Original Study

Outcomes of Adolescents and Young Adults With Acute Myeloid Leukemia Treated in a Single Latin American Center

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Abstract

Hispanic patients aged < 40 years with a diagnosis of acute myeloid leukemia (AML) during 2003 to 2016 in Northeast Mexico were evaluated. The group included 46 children and 88 adolescents and young adults (AYAs) aged 15 to 39 years. A greater overall response rate was found in the children (87.2% vs. 69% in AYAs). Low event-free and overall survival rates for AYA patients with AML were documented.

Introduction: The outcomes for adolescents and young adults (AYAs) with acute myeloid leukemia (AML) have been poorly characterized in Hispanics in low- to middle-income countries. The results are influenced by biologic and socioeconomic factors. The clinical paths for AYA patients with AML are reported. **Patients and Methods:** A retrospective analysis of AYA and pediatric AML patients aged 1 to 39 years during 2003 to 2016 from a single reference center in Northeast Mexico treated with a 7+3 standard protocol was performed. The 5-year overall survival (OS) and event-free survival (EFS) were estimated using Kaplan-Meier analysis. The hazard ratios for relapse and death were estimated using a Cox regression model. The patients with promyelocytic leukemia were analyzed separately. **Results:** The study included 110 non-PML AML patients, 39 children and 71 AYAs. No difference in complete remission was found ($P = .446$), although the overall response rate was greater in the children (87.2% vs. 69% in AYAs; $P = .034$). The 5-year EFS rate was 33% for the children versus 9.3% in the AYAs at a median follow-up of 22 and 9 months, respectively ($P = .008$). The 5-year OS rate was 51% in the children and 22% in the AYAs ($P = .001$). Of the 44 AYAs with complete remission, 29 (65%) developed a relapse. Of the 39 children and 71 AYAs, 20 children (51.3%) and 21 AYAs (29.6%) underwent transplantation ($P = .024$). Patients with refractory disease had a 1-year OS rate of 14.4%. Older age (hazard ratio [HR], 2.55; $P = .002$) and white blood cell count $> 50 \times 10^9$/L (HR, 1.79; $P = .023$) were significant for death, and transplantation was protective (HR, 0.57; $P = .023$). **Conclusion:** Low EFS and OS rates were found for AML patients in the AYA group. To improve survival rates, intensified chemotherapy regimens and early hematopoietic stem cell transplantation are needed.

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Introduction

Acute myeloid leukemia (AML) accounts for 60% to 80% of acute leukemia cases in adults, with a median age at diagnosis of 67 years. AML also accounts for 15% to 20% of acute leukemia cases in children and 20% to 35% in adolescents. Thus, the incidence increases with age, with 5 cases per 1 million in children aged 5 to 9 years, 9 cases per 1 million in those aged 15 to 19 years, and 37 cases per 100,000 in adults aged ≥ 20 years.[1] Adolescents and young adults (AYAs) encompass a group of the population that arbitrarily combines pediatric and adult patients. It has been defined as the age range of 15 to 39 years,[2] with treatment protocols that

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offer the best therapeutic results for this population not well defined. In addition, ethnic disparities in the clinical outcomes for AML patients have been recently identified, with Hispanics having superior overall survival (OS) compared with both white and black patients, with white patients the only group showing progressive improvement in OS.[3]

Controversy exists regarding the differences in outcomes between AYA and pediatric patients, with some populations experiencing inferior outcomes with older age,[4,5] but no differences were found in other studies.[6,7] Several factors that might contribute to these results have been observed, including genetics, disease biology, psychosocial factors, less tolerance to intensive treatments, delayed diagnosis, and sociocultural aspects of the studied population.[8] In contrast to acute lymphoblastic leukemia,[9-12] a group analysis of AYAs with AML has frequently been omitted in most trials. This has resulted in division of the treatment groups into patients aged < 18 to 20 years and those aged > 20 years.[13] Information on the therapy and outcomes for AYAs with AML is scarce worldwide and more so in low- to middle-income countries.

The incidence and factors of AML in AYAs have not been documented in Latin America. We decided to analyze the clinical characteristics, response to therapy, and survival rates of patients in Northeast Mexico to document the current state of treatment results for these young patients and detect opportunities for improving the outcomes.

Patients and Methods

An observational, longitudinal, and retrospective analysis of patients aged 1 to 39 years with a diagnosis of AML from 2003 to 2016 at the hematology department (Dr. José E. González University Hospital of the School of Medicine of the Universidad Autónoma de Nuevo León, Monterrey, México) was performed. Our institution is the reference center for low-income patients from the open population in Northeast Mexico, and patients are routinely referred from public primary and secondary care centers. Data were extracted from the digital and clinical medical records. The institutional research board and ethics committee approved the study protocol. For comparison purposes, the patients were classified into 2 groups: the pediatric group, which included patients aged 1 to 14 years, and the AYA group, which included patients aged 15 to 39 years, as defined by the National Comprehensive Cancer Network.[2]

The diagnosis and immunophenotype were confirmed by multiparametric flow cytometry using FACSCalibur equipment (BD Biosciences, San José, CA). A morphologic subtype was assigned using the French–American–British (FAB) classification.[14] Because of financial restrictions, cytogenetic studies were performed for only 38% of patients attending our public institution. These patients were stratified into favorable, standard, and high-risk disease groups. The favorable-risk abnormalities were inv(16), t(8;21), t(16;16), CEBPA, and mutated NPM1 without FLT3-ITD mutations. The high-risk abnormalities were inv(3), t(3;3), t(6;9), t(9;11), monosomy 7, monosomy 5, deletions of 5q, and high FLT3-ITD. High-risk disease in the patients without cytogenetic studies available was defined by the presence of hyperleukocytosis > 50,000 μL, a monocytic component, or extramedullary infiltration. Patients without these abnormalities were classified as having standard-risk disease.[15]

Definition of Treatment Response

Complete remission (CR) was defined as < 5% bone marrow blasts, the absence of blasts with Auer rods, the absence of extramedullary disease, an absolute neutrophil count > 1.0×10^9/L, a platelet count > 100×10^9/L, and independence of blood transfusion support. Partial remission was defined as meeting all the hematologic criteria for CR but with bone marrow blasts of 5% to 25% and a decrease in pretreatment bone marrow blasts by ≥ 50%. Minimal residual disease was confirmed by flow cytometry and was considered positive if ≥ 0.01%.[15]

The patients with treatment failure were divided into 3 groups: (1) resistant disease (failure to achieve CR, including patients surviving ≥ 7 days after completion of initial treatment, with evidence of persistent leukemia on blood and/or bone marrow examination); (2) death in aplasia (occurring ≥ 7 days after completion of initial treatment with the patient cytopenic, with aplastic or hypoplastic bone marrow obtained within 7 days of death, without evidence of persistent leukemia); and (3) death from an indeterminate cause (occurring before or < 7 days after therapy completion or occurring ≥ 7 days after completion of initial therapy with no blasts in the peripheral blood but no bone marrow examination findings available). Relapse was defined as the presence of ≥ 5% bone marrow blasts, the reappearance of blasts in the blood, or the development of extramedullary disease.[15]

Treatment

A 7+3 standard protocol was administered for treatment and consisted of 3 days of an anthracycline (Adriamycin 40 mg/m^2 or mitoxantrone 10 mg/m^2) and 7 days of continuous intravenous cytarabine (100 mg/m^2).[16] Owing to the high prevalence of relapse in our population, central nervous system triple intrathecal prophylaxis was administered once after the first course of therapy and included methotrexate 15 mg, cytarabine 30 mg, and dexamethasone 4 mg. Systemic intensification was administered after induction to remission and consisted of intravenous cytarabine at 3 g/m^2 delivered by a 4-hour infusion on days 1 to 4 and etoposide at 150 mg/m^2/d in a 2-hour infusion on days 1 to 3. After recovery, defined as neutrophil count > 1.0×10^9/L and platelet count > 100×10^9/L, 2 additional cycles of intensification as described were administered. All patients received prophylaxis for post-chemotherapy neutropenia with trimethoprim/sulfamethoxazole and itraconazole. All the patients with febrile neutropenia were hospitalized and treated with a combination of carbapenem (imipenem or meropenem) and vancomycin.[15] For those with persistent fever, amphotericin was added. A red blood cell transfusion was administered to patients with hemoglobin < 8.0 g/dL, and prophylactic platelet transfusion was given to those with a platelet count of < 20×10^9/L. Since 2012, pediatric patients have received an intensive scheme for induction to remission, with daunorubicin (50 mg/m^2 on days 2, 4, and 6) and etoposide (100 mg/m^2 on days 2-6) plus cytarabine (100 mg/m^2 every 12 hours on days 1-10).[17]

High-risk patients who achieved CR or those with second remission and in good clinical condition were evaluated for hematopoietic stem cell transplantation (HSCT); only patients with an identical human leukocyte antigen-matched related donor underwent allograft transplantation.