CONFERENCIAS MAGISTRALES

Acute Myeloid Leukemia

Raúl C. Ribeiro*

Acute myeloid leukemia (AML) comprises a group of heterogeneous bone marrow disorders that accounts for approximately 20% of the childhood acute leukemías. There are approximateiy 500 new cases of childhood AML diagnosed per year in the United States. In contrast to acute lymphoblastic leukemia (ALL) that peaks before the age of 5 years, the incidence of AML is relatively constant except for a siight peak in the **fírst** year of age and anoíher in adolescence. In **infants,** the ratio of ALL to AML is approximately 1:1. AML is equally distributed among ethnic groups, **with** the possible exception of an increased incidence in acute promyelocytic ieukemia (APL) in Hispanics.

Genetic, environmenta! and iatrogenic factors have been associated with an increase risk of developing AML, but íhey account for the minority of cases of AML. Down syndrome and Fanconi anemia are cíearly associated with an increased risk of AML. Exposure to radiation and oceupational exposure to benzene are well established risk factors. Treatment with alkylating agents and epipodophyllotoxins predispose to AML as well.

Classiflcation of childhood AML follows the same critena developed for adult AML by the French-American-British (FAB) group. Morphologic interpretation of bone marrow specimens obtained at diagnosis and stained using the Romanowsky method in conjunction with cytochemistry, karyotyping, immunophenotyping, and molecular genetics allows the classification of eight groups-M0-M7. This classification is based on the demonstration of commitment to the granulocytic, monocytíc, erythroid, or megakaryocytic lineage. The valué **of** immunophenotyping in AML is to recognize the M0 and M7 subtypes. Severa] chromosomal abnormalities have been detected in AML. Many of them have abnormalities restricted *Xo* a specifíc FAB subtype of AML and may require individualized treatment. For exampie, the treatment of patients with the t(15; 17) should include all-trans-retinoic acid.

The most common presenting features of children with AML include pallor, bleeding, and fever. Lymphadenopathy, massive hepalosplenomegaly, and bone pain and arthralgias are rare. Clinically significan! bleeding is rare, bul patients with acute promyelocytic leukemia (FAB M3) have a coagulopathy and therefore are at an increased risk of this complication. Compared with older children with AML, infants with AML are more likely to have high leukocyte counts at diagnosis, leukemia cutis, CNS leukemia and massive organomegaly. Young children with acute megakaryoblastic leukemia may present without evidence of circulating blasts, extramedullary leukemia deposits and flbrotic bone marrow. Some of these patients have been incorrectly diagnosed as having solid tumors.

The outeome of children with AML has improved slowly over the last 20 years. The increase in sur-

Oneólogo Pediatra. Director International Outreach. St. juile Children 's Research Hospital Memphis, Tennesse. V.S.A.

vi val has been due to more effective chemotherapy regimens, the use ofbone marrow transplantation and improved supportive care. Initial management of a child with AML is targeíed to treat infectious processes, bíedding and metabolic complications. The standard régimen for remission induction in AML includes cytosine arabinoside, etoposide and daunorubicin. The compiete remission rate ranges between 80% and 85%. Patients who achieve remission require more chemotherapy and sometimes bone marrow transplantation. The decisión to recommend bone marrow transplantation for children with AML in fírst remission is not always clear. Nonetheless, most investigators agree that children with adverse cytogenetic features such as monosomy 7, 5q- or complex karyotyping should undergo bone marrow transplantation in fírst remission.

Acute Lymphoblastic Leukemia

Raúl** C. **Ribeiro*

Acute lymphoblastic leukemia is the most common form of childhood cáncer. It accounts for 30% of all childhood malignancies and 80% of all cases of childhood leukemia. The incidence of childhood ALL in the United States is approximately 3.4 cases per 100,000, with a peak incidence occurring between the ages of 3 and 4 years. The frequency, age, and subtypes of ALL vary worldwide. Numerous constitutiona! genetic defects, including Down syndrome and ataxia telangiectasia have been associated with an íncreased risk of ALL. However, constitutional genetic syndromes account for just a minority of cases of ALL. It is likely that other genetic factors stíll to be discovered play a role in the development of childhood ALL. For example, siblings of children with ALL have a two to four fold increased risk of developing ALL than do children in the general population.

ALL can be classifíed into several subtypes based on the presence of certain cellular structures in the leukemia cells. Morphologic examination and cytochemical staining of blast cells reveal cellular contents that are useful in distinguishing ALL from acute myeloid leukemia. Based on reactivity with a panel of lymphocyte-associated antibodies, ALL is broadly considered to have two lineages, B and T. B-lineage and T-lineage cases can be subdivided into several distinct subtypes. **How**ever for treatment purposes only immature B-cells and mature B cells and T-cells are treated with different approaches. Numeric and structural chromosomal changes can also be used to refíne the ALL ctassification. However, in addition to contributing to the diagnosis, cytogenetic information has prognostic and treatment implications. For example, patients with hyperdiploid karyotypes tend to have a very good prognosis, whereas those with hypodiploid fare very pooriy. Recently, molecular techniques have been added to the clasifícalion armamentarium and have contributed to the classification, prognosis and treatment of this disease. Adverse prognostic factors in ALL include age íess than one year at diagnosis, hyperleukocytosis, T-cell martas, chromosome Philadelphía and persistence of disease añer induction and consolidation. With the realization that disease outcome is associated with the kínetics of the dísappearance of leukemia cells from the bone marrow, immunophenotype and molecular techniques have allowed for the tracking of leukemia

cefls at submicroscopic levéis. By combining all of these techniques, 75% or more of newly diagnosed ALL cases can be classifíed into prognostic and therapeutically relevant subgroups.

Childhood leukemia (excepí mature B-cell ALL) requires prolonged treatment (2.5-3.0 years). Leukemia treatment has evolved by intensifying the induction, consolidation and maintenance phases, developing strategies to prevent central nervous system (CNS) leukemia and improving supportive care. Remission induction usually consists of the administration of prednisone, vincristine, and L-asparaginase. Current treatment protocols are associated with a 98% to 99% remission rate. Soon after remission is achieved, most treatment plans specify a period of reinforcement. Continuation íreatment with standard doses of methotrexaíe and 6-mercaptopurine is effective in most patients with B-lineage. Recent advances in postremission therapy include the use of high-dose methotrexate and intensive L-asparaginase for patients at high-risk of relapse. Effective therapy directed to the CNS is an essential part of treatment for ALL. ín addition to more systemic treatment, frequent use of intrathecal chemotherapy during the first year of treatment virtually eliminates CNS leukemia. Cranial or craniospinal irradiation is rarely used to control CNS leukemia, because of the growing concern that CNS irradiation can cause significan! neurotoxicity and occasional brain tumors, especially in girls and young children. Allogeneic hematopoietic stem cel! transplantation is recommended for less than 10% of patients with ALL in first complete remission. Patients with Philadelphia positive ALL, infants with Ílq23 rearrangement and patients who did not respond to the initial therapy are candidates for allogeneic hematopoietic stem cell transplantation.

Pediatric Non-Hodgkin Lymphomas

*Raúl C. Ribeiro**

Lymphomas are the third most common **nialíg-**nancy among children and adoíescents. Approximately 60% of them are non-Hodgkin lymphomas (NHL) vvhile the remainder consists of Hodgkin disease. Approximately 500 cases of lymphomas are diagnosed in children and adoíescents annualiy in the U.S., accounting for 12% of all newly diagnosed childhood cancers. Boys are three times more affected than girls. There is extensive geographic variation in the incidence of childhood NHL throughout the world. In certain African regions, pediatric NHL accounts for approximately 50% of childhood cancers. Pediatric NHL is one of the few pediatric malignancies in which the incidence has steadily increased.

Contrary to adult NHL, the histological spectrum of childhood NHL is considerably simpler. For example, the most common types of lymphomas in adults have a nodular histology and an indolent clinical course. These are exceedingly rare in children and adoíescents. The predominan! histology of pediatric lymphomas is of a diffuse appearance that predicts for an aggressive **behavior.** In fact, pediatric lymphomas have a propensity for a rapid widespread dissemination. Small, noncleaved cell (Burkitt) lymphomas comprise one third of pediatric NHL, another one third are íymphoblastic lymphomas, and the remainder are large cell lymphomas.

Immunophenotypically, the majority of lymphoblastic NHL is derived from immature T cells. A small proportion of lymphoblastic NHL expresses the common ALL antigen, mtracytoplasmic immunoglobulin (pre-B cells) or other B-cell markers. By defínition, Burkitt NHL expresses surface immunoglobulins. Half of the large ceil lymphomas are of B-cell origin, the remaining being T-cell or undifferentiated. Ahnost 30% of large-ceíl lymphomas express CD30, and generally at ieast some T-cell surface markers.

Pediatric lymphomas have several characteristic chromosomal abnormalities. In Burkitt lymphoma, the chromosome 8 at band q24—the location of the c- myc oncogene—is invariably involved. ín the 8; 14 translocation, c- myc is translocated from chromosome 8 to the immunoglobulin heavy chain locus on chromosome 14. Fewer translocations are seen in lymphoblastic lymphoma. These involve the T-cell receptor genes on chromosome 14ql 1 and on chromosome 7. The most frequent translocation ín large ceil lymphoma is the t(2;5, p!2;q35), which involves the tyrosine kinase gene (ALK) and the nucleoplasmin gene (NPM). The 2;5 translocation is considered specific for anaplastic large ceil lymphomas and is found in approximately 50% of cases.

In the U.S., patients with Burkitt NHL usually present with an abdominal mass. Jaw involvement—the most common presenting feature in equatorial África—is rare among American children. Patients with lymphoblastic NHL usually present with mediastinal involvement and/or enlarged peripheral lymph nodes. The clinical manifestations of patients with large ceil NHL are varied reflecting the heterogeneity of this histiotype. Due to the rapid growth of NHL, many patients present with acute syndromes such as abdominal emergencies (e.g., intussusception, perforation) or respiratory difficulties related to the compression of upper mediastinal structures.

Extent of disease at diagnosis is important for therapeutic approaches. There are several disease-staging systems, which reflect the tumor burden and specific sites of disease. The most widely used is that of St. Jude, which takes into accouní common presenting features and sepárales patients with limited-stage disease from those with advanced disease, including CNS or bone marrow involvement.

Effective treatment of childhood NHL is based on intensive chemotherapy. Surgery has a very limited role as does radiotherapy. With treatment tailored to disease extent and immunophenotype, more than 2/3 of the children and adolescents with this disease will be cured with minimal morbidity.