

Annals of Leukemia Research

Research Article

Early Deaths Before or During the Induction Phase in Children with Acute Myelocytic Leukemia (Aml) in Two Different Periods 1979-1985 and 1986-1996

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Received: 05 January 2022; **Accepted:** 08 February 2022; **Published:** 12 February 2022

Citation of this article: Paredes-Aguilera, R., León-Figueroa, R., López-Santiago, N., Monsivais-Orozco, A., González-Pedroza, ML., Tavera-Rodríguez, MG., Campo-Martínez, MA., Romero Guzmán, L. (2022) Early Deaths Before or During the Induction Phase in Children with Acute Myelocytic Leukemia (Aml) in Two Different Periods 1979-1985 and 1986-1996. Ann Leuk Res, 3(1): 01-15.

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Summary

To assess the incidence, clinical and laboratory spectrum of early deaths before or during the induction phase of treatment in patients with AML, we conducted a retrospective study in 69 patients enrolled in protocol AML I of the Hematology Department at the Instituto Nacional de Pediatría, Mexico City, between 1979-1985. Thirty patients (40.8%) died in the first six weeks after diagnosis, before treatment was initiated or a result of treatment-related complications. Thirteen patients (18.8%) died before treatment, eight of them (61.5%) in the first 24 hours and five (38.4%) during the first week of admission, mainly a result of bleeding or leukostasis. Age 10 years-old or older, bleeding diathesis, disseminated intravascular coagulation (DIC),

severe thrombocytopenia and FAB subtypes AML M-3 and M-4, M-5 were the main risk factors. Fifty-six patients received the induction phase of treatment and seventeen patients (30.3%) died before remission was reached as a result of treatment-related complications and the predominant cause of death were infections, particularly bacterial infections which occurred in 14 patients (82.3%); risk factor for death during induction was mainly sepsis, although hemorrhage was a frequent symptom as a terminal event, and active bleeding in conjunction with severe thrombocytopenia was the cause of death in 3 patients (17.6%). Seven (61%) out of the 17 patients who died on days 14-42 were FAB M-3 and 13 out of 23 (56.5%) patients with early death (first six weeks after diagnosis) had FAB M-3 subtype. In the second study (1986-1996 period) only 24 patients with FAB M-3 subtype were analyzed, Of the 24 patients, five (20.8%) died of ICH before receiving treatment and the principal risk factors were bleeding diathesis 5/5 (100%), DIC 5/5 (100%), 3 (60%) with overt DIC and 2 (40%) with low grade DIC and severe thrombocytopenia 5/5 (100%). Seven (36.8%) out of 19 patients died after day 15 of initiating induction phase of therapy and the cause of death was mainly sepsis particularly gram-negative microorganisms, in some cases in combination with active bleeding symptoms. Twelve (50%) out of 24 patients with FAB M-3 were ED.

In conclusion the rates of early death before (18.8%) and during the induction phase of treatment (30.7%) in the early 1980s in children undergoing therapy for AML in our hospital were unacceptable high. There was also a high rate of early death before (20.8%) and during induction treatment (36.8%) in FAB M-3 subtype of AML in the following ten years period. The purpose of this article is to increase clinical awareness of risk factors for early death before treatment and in the first two weeks of induction treatment in developing countries, the need for better strategies of supportive care to minimize the risk of fatal complications during the induction phase of treatment, and the incorporation of new and less toxic chemotherapy options in the future.

Introduction

Acute myeloid leukemia (AML) accounts for approximately 15-20% of acute leukemias in patients age < 15 years in the United States of America (USA), with a peak incidence rate in the first year of life and then decreases steadily up to the age of 4 years, at which point it remains relatively constant throughout the years of childhood and early adulthood [1-4]. A similar incidence rate of AML that has remained relatively stable has been reported in children in Europe and Mexico in the last two decades [5-9]. Studies in Mexico have reported an average annual incidence rate of 12.3% and a standardized average annual incidence rate of 6.9 per million for AML with a small incidence peak at one year and between 10-11 years and the incidence then decreases and remains constant throughout the years of childhood [7-9]. Marked differences in the incidence of various malignant diseases in childhood between industrialized and developing countries have been well

documented since the 1980s, and a 1985 report of a collaborative study group of childhood acute lymphoblastic leukemia (ALL) in different geographic and ethnic settings revealed striking variations in the incidence, age distribution and immunologic subtypes [10-12], and the same variations have been reported with regard to AML, where somewhat higher incidence rates have been reported in more developed countries and lower rates in underdeveloped nations [13-15]. The French-American-British (FAB) classification subtypes of AML are equally represented across ethnic and racial groups with the exception of acute promyelocytic leukemia, FAB M-3 AML. Several large cooperative group studies and single Oncologic Centers have reported a 3 to 9% incidence rate of FAB M-3 AML in white Caucasian population [16-21], which is somewhat lower than the 20-25% reported several years ago in some studies among patients of mixed-ethnic (Amerindian) origin in

the USA [22,23], certain regions of Italy [24-27], Spain [28], and in some countries of Latin-America and Mexico [29-34].

The rates of death before treatment (DBT) and early death (ED) in children undergoing therapy for AML are extremely high especially in developing countries. Until the middle of the 1990s, acute promyelocytic leukemia, French-American-British (FAB) M-3 AML and acute monocytic leukemia FAB M-5 AML, were catalogued as two of the most rapidly fatal human tumors, with the majority of patients with AML M-3 dying of intractable hemorrhages, mainly intracranial hemorrhage (ICH) and the majority of patients with AML M-5 dying of pulmonary or cerebral leukostasis [35,36].

The high rate of ED in newly diagnosed children with AML and induction treatment related mortality, prompted us to perform a retrospective analysis of AML patients attending the Hematology department in two different periods 1979-1985 and 1996-2006. The objectives of this study were to identify the incidence, clinical presenting features and risk factors for DBT and during the induction phase of treatment, to increase clinical awareness of risk factors for lethal complications. The results of this analysis highlight the need for better supportive care strategies in our country and the incorporation of new therapies or less toxic chemotherapeutic regimens.

Patients and Methods

Seventy-nine children 17 years-old or younger with acute myeloid leukemia were admitted in the Hematology Department over a 7-year period between 1979-1985. Ten patients refused treatment and were referred to other institutions. Sixty-nine patients were enrolled in protocol AML I of the Hematology Department and only 24 patients with FAB M-3 AML in the 1986-1996 period because complete information was available from data files, but with the other AML FAB subtypes information of medical records from death files was incomplete or missing, so incidence of early death rate or death during induction treatment (days 15-42) could not be estimated. Both studies were considered together in terms of the problem of ED. Clinical and hematologic features are described.

Diagnosis

The diagnosis of AML was established if at least 30% blasts were present in the bone marrow aspirates (BMA) smears analyzed after a Wright staining technique. AML was classified on the basis of standard morphological and cytochemical criteria of the French-American-British (FAB) cooperative study group [37,38]. In addition, cytochemical staining was performed using Sudan black, periodic acid Schiff (PAS), acid phosphatase, alpha-naphthyl AS-D chloroacetate and alpha-naphthyl butyrate esterase. Peripheral blood (PB) smears as well as cerebrospinal fluid (CSF) cyto-spin preparations were also analyzed after a Wright staining technique in the Hematology-Oncology laboratory, and all positive cases reviewed by hematologists of our department. Patients were classified as CNS - (< 5 WBC/uL and negative cytomorphology), and CNS + (>5 WBC/uL and positive cytomorphology). Hematocrit and leukocytocrit was measured in a high speed microcytocrit centrifuge [39].

Definitions

Death before treatment (DBT) was defined as any death occurring before chemotherapy was initiated.

Early death (ED) was defined as a fatal event occurring before or in the first two weeks after initiating induction treatment (days 1-14) or death before remission was achieved (days 15-42).

Infections

Infections were categorized as clinically, radiologically or microbiologically documented. Viral disease was registered when both relevant or characteristic disease symptoms and virus were detected in the organ (e.g.cytomegalovirus pneumonia was defined as the combination of symptoms of pulmonary disease together with the detection of CMV in bronchoalveolar lavage or in lung tissue fluid. Fungal infections were defined as proven invasive infection (positive histopathological findings or positive culture) or probable invasive infection (at least one host factor criterion, such as neutropenia, for more than 10 days or persistent fever refractory to broad-spectrum antibacterial treatment in high-risk patients.

Epticemia

Confirmed septicemia: Patients with at least two separate positive blood cultures growing the same organism. Presumptive (clinical) septicemia: Patients with high fever, toxic-infectious facies, rapid deterioration of their clinical condition, acute vascular collapse and/or clinical evidence of an inflammatory process in three distal organs.

Local Infection

Refers to a severe local cellulitis always associated with gangrene or abscess formation; transient episodes of local inflammation, e.g. around intravenous drip sites or associated with oral ulcers [40].

Cause of death

Hemorrhage was assumed to be the cause of death when it occurred in a vital organ and was described at autopsy as extensive. In the non-autopsied cases when one or more of the following findings were present: cerebral hemorrhage (loss of consciousness) and/or CNS clinical signs; pulmonary hemorrhage (massive hemoptysis accompanied by acute respiratory failure); and gastrointestinal hemorrhage (massive melena or hematemesis accompanied by fall of blood pressure).

Leukostasis was defined as blast accumulation in the vessels and could only be confirmed by an autopsy. Pulmonary leukostasis signs are tachypnea, dyspnea, and hypoxia and diffuse interstitial infiltration. Clinical signs of high leukemic tumor cell burden or leukostasis with or without ICH are stupor, delirium, dizziness, tinnitus, ataxia, visual blurring, papilledema, and retinal venous distention [36].

Treatment

Induction remission phase consisted of two cycles of Vincristine 2.0 mg/sq m/ (maximum dose 2.0 mg)/day, days 1, 8, 15, 22 IV, Adriamycin (doxorubicin) 30 mg /sq m/day/days 5,6, and 19, 20 IV, prednisone PO 60 mg sq m (maximum dose 60 mg)/day, days 1-28 and cytosine arabinoside (ara-C) 100-120 mg sq m/day, days 1-5 and 15-19 IV by push or 3hs infusion. Patients achiev-

ing remission were treated with intensive sequential combination chemotherapy COAP, POMP, TAAP for 24 months. VAPA or AdOAP are the acronym of the induction phase [41].

Supportive Therapy

In the 1986-1996 period every patient with FAB M-3 AML and FAB M-5 with hyperleukocytosis were considered as high-risk patients of ED and considered true hematologic emergencies, and replacement therapy with coagulation factors (fresh frozen plasma, cryoprecipitates) platelet transfusions and prophylactic heparin were started in the emergency service in FAB M-3 patients, and cytoreductive measures or procedures, as slow cytoreduction with hydroxyurea or chemotherapy as a pre-induction phase or exchange transfusion in patients with FAB M-5 with hyperleukocytosis.

To minimize the risk of fatal complications after 15 days of initiating therapy, all patients had antiseptic mouth washes and all patients who developed fever > 38.5°C without an obvious precipitating factor were subjected to a thorough search for an infectious process and responsible agent, with blood cultures, mid-stream urine, appropriate swabs, and a chest x-ray, and if pyrexia continued or was registered on two occasions in 24 hours, broad spectrum antibiotics were started immediately. Patients also received antifungal prophylaxis to reduce the high-risk of invasive fungal infection.

Statistical Analyses

The prognostic factors were tested for significance by analysis of contingency tables using analysis of association, chi-square tests and stratified analysis. Associations between clinical characteristics and subgroups were evaluated with the X^2 test or Fisher exact test for categorical variables. Some characteristics were analyzed by the method of maximum difference of Kolmogorov Smirnov. In some individual variables (age, WBC), we applied cut-off points that were selected for their higher discriminant power to predict long term survival in univariate analysis in previous studies of other investigators and in other variables (AML FAB subtypes) we did correlation analysis between two different independent variables selecting clinical, hematologic and early death risk informed

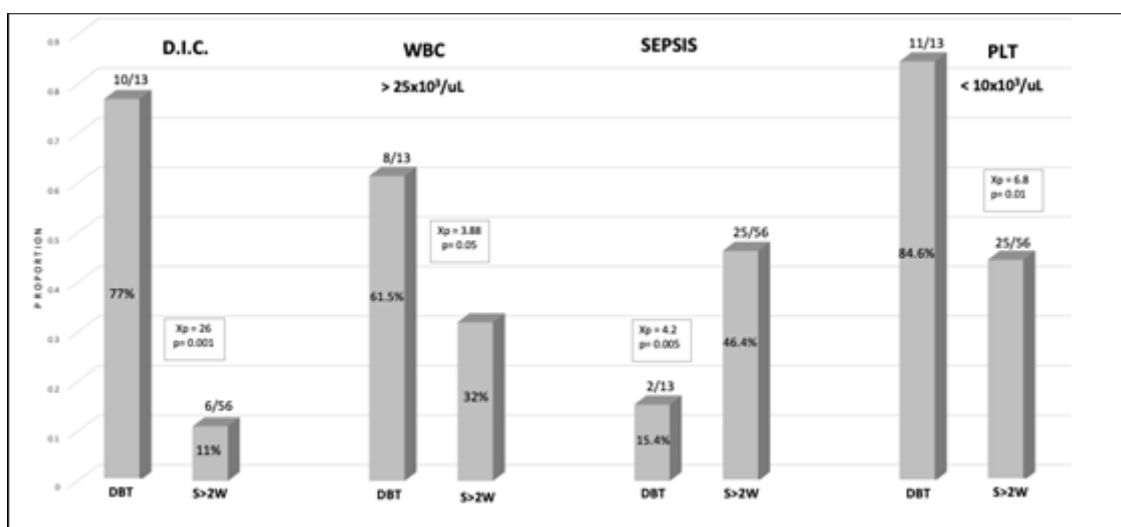
in previous reports.

Results

Of the 69 patients enrolled in protocol AML I of the Hematology Department in 1979-1985, thirteen patients (18.8%) died shortly after diagnosis, eight (61.5%) of them in the first 24 hours and five (38.4%) during the first week of admission of ICH before treatment was initiated, mainly a result of bleeding and leukostasis. Clinical, laboratory features and risk factors of this group of patients was age 10 years-old or older 9/13 (69.2%), bleeding diathesis 12/13 (92.3%), DIC 10/13 (76.9%) and severe thrombocytopenia ($< 10 \times 10^9/L$) 11/13 (85%). WBC at the time of diagnosis was, mean $112 \times 10^9/L$ (range $1-352 \times 10^9/L$), median $64 \times 10^9/L$ and most of the patients (61.5%) had leukocytosis (WBC $> 50 \times 10^9/L$) and four of them (30.8%) hyperleukocytosis (WBC $> 100 \times 10^9/L$). All (100%) patients had circulating blast cells which in 46% were the predominant cells (50-95%) in the WBC differential count. We found a high statistically significant difference ($p < 0.001$) between patients who died before starting treatment vs patients surviving 15 days or more, when comparing patients with or without DIC, a statistically significant difference in patients with WBC $< \text{or} > 25 \times 10^9/L$

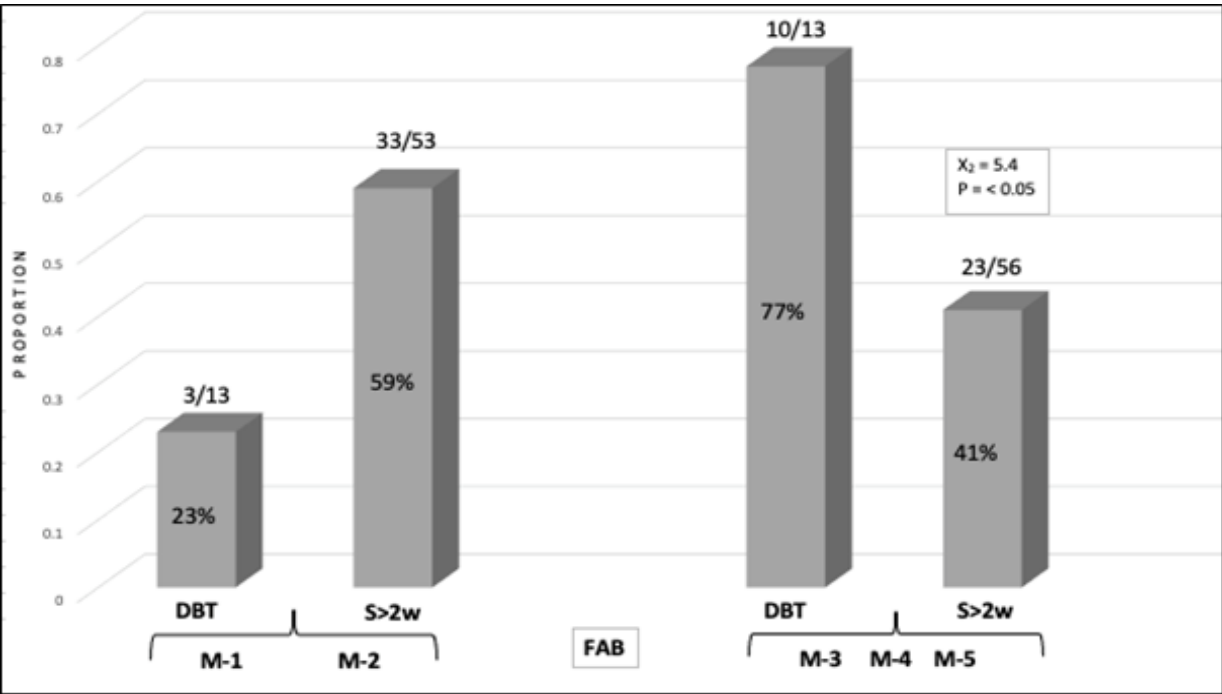
($p < 0.05$) and platelet counts $< \text{or} > 10 \times 10^9/L$ ($p < 0.01$) (Figure 1). We also found a statistically significant difference ($p < 0.05$) when comparing FAB AML subtypes M1, M2 vs M3, M4, M5 (Figure 2). We also found a statistically significant difference ($p < 0.01$) according to platelets counts $< \text{or} > 10^9/L$ (Fig. 2). Although there was no significant difference when comparing age < 2 years and > 10 years old vs 2-10 years old, there was a significant difference ($p < 0.05$) when comparing 2-10 years vs > 10 years (Figure 3).

However, we could identify two different risk factors and pathogenesis mechanisms as causes of early deaths in the thirteen patients. One group (group A) consisting of nine patients (69.2%) in whom hemorrhage was the principal cause of death a result of intracranial hemorrhage (ICH) in 6 patients (66.7%), gastrointestinal bleeding in 2 (22.2%) and massive pulmonary bleeding in 1 (11.1%). Principal risk factors in this group of patients were: severe bleeding diathesis 8/9 (88.9%), DIC 8/9 (88.9%), severe thrombocytopenia 8/9 (88.9%), age 10 years-old or older 7/9 (77.8%), and AML M-3 subtype 6/9 (66.7%), factors that had a higher impact than leukemic tumor cell burden, as was evident by CBC that showed WBC mean $26.3 \times 10^9/L$ (range $1-76 \times 10^9/L$),



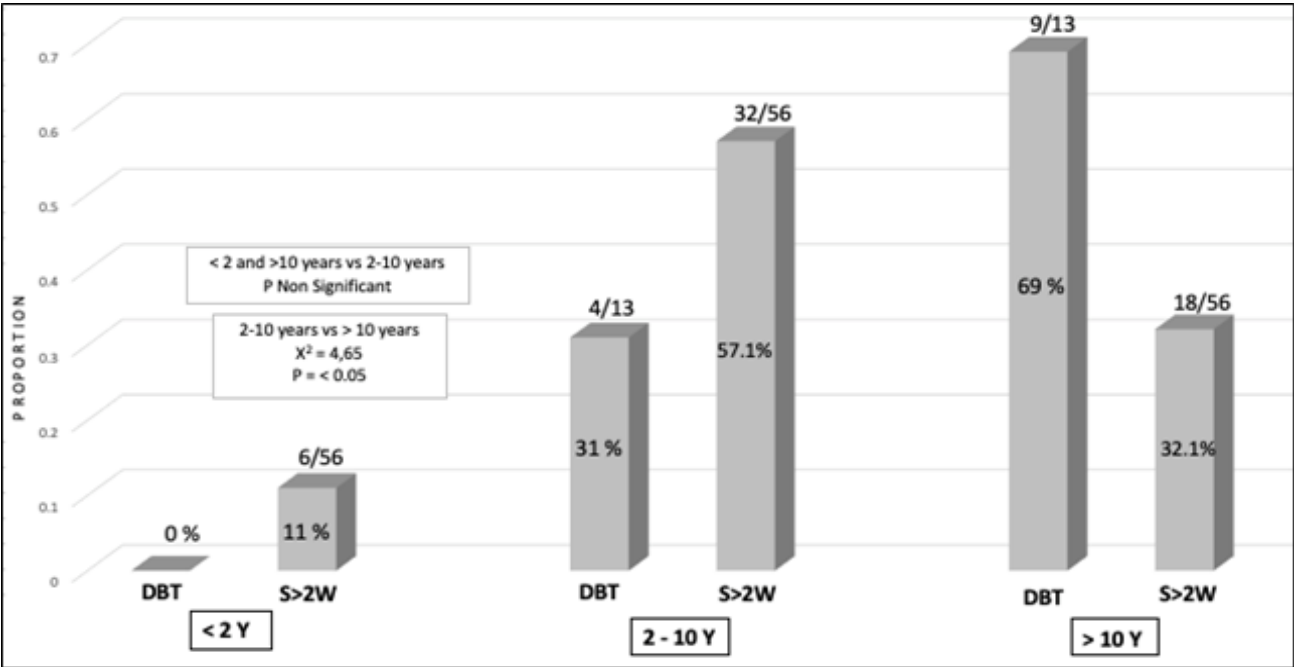
Initial Parameters

Figure 1: Initial risk factors in patients who died before treatment (days 1-14) vs patients surviving ≥ 2 weeks (days 15-42).



FAB SUBTYPES M1, M2 vs M3, M4, M5

Figure 2: Initial risk factors in patients who died before treatment (days 1-14) vs patients surviving ≥ 2 weeks (days 15-42).



AGE <2 y>10y vs 2-10y >10y vs 2-10y

Figure 3: Initial risk factors in patients who died before treatment (days 1-14) vs patients surviving ≥ 2 weeks (days 15-42).

median $11 \times 10^9/L$, few peripheral circulating blast cells, absolute number ($0.29-67.6 \times 10^9/L$), median $5.7 \times 10^9/L$. Another group (group B) consisting of four patients (30.8%) in whom cerebral leukostasis and ICH associated with a high leukemic tumor cell burden was the principal cause of death, as evidenced by the following clinical and laboratory features of the patients: short onset of the disease, active bleeding in 4/4 (100%), hyperleukocytosis 4/4 (100%), high leukemic tumor cell burden WBC mean $284 \times 10^9/L$ (range $190-352 \times 10^9/L$), median $297 \times 10^9/L$, many peripheral circulating blast cells number 35% (range 13-83%), absolute circulating blast cells, mean $167 \times 10^9/L$, range ($24.7-292 \times 10^9/L$) median $65.5 \times 10^9/L$, DIC 3/4 (75%), severe thrombocytopenia 3/4 (75%), FAB AML-M4-M5 subtype 3/4 (75%), cytotrit >30 (hematocrit + leukocrit) 3/4 (75%), range (26-34) and increasing blood viscosity following packed red cell transfusion 4/4 (100%). Of particular interest was a patient with FAB M-5 AML, in whom his initial WBC of $352 \times 10^9/L$ and 83% circulating blast cells and absolute circulating monoblasts $292 \times 10^9/L$, increased to $741 \times 10^9/L$, 80% circulating blast cells and absolute circulating mono-

blasts ($593 \times 10^9/L$) in 24 hours, and who suddenly developed a fulminant ICH following a packed red cell transfusion, probably due to an increase in blood viscosity as evidenced by an increase in his cytotrit from 35 to 53.

Fifty-six patients received the induction phase of treatment, 34 (60.7%) attained complete remission, 5 (8.9%) were non-responders and 17 (30.3%) died 15 days or more after initiating induction treatment. Eleven (32.3%) of the 34 patients achieving complete remission were < 2 or > 10 years old, and the remaining 23 (67.6%) were 2-10 years old. CBC showed WBC mean $16.1 \times 10^9/L$ (range $1-76 \times 10^9/L$), median $10 \times 10^9/L$, and only 3 patients (8.8%) had $> 50 \times 10^9/L$ WBC. Absolute circulating blast cell number mean $7.7 \times 10^9/L$, range ($0-53.9 \times 10^9/L$) median $8 \times 10^9/L$. Only 11 of the 34 patients (32.3%) had a platelet count $< 10^9/L$ and there was a predominance of FAB M1, M2 subtypes (61.7 %). Fifty percent of the patients had a bleeding diathesis at the time of diagnosis and $< 10\%$ DIC. Seventeen patients (30.3%) died 15 days or more after initiating induction treatment and the principal cause of death was sepsis in 14 patients (82.3%), and in 3 (17.6%) massive gastro-

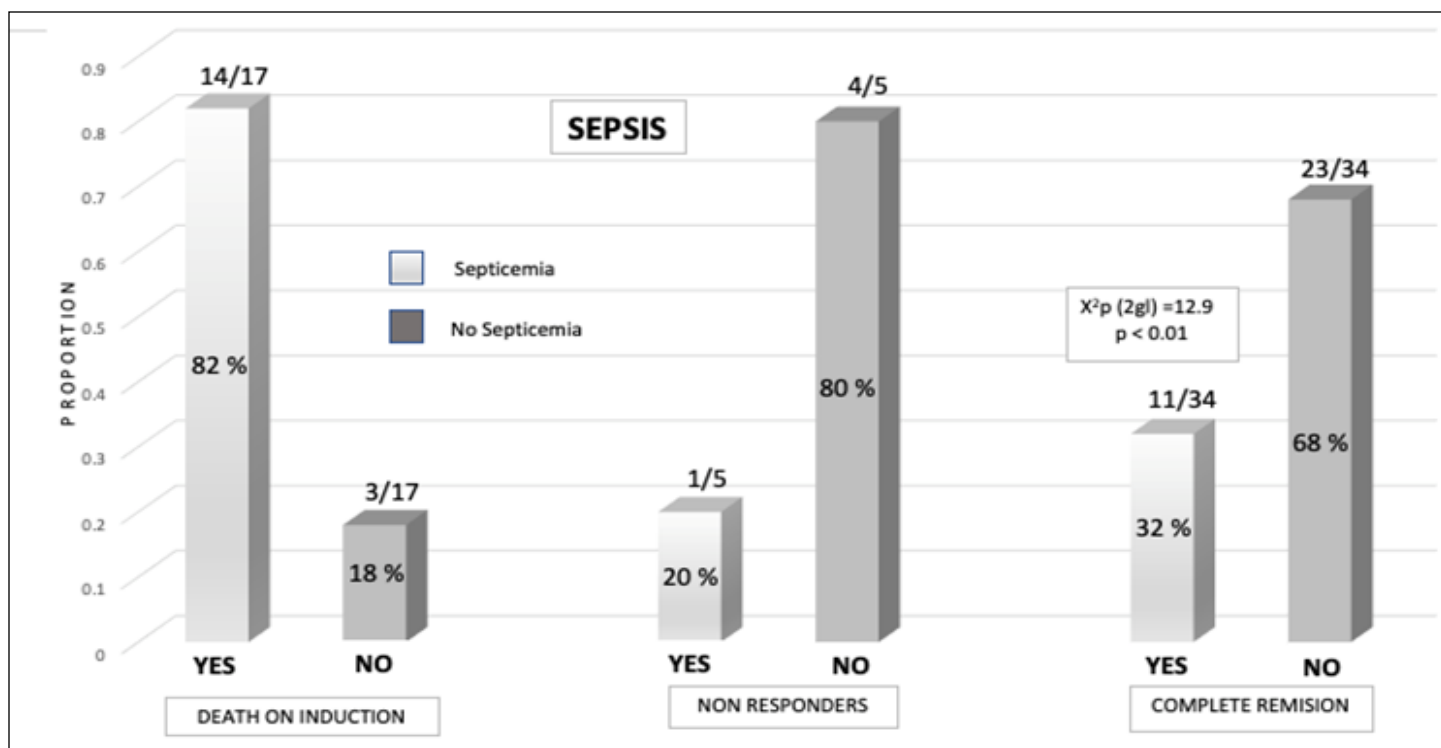


Figure 4: Risk factors and induction treatment response

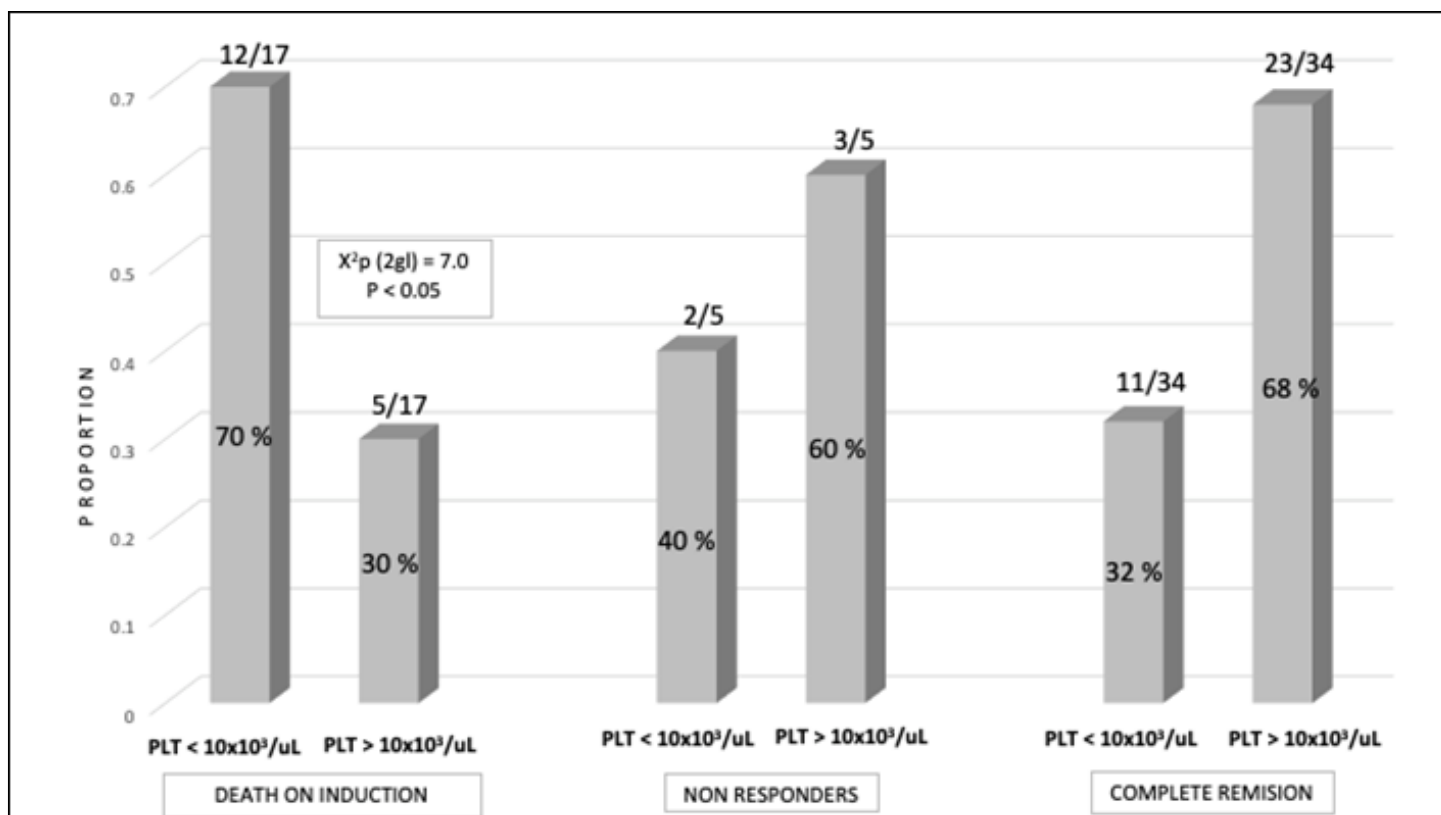


Figure 5: Risk factors and induction treatment response

intestinal hemorrhage in 2 and massive pulmonary hemorrhage in one. Four patients with neutropenic enterocolitis eventually developed bowel perforation. In 8 patients (47%) we identified a causal microorganism of the nosocomial bloodstream infection and in 2 (11.7%) a gram + microorganism was probably the cause because although it was not cultured in blood, it was identified in two distal organs. Gram negative microorganisms accounted for 3 (37.5%), staphylococcus aureus for 2 (25%) and in 2 (25%), multiple microorganisms were recovered from blood isolates (Table 1). Cellulitis around intravenous drip sites, and mucosal barrier breakdown particularly in oral or peri-anal region by chemotherapy, were the strongest risk factors contributing to sepsis. We found a statistically significant correlation between sepsis ($p < 0.01$) (Figure 4) and thrombocytopenia $< 10 \times 10^9/L$ ($p < 0.05$) (Figure 5) and death on induction. Seven (61%) out of the 17 patients who died on days 15-42 were FAB M-3 and 13 (56.5%) out of 23 which was the total number of patients with FAB M-3 suffered ED.

In the 1986-1996 period we analyzed the clinical records of 123 patients with AML, 28 of whom were patients with AML FAB M-3 subtype. Four patients (14.2%) of this group refused treatment at our hospital and were referred to other institutions and included only for analysis of clinical and laboratory features. Twenty-seven patients had pallor and hemorrhagic diathesis (96%), fever or local infection 25/28 (89%), hepatomegaly 18/28 (64%) and splenomegaly 6/28 (21.4%). Main laboratory features were anemia 27/28 (96.4%) which was grade III and IV ($Hb < 7g/dL$) in 14/28 (50%), $WBC < 5 \times 10^9/L$ (39%), $> 50 \times 10^9/L$ in 6/28 (26.4%), but in 2/28 (7.1%) the WBC was $> 100 \times 10^9/L$. Platelets $< 20 \times 10^9/L$ was registered in 17/28 (60.7%) of the cases and DIC in 22/28 (78.5%) which was overt (high grade DIC) in 15 cases (68.2%) and of low grade in seven cases (31.8%). In six patients (24.1%) coagulation profile was normal.

Five patients with AML FAB M-3 (20.8%) died of ICH in the first 24 hours of admission before receiving treatment and the cause of

early death was hemorrhage; risk factors for early death were DIC 5/5 (100%), 3 (60%) overt DIC and 2 (40%) low-grade DIC and severe thrombocytopenia 5/5 (100%). Nineteen patients with AML FAB M-3 received induction treatment and 11 (57.8%) attained complete remission, 7/19 (36.8%) died 15 days after initiating therapy, and the cause of death was mainly sepsis by gram negative microorganisms directly attributed to chemotherapy toxicity. Bacterial gram-negative microorganisms were the predominant pathogens. Twelve (50%) out of 24 patients with FAB M-3 resulted in ED. Of the 11 patients that achieved remission, two refused further treatment, and of the remaining 9 patients 4 reached the stage of elective cessation of chemotherapy after two years in continuous complete remission, 2 of them the first patients treated with all-trans retinoic acid available in our country since the middle of 1990s, and five relapsed to bone marrow and leukemia was refractory to other induction regimens.

Discussion

The analysis of both studies showed that that 18.8% and 20.8% of

children diagnosed with AML or AML M-3 died before or during the first 15 days of initiating treatment, and 30.3% and 36.8% died from day 15-42 of induction treatment from treatment related

complications. ED rates before or during the first 2 weeks of induction treatment or from day 14-42 of induction treatment were unacceptable high in our hospital. Early death rate before day 15 was 4 to 6-fold higher and 3 to 15-fold higher during induction treatment (days 15-42) than studies conducted in countries with higher resources [41-46]. However in the same time period of our first study, two reports informed of the high mortality rate 10% in the first two weeks, and 29 % in the first six weeks of treatment in pediatric and adults patients with AML [35,39]. There are several possible explanations for the great difference in DBT (days 1-14) in our study and those reported in Caucasian white populations: delay in diagnosis and progression of disease that contributes to other potential problems, as was evidenced in 16 % of patients of our first cohort with weight and height below the third percentile in whom early diagnosis before 3 months of onset of the

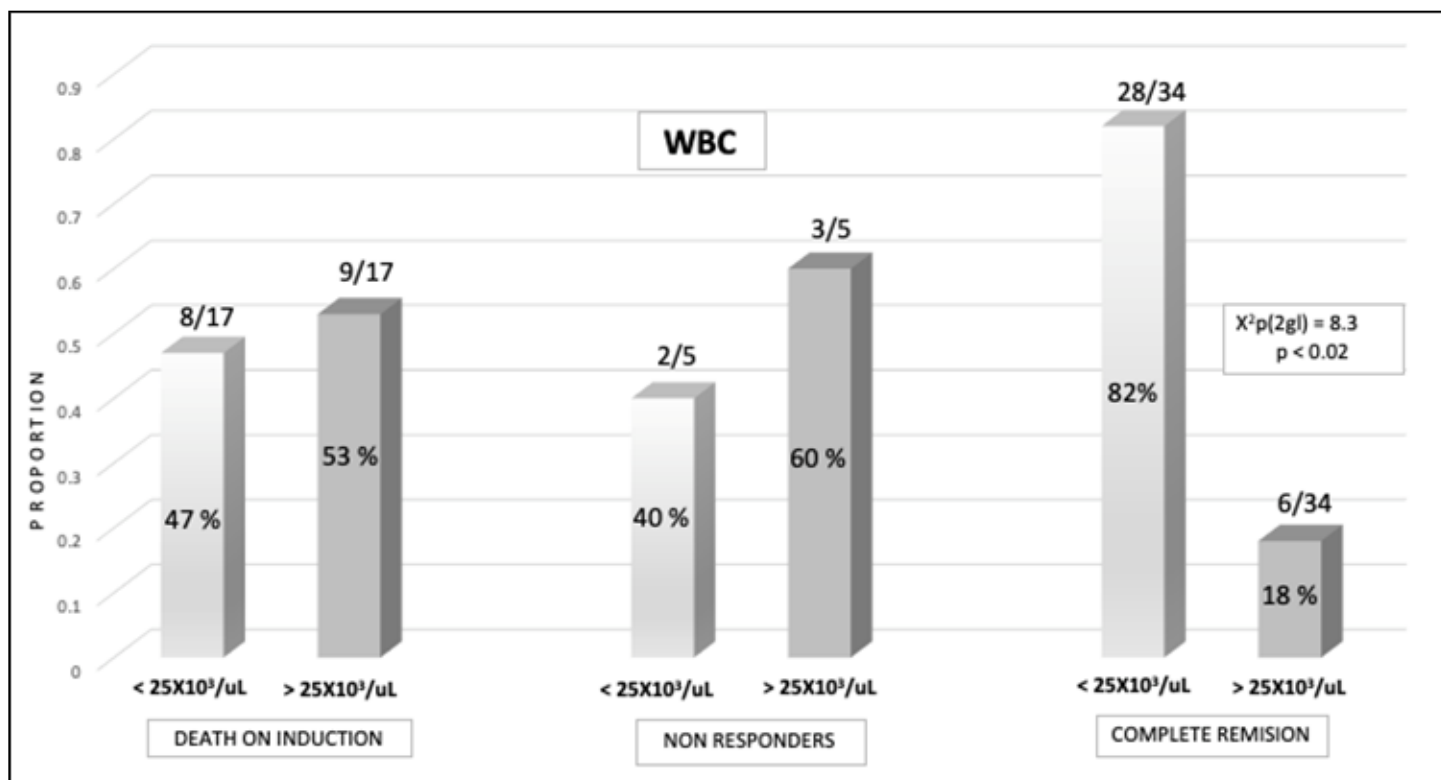


Figure 6: Risk factors and induction treatment response

disease was elaborated in 45% of the cases in contrast to patients with normal weight and height in whom early diagnosis was established in 83% of the cases. Other important factors were lower socioeconomic and nutritional status, deficient supportive care of critically ill patients and delay in initiating empiric antibiotic therapy during induction treatment. Another important factor is the difference in the incidence of AML FAB subtypes, with FAB M-3 predominance in Hispanic and Latinos populations in USA and in several South American countries and Mexico, incidence varying from 20-30% [22-34], in contrast to the 3-9% incidence reported in western countries [16-21].

FAB M-3 and FAB M-5 AML were catalogued in the early 1980s and 1990s as two of the most rapidly fatal tumors responsible of ED, with most of the patients dying of intractable hemorrhage or leukostasis. Even in countries with advanced medical systems, the main cause of DBT or in the first 14 days of admission was hemorrhage and hyperleukocytosis, mainly FAB M-5 AML and though the incidence of FAB M-3 is very low in these countries, in one study four out of seven patients died early, and this subtype was a risk factor for ED after day 14 before All-trans retinoic acid (ATRA) was introduced in their treatment protocols [45,47].

Risk factors of DBT informed in most studies in this period, were

age <2 or > 10 years, hemorrhage mainly ICH, hyperleukocytosis, FAB M-5, FAB M-3 and DIC [35,36,40,42,45,47]. In our first cohort risk factors for ED were age > 10 years, FAB M-3, M-4 and M-5, DIC and hyperleukocytosis. In 6 (26%) out of the 23 patients with FAB M-3 and 5 (20.8%) out of the 24 patients of the 1986-1996 period, the cause of DBT was ICH a result of intractable hemorrhage which occurred before ATRA became available in our country in the middle of the 1990s. The ED rate due to coagulopathy in FAB M-3 has dropped significantly with the introduction of ATRA as evidenced in that none of our patients with FAB M-3 included in our last AML protocol in the 2008-2015 period DBT (data not published).

After day 15 treatment related complications, particularly bacterial and fungal infections were the principal causes of death in most studies. Treatment related deaths in 525 children included in three cohort studies AML 84, 88, 93 of the Nordic Society of Paediatric Hematology and Oncology (NOPHO) rose from 11% in AML 84 to 29% in AML 88, but then fell to 8% in AML 93. Indwelling central line catheters, and skin and mucosal barrier breakdown by chemotherapy were the principal risk factors [48-50]. In our study cellulitis around intravenous drip sites, mucosal barrier breakdown particularly in oral or peri-anal region and gastrointestinal

Table 1: Blood stream isolates	
Case 5	Klebsiella Enterobacter
Case 6	Klebsiella Enterobacter
Case 7	Gingivae-stomatitis- Staphylococcus Aureus coag. (+), E Coli. Candida Sp. Catheter-line abscess- Staphylococcus Aureus coag. (+), Candida Sp
Case 8	Staphylococcus Aureus coag. (+), Pseudomonas Sp, Aeromonas Shigelloides
Case 10	Lysteria Monocytogenes
Case 12	Klebsiella Enterobacter
Case 13	Hafnia Alvei
Case 15	Aeromonas Shigelloide, S. Liquefaciens
Case 16	Gingivae- stomatitis- Staphylococcus Aureus coag. (+), Left Foream abscess around drip site of IV infusion, Staphylococcus Aureus coag
Case 17	Staphylococcus Aureus coag (+)

toxicity, were the main factors contributing to the development of sepsis. We found a statistically significant correlation between sepsis ($p < 0.01$) and platelets $< 10 \times 10^9/L$ ($p < 0.05$) and death on induction. Children 2-10 years old had a lower rate of death on induction than children < 2 or > 10 years old, the same as patients with WBC $< 25 \times 10^9/L$ and platelets $> 10 \times 10^9/L$, and a higher probability of attaining complete remission (Figure 5-6)

There has been a significant reduction in the number of ED prior to or during induction treatment over time in most studies, probably because of a learning process in treatment centers and increasing experience of the medical staff [41,42], Also the introduction of aggressive treatment of bleeding complications, ATRA in FAB M-3 AML protocols since the middle of 1990s, restricted packed red blood cell transfusion and IgG administration policy to avoid increasing blood viscosity, and slow cyto-reduction of tumor cell burden with hydroxyurea or low dose cytarabine in patients with hyperleukocytosis mainly FAB M-4 and M-5 AML, and the use of broad-spectrum antifungal agents for empiric treatment and prophylaxis in high-risk patients, has greatly contributed to this significant reduction of ED.

In the middle of 1990s there was a renewed interest in acute promyelocytic leukemia in children and various protocols were designed that included ATRA, followed by intensive chemotherapy (consolidation or combination chemotherapy), and in some studies maintenance treatment with intermittent ATRA and continuous low-dose chemotherapy with complete remission rates of 80-90% and event free and overall survival 70-80% [51-54]. By the same time there were ongoing studies of the use of arsenic trioxide in acute promyelocytic leukemia in relapse and later in relapsed and newly diagnosed patients without ATRA and/or chemotherapy [55]. The development of new protocol treatments as the combination of ATRA and arsenic trioxide (ATO) has converted acute promyelocytic leukemia from a rapid many times fatal disease, into one of the most curable malignant diseases in humans. Unravelling the heterogeneity of AML at the clinical, cytogenetic and molecular levels has led to an exciting new era in the development of small molecules that target the disease at a molecular level like gemtuzumab, ozogamicin, venetoclax, FLT3

inhibitors (midostaurin, gilteritinib, IDH inhibitors (ivosidenib, enasidenib), CPX-351, glasdegib, oral decitabine and oral azacitidine. Hopefully some of these new drugs could be incorporated in future pediatric protocols.

In conclusion, the aim of this report is to increase clinical awareness of risk factors for ED prior to or during the induction phase of treatment in childhood patients with AML in our country and in developing countries, the need for better support care strategies, and the incorporation of new and less toxic chemotherapy options in the future.

Acknowledgements

Pamela Mancilla Paredes and Mireya de la Rosa for technical support

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