Nelarabine for the Treatment of Patients with Relapsed or Refractory T-cell Acute Lymphoblastic Leukemia or Lymphoblastic Lymphoma

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- Nelarabine • Compound 506078 • Arranon
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RELAPSED T-CELL ACUTE LYMPHOBLASTIC LEUKEMIA AND LYMPHOMA

T-cell acute lymphoblastic leukemia/lymphoblastic lymphoma (T-ALL/LBL) is an aggressive disease affecting a small number of adult and pediatric patients that progresses rapidly in the absence of effective therapy. There are an estimated 4300 patients diagnosed with ALL annually in the United States, approximately one third of whom are over 20 years of age[1] and approximately 20% to 25% of whom have T-cell disease.[2,3] Approximately 54,000 patients are diagnosed with non-Hodgkin's lymphoma annually in the United States,[1] 1.7% of whom have T-LBL.[4] Although historically classified separately, T-ALL and T-LBL are now considered different manifestations of the same disease entity and are treated according to the same regimens.

Optimal first-line therapy consists of intensive multiagent systemic chemotherapy (induction, consolidation, and maintenance) together with central nervous system

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(CNS)-directed treatment, usually consisting of intrathecal (IT) chemotherapy and cranial irradiation. Patients with T-ALL/LBL receiving first-line therapy with a five-drug induction regimen and intensive consolidation had a complete remission (CR) rate of 97% with 69% survival at 3 years.[5] Subsequent studies have estimated that the relapse rate is 30% to 40% in adults and 10% to 20% in children. Unlike pre-B cell ALL, relapses in patients with pre–T-ALL/LBL usually occur within the first 2 years.[6]

Patients who are refractory or relapse shortly after first-line therapy have an especially poor prognosis. These patients tend to have biologically aggressive disease and, as a result, they often have residual bone marrow compromise and comorbidity from their initial therapy and underlying disease. No standard second-line therapy has emerged for refractory or relapsed adult patients, and second remission rates are low with standard and high-dose chemotherapy and with high-dose therapy with autologous stem cell transplant (SCT). Second remission rates in the relapsed/refractory adult T-ALL population are less than 35% with high- or intermediate-dose cytarabine-based combination chemotherapy with anthracyclines and 10% to 15% with amsacrine, teniposide, and etoposide,[7] and remissions are short-lived.[8–11] After salvage chemotherapy, allogeneic hematopoietic SCT remains the only treatment offering long-term survival, and those patients undergoing SCT while in remission have the best chance for prolonged survival.

There are remarkably few studies in adult and pediatric T-ALL/LBL patients in second or greater relapse due to a small and difficult patient population. Outcomes are expected to be no better and probably inferior to results for patients in first relapse.[11] Based on the collective results of multiple studies, the most effective strategy in relapsed/refractory patients seems to be allogeneic SCT after induction of a second or greater CR, but the benefit of such therapy has not been demonstrated in a randomized study. Furthermore, because of age limitations, disease-related comorbidity, and the need for histocompatible donors, only a fraction of subjects are candidates for allogeneic SCT.

NELARABINE

Nelarabine (compound 506U78; Arranon) is a prodrug, which is demethylated by adenosine deaminase to the deoxyguanosine analog, 9-β-D-arabinofuranosylguanine (ara-G).[12] T lymphoblasts are exquisitely sensitive to the cytotoxic effects of deoxyguanosine (**Fig. 1**).[12–18] The accumulation of deoxyguanosine triphosphate and subsequent inhibition of ribonucleotide reductase, inhibition of DNA synthesis, and resultant cell death account for nelarabine's T-cell activity.[14–18]

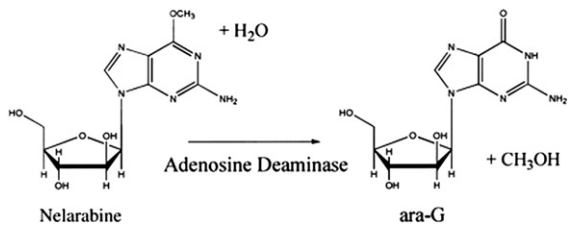

Fig. 1. The chemical structures of nelarabine and ara-G on conversion via adenosine deaminase. (*From* Kisor DF, Plunkett W, Kurtzberg J, et al. Pharmacokinetics of nelarabine and 9-beta-D-arabinofuranosyl guanine in pediatric and adult patients during a phase I study of nelarabine for the treatment of refractory hematologic malignancies. J Clin Oncol 2000;18:995–1003; with permission.)