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Advances in Cancer Chemotherapy 2006: Acute Lymphoblastic Leukemia and Lymphoblastic Lymphoma: Nelarabine

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Goals. The goals of this lesson are to provide background information on acute lymphoblastic leukemia and lymphoblastic lymphoma, and discuss their treatment with a newly-approved chemotherapeutic regimen.

Objectives. At the conclusion of this lesson, successful participants should be able to:

1. describe the etiology and incidence of T-cell acute lymphoblastic leukemia and T-cell lymphoblastic lymphoma;



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2. identify the pharmacologic classification and therapeutic considerations for nelarabine; and
3. select from a list, the indications, mechanisms of action, adverse effects and toxicities, drug interactions, and benefits and limitations of nelarabine.

FDA has approved a new-molecular entity drug for use in treatment of two rare, but very aggressive malignancies: T-cell acute lymphoblastic leukemia and T-cell lymphoblastic lymphoma. Before its approval, there was no standard of treatment for these patients and their prognosis was poor. Nelarabine (Arranon[®]), thus, became the first drug approved to treat this limited population of patients.

Arranon was cleared under FDA's accelerated approval program, which permits the agency to approve products for cancer based on early evidence of effectiveness. Evidence consisted of complete disappearance of cancer cells in some patients. Arranon also received Orphan Drug designation, which is granted to products that treat rare diseases (i.e., those that affect fewer than 200,000 people in the United States). The Orphan Drug Act provides the sponsor with seven years of exclusive U.S. marketing.

Progress in Cancer Control

Prevention and treatment of cancer are among the nation's most urgent health concerns. Cancer remains the primary cause of death in the United States, and the disease that many people fear most. More than 1.3 million new cancer cases will be diagnosed in the United States this year, and more than a half million people will die from the direct or indirect effects of cancer or its complications. At the same time, there is good news. Nearly 10 million people in the United States today are living with a cancer history. Of this group, 1.5 million were diagnosed more than 20 years ago. This means that cancer victims are living longer today than ever before. Their quality of life is also better than at any other time in history. More than two-thirds of people with cancer can now expect to live five or more years; for children with cancer, the five-year survival now exceeds 75 percent. Cancer chemotherapy and auxiliary drug treatments are definitely improving mortality, morbidity, and overall quality of life.

Leukemia

Normal formation and development of blood cells (hematopoiesis) is a closely regulated symphony of biological events that lead to proliferation and differentiation of hematopoietic stem cells that develop into mature peripheral blood cells. Acute leukemia results when a malignant event (or events) occurs during an early stage in the hematopoietic process. Instead of proliferating and differentiating normally, the af-

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fect cells continue to proliferate but in an uncontrolled fashion. As a result, immature lymphoid cells (in acute lymphoid leukemia) or myeloid cells (in acute myeloid leukemia) called *blasts*, that normally compose <5 percent of cells manufactured by the bone marrow, accumulate rapidly, and progressively replace the normal cells within bone marrow. The outcome is diminished production of normal erythrocytes (red blood cells), leukocytes (white blood cells), and thrombocytes (platelets). This, in turn, leads to the familiar clinical complications of leukemia: anemia, infection, and hemorrhage. With time, the leukemic blasts enter the bloodstream and eventually invade normal organs; they concentrate in the lymph nodes, spleen, liver, and other vital tissues. Left untreated, acute leukemia is rapidly fatal with most patients dying within several months to a year of diagnosis.

Leukemia's impact is magnified greatly because of the young age of some of its patients. To illustrate, acute lymphoblastic leukemia (ALL) affects children, accounting for approximately one-fourth of cancer diagnoses among people younger than 15 years of age, and is the second leading cause of death in children in this age group. Caucasian children are affected more frequently than African-American children. There is little difference in incidence rates by gender among children. In older age groups, ALL occurs more commonly in males. Its occurrence peaks between ages two and 10 years. It then undergoes a second, more gradual increase in frequency later in life. An estimated 2400 children and 1200 adults are diagnosed with ALL in the United States each year. Approximately 700 of these victims have T-cell-ALL (T-ALL), explained subsequently.

Classification. The leukemias are classified as acute or chronic. Cancerous cells reproduce rapidly and accumulate in both forms, crowding out normal white blood cells. The primary difference between the two forms is that, with

acute leukemia, bone marrow cells do not reach maturity and immature cells accumulate. In *chronic* leukemia, the bone marrow cells appear mature but are abnormal in function, and live longer than normal white cells.

ALL can be divided into several forms based on cell surface antigen expression. The five most common forms are early pre-B-cell, pre-B-cell, B-cell, T-cell, and null-cell ALL. T-ALL is less common with increasing patient age, being truly rare in patients exceeding 60 years of age.

Non-Hodgkin's Lymphoma

Non-Hodgkin's lymphomas are cancers that affect the lymphatic system, particularly lymphocytes. Lymphoblastic lymphoma (LBL) is an especially aggressive type of non-Hodgkin's lymphoma that occurs more often in children than adults. Patients with predominantly nodal disease, who have minimal or no involvement of the bone marrow, are frequently classified as having *lymphoblastic lymphoma*, whereas persons with more than 25 percent of neoplastic cells in the marrow are described as having *lymphoblastic leukemia*. These distinctions are arbitrary and, as a rule, reflect the stage of disease rather than different diagnoses. The pathological basis for this is not understood. Of an estimated 50,000 patients diagnosed with non-Hodgkin's lymphoma each year, approximately 900 have T-cell LBL (T-LBL).

There is significant biological and clinical overlap between cancers diagnosed as acute lymphoblastic leukemia and lymphoblastic lymphoma. Some patients have predominantly lymphomatous involvement (e.g., presence of a mediastinal [area between the two lungs] mass or other solid lesion). Most, however, have or later develop marrow involvement. In a similar fashion, patients who present with leukemia may have or develop extramedullary tumors. Both lymphoblastic leukemia and lympho-

blast lymphoma can, therefore, be considered the same disease with different clinical characteristics.

Clinical Manifestations

Acute Lymphoblastic Leukemia. At the time of diagnosis, most patients with ALL have symptoms of anemia, expressed by fatigue, pallor (paleness), and headache. Predisposed patients may experience angina or heart failure. Thrombocytopenia (decreased platelets) is often present, with approximately one-third of patients experiencing clinically evident bleeding, usually in the form of petechiae (small, pinpoint, nonraised blood spots on the skin's surface), ecchymoses (extravasation of blood under the skin), or bleeding from the gums or nose. Granulocytopenia (deficiency of granulocytes) will usually be noted and, as a result, patients with ALL will have significant, perhaps life-threatening, infections that are usually bacterial in origin.

Leukemic cells that invade normal organs can cause enlargement of lymph nodes, liver, and spleen. Bone pain probably results from leukemic cell infiltration of the periosteum (thick, fibrous membrane covering bone) or expansion of the medullary cavity (narrow cavity in the shaft of long bones), and is a common symptom, especially in children with ALL. Leukemic cells that infiltrate the skin can result in a nonpruritic rash, called *leukemia cutis*. Leukemic cells that invade the brain's pia-arachnoid meninges (leptomeninges) can cause *leukemic meningitis* leading to headache and nausea. With disease progression, seizures may occur. Fewer than 5 percent of patients experience CNS involvement at the time of diagnosis; however, the CNS is a common site of relapse. Testicular involvement is also seen in males, and the testicles are a frequent site of relapse.

Lymphoblastic Lymphoma. Lymphadenopathy (disease of the lymph glands) is the most common symptom at the time of diagnosis.

Patients may notice swelling and tenderness in the groin, neck and underarm area. Lymph nodes containing lymphomatous cells generally are firm and nontender, and not associated with infection. In some patients, lymphadenopathy in sites such as the mediastinum or retroperitoneum (area behind the peritoneum) provokes symptoms such as pain in the chest, abdomen or back, and cough that cause them to seek a physician's advice. Spinal cord compression, and symptoms of renal insufficiency associated with ureteral compression are characteristic.

Non-Hodgkin's lymphomas may cause nonspecific systemic symptoms. The most common ones include fever, night sweats, and unexplained weight loss. Other less characteristic symptoms are fatigue and itching.

Any organ system can be affected in non-Hodgkin's lymphoma, and symptoms resulting from malfunction of that system may lead to the diagnosis. For example, skin lesions occur with cutaneous lymphomas, neurologic symptoms with primary brain lymphoma, shortness of breath with pulmonary lymphoma, epigastric pain and vomiting with gastric lymphoma, and bowel obstruction with small bowel lymphoma. Lymphoma that involves the bone marrow can cause extensive marrow failure that results in infection, bleeding, and anemia, as noted with leukemia. Non-Hodgkin's lymphomas can also result in a variety of immunologic abnormalities; for example, symptoms of autoimmune hemolytic anemia and/or immune thrombocytopenia may be the patient's noticeable manifestation.

Arranon (nelarabine)

Nelarabine is a T-cell-selective cytotoxic deoxyguanosine prodrug that is demethylated by adenosine deaminase into ara-G, then monophosphorylated by deoxyguanosine kinase and deoxycytidine kinase, and subsequently converted to the

active 5'-triphosphate, ara-GTP. Ara-GTP accumulates in leukemic blasts as a fraudulent nucleoside triphosphate where it competes with the native substrate for incorporation into DNA by DNA polymerase. This disrupts DNA synthesis, thus inducing cellular apoptosis (programmed cell death). Additional cytotoxic actions, including inhibition of RNA synthesis and ribonucleotide reductase, may contribute to the drug's overall activity, but these actions are not fully understood.

Clinical Trials. Arranon approval was recommended following completion of two clinical trials designed to investigate the drug in pediatric and adult patients. Both trials were multicenter, phase II, single-arm (i.e., test drug only; no placebo or comparator drug controls) by design. Every patient had relapsed or refractory T-ALL or T-LBL. Most patients in both groups had T-ALL and most were white males. At the time of writing this lesson, Phase III studies were underway to evaluate long-term efficacy and safety.

One trial enrolled 84 pediatric patients, aged 21 years and younger at the time of initial diagnosis. Thirty-one subjects had received one prior chemotherapy regimen, and 39 had received two or more. The drug was administered at the recommended dose of 650 mg/m² via one-hour infusion for five consecutive days in 21-day treatment cycles. Thirteen percent of subjects achieved complete disease response (bone marrow blast counts \leq 5 percent) and full recovery of peripheral blood counts. Another 10 percent achieved complete disease response without full hematological recovery. Response to treatment persisted 3.3 to 9.3 weeks. The median overall survival was 13.1 weeks.

In another study, 39 adult patients aged 16-65 years (mean 34 years) were enrolled. Twenty-eight patients in this group had received at least two courses of chemotherapy. Arranon achieved a

complete response and hematological recovery in 18 percent of this cohort. The duration of complete response was four to \geq 195 weeks, with a median overall survival of 20.6 weeks. Response duration assessment was complicated by the fact that patients in Arranon-induced complete remission may have received additional therapy, including stem-cell transplantation, prior to disease progression or recovery of normal peripheral blood cell counts.

Adverse Effects and Warnings. Arranon was evaluated for safety in phase I and phase II clinical trials. The safety profile is based on data from 103 adults and 84 children.

The most common adverse events in children included hematologic disorders (anemia, leukopenia, neutropenia, and thrombocytopenia). The most frequent non-hematologic adverse events reported were headache, vomiting, increased transaminase and bilirubin levels, and decreased potassium and albumin levels.

The most common adverse events in adults were fatigue; gastrointestinal disorders (nausea, diarrhea, vomiting, and constipation); hematologic disorders (anemia, neutropenia, and thrombocytopenia); respiratory disorders (cough and dyspnea); nervous system disorders (somnolence and dizziness); and fever. Blurred vision was reported in 4 percent of adult patients.

Arranon is a potent chemotherapeutic drug that has potentially significant toxic side effects. The product's label contains a "boxed warning" of its potential to cause neurotoxicity, and neurotoxicity is the dose-limiting outcome. Common signs and symptoms of neurotoxicity include ataxia (loss of muscle coordination), confusion, convulsions, drowsiness, and tingling and/or numbness in the fingers and toes. Full recovery following severe neurologic toxicity may not occur with cessation of therapy. Patients treated previously or concurrently

Table 1
Patient Information for
Arranon

- The manufacturer supplies a patient information brochure for Arranon. Be sure to request one and ask your doctor or pharmacist if you have questions.
- Tell your doctor about all health conditions you (or your child) have, including nervous system or kidney problems, before receiving Arranon therapy.
- Tell your doctor about all prescription or nonprescription medicines you (or your child) take, including vitamin/mineral supplements and herbal remedies.
- Tell your doctor right away if you (or your child) develop fever or signs of infection while receiving Arranon. Also tell your doctor right away if you (or your child) are more tired than usual, pale, or have trouble breathing.
- Tell your doctor right away if you (or your child) bruise easily or have any unusual bleeding.
- This drug may cause serious side effects including extreme sleepiness; seizures; coma; numbness and tingling in the hands, fingers, feet, or toes; and weakness and paralysis. Call your doctor at once if you (or your child) have these symptoms, are unsteady or experience increased tripping while walking, feel weak when getting out of a chair or walking up stairs, or have problems with fine motor skills such as buttoning clothes.
- Do not operate dangerous machines or drive while receiving Arranon.
- You or your child should not receive vaccines made with live germs while receiving Arranon.
- Women: Tell your doctor if you become pregnant or are expecting to become pregnant, or are breastfeeding.

with intrathecal chemotherapy or previously with craniospinal irradiation may be at increased risk for neurologic damage.

Drug Interactions. Arranon and ara-G have been shown to not significantly inhibit the activities of the human hepatic cytochrome P450 isoenzymes 1A2, 2A6, 2B6,

2C8, 2C9, 2C19, 2D6, or 3A4. Fludarabine (Fludara®) administered by infusion does not affect the pharmacokinetics of Arranon, ara-G, or ara-GTP.

Indications and Uses.

Arranon is indicated for treatment of patients with T-ALL and T-LBL whose disease has not responded to or has relapsed following treatment with at least two chemotherapy regimens. This use is based on the induction of complete responses. The term *complete response* (i.e., *complete remission*) is defined as the disappearance of all signs of cancer in response to treatment. Studies to confirm increased survival or other benefit from drug treatment have not been conducted.

Dosage, Administration, and Availability. The recommended pediatric dose is 650 mg/m² administered intravenously over one hour daily for five consecutive days, repeated every 21 days. The adult dose is 1,500 mg/m² administered intravenously over two hours on days 1, 3, and 5, and repeated every 21 days. Patient information for Arranon is summarized in Table 1.

The appropriate dose of Arranon should be transferred into polyvinylchloride (PVC) infusion bags or glass containers and administered undiluted. The drug is stable in PVC bags and glass containers for up to eight hours at 30° C. The recommended duration of treatment has not been established. During clinical trials, treatment was generally continued until there was evidence of disease progression or unacceptable toxicity, the patient became a candidate for bone marrow transplantation, or the patient no longer derived benefit from treatment. Appropriate measures (e.g., hydration, urine alkalinization, and prophylaxis with allopurinol) must be instituted to prevent hyperuricemia or tumor lysis syndrome.

Patients with severe renal impairment (CL_{CR} <30 mg/dL) or severe hepatic impairment (bilirubin >3.0 mg/dL) should be monitored closely for toxicity when treated with Arranon.

Immunocompromised patients should not receive vaccines containing live microbials. Because Arranon is a cytotoxic agent, proper aseptic technique should be used during handling and preparation. Wearing rubber gloves and other protective clothing to prevent skin contact is recommended.

Arranon is supplied by GlaxoSmithKline as a clear, colorless, sterile solution designed for intravenous infusion. The solution contains 5 mg of nelarabine per mL.

Summary and Conclusions

T-ALL and T-LBL are aggressive malignancies that have high mortality rates in patients who do not receive adequate treatment. Nelarabine is a prodrug of ara-G that, intracellularly, is converted to active ara-GTP, which has activity in the treatment of T-cell hematologic neoplasms. Although treatment outcome is modest at best, nelarabine remains the only proven option at present to treat T-ALL and T-LBL.