL) is a rare, extranodal form of non-Hodgkin lymphoma that most commonly presents with neurologic changes. Comprehensive workup to diagnose PCNSL and rule out nodal non-Hodgkin lymphoma is critical to the development of an appropriate plan for therapy. Past PCNSL treatments have included whole-brain radiation or steroids, but high-dose methotrexate (MTX) has emerged as initial therapy. Although high-dose MTX is well tolerated, special considerations must be taken to administer the drug safely. Specific interventions include aggressive IV hydration with sodium bicarbonate fluids, monitoring blood chemistries, and the administration of leucovorin rescue. Nurses should evaluate and monitor patients closely during treatment to ensure safety and decrease drug toxicity.