HEMATOLOGY, TRANSFUSION AND CELL THERAPY

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Original article

Acute promyelocytic leukemia in childhood and adolescence: treatment results of a modified AIDA protocol at a Brazilian center

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ARTICLE INFO

Article history:
Received 20 February 2022
Accepted 11 September 2022
Available online 7 November 2022

Keywords:
Acute promyelocytic leukemia
All-trans-retinoic acid
Anthracyclines
Early mortality
Disseminated intravascular coagulation
Child

ABSTRACT

Introduction: Acute promyelocytic leukemia currently presents an excellent chance of cure with protocols based on all-trans-retinoic acid (ATRA) and anthracycline or only differentiation agents. However, high early mortality rates continue to be reported

Methods: Between 2000 and 2018, patients were enrolled and retrospectively analyzed by medical records. A modified AIDA protocol, with a 1-year shortening of the treatment duration, reduction in the number of drugs and a strategy to reduce early mortality by the postponement of the initiation of anthracyclines were employed. Overall and event-free survival rates and toxicity were analyzed

Results: Thirty-two patients were enrolled, of whom 56% were female, with a median age of 12 years and 34% belonged to the high-risk group. Two patients had the hypogranular variant and three had another cytogenetic alteration, in addition to the t(15;17). The median start of the first anthracycline dose was 7 days. There were two early deaths (6%) due to central nervous system (CNS) bleeding. All patients achieved molecular remission after the consolidation phase. Two children relapsed and were rescued by arsenic trioxide and hematopoietic stem cell transplantation. The presence of disseminated intravascular coagulation (DIC) at diagnosis ($p = 0.03$) was the only factor with survival impact. The five-year event-free survival (EFS) was 84% and 5-year overall survival (OS) was 90%

Conclusion: The survival results were comparable to those found in the AIDA protocol, with a low rate of early mortality in relation to the Brazilian reality.

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https://doi.org/10.1016/j.htct.2022.09.1276

Introduction

Acute promyelocytic leukemia (APL) is a specific type of acute myeloid leukemia (AML), characterized by the presence of translocation t(15;17), involving the *PML* and *RARA* genes. Thrombohemorrhagic manifestations are its most impactful characteristic, which presents distinct cellular morphology. When not managed as an emergency medical situation, it has a rapid and often fatal evolution.

It is currently highly curable with the use of all-trans-retinoic acid (ATRA) combined with anthracycline-based chemotherapy or arsenic trioxide (ATO). Good results have been described with chemotherapy-free regimens, only with differentiation agents (ATRA and ATO).[1]

Despite the good outcome, APL has high early mortality rates due to hemorrhagic complications, which are still the main cause of death.

The APL represents more than 20% of the AML in Brazil and other Latin American countries.[2-4] Access to the ATO in low-income countries is restricted and the use of ATRA and chemotherapy is still the pillar of treatment. In this manner, all efforts to refine this approach are still of current and desired interest.

Objective

The primary objective of this study was to evaluate 5-year event-free-survival of children and adolescents treated according to an institutional protocol for acute promyelocytic leukemia. Secondary endpoints were 5-year overall survival, description of clinical features, hematologic and molecular response to treatment and major adverse events and toxicities.

Methods

This study was approved by the local Ethics Committee under protocol number 2,966,163. The data were obtained retrospectively by analyzing medical records of consecutive patients under 18 years of age, diagnosed with APL in the period between 2000 and 2018. Patients who had undergone previous chemotherapy were excluded. The diagnosis was made by morphology, immunophenotyping and detection of *PML/RARA* by RT-PCR. The last data update was carried out in January 2021.

Treatment performed: The induction phase consisted of the use of ATRA (45mg/m^2/day in those over 14 years of age and 25mg/m^2/day in the younger ones) until morphological remission or for a maximum of 90 days and an anthracycline, that could be either idarubicin (12mg/m^2/day for four doses every other day) or daunorubicin (50mg/m^2/day for three days every other day), depending on the availability of the drug at the service. The dose equivalence for the two drugs was 3:1 for daunorubicin: idarubicin, according to the conversion established by the Childhood Cancer Survivor Study.[5] The introduction of anthracycline was based on leukometry and was generally initiated with leukocytes around 20,000/mm^3. No systematic recommendation for cytoreduction with hydroxyurea was made and its use was at the discretion of the attending physician. All patients received three forward consolidation anthracycline-based (without ATRA, cytarabine or etoposide) blocks. The first block consisted of idarubicin 5mg/m^2/day for four days or daunorubicin 50mg/m^2/day for one day. The second block was based on mitoxantrone 10mg/m^2/day for five days and the third one with one day of idarubicin 12mg/m^2 or daunorubicin 50mg/m^2. After consolidation, patients in molecular remission received one year of maintenance therapy (instead of two years maintenance as in the AIDA protocol) consisting of 6-mercaptopurine and methotrexate, alternating with 15 days of ATRA, every three months.[6] There was no difference in treatment according to the risk groups. Prophylaxis for the differentiation syndrome was not performed, so treatment was initiated immediately at diagnosis.

Supportive therapy

The ATRA therapy was initiated at the first clinical suspicion of APL. During the induction period, invasive procedures were avoided, including a spinal tap for CNS involvement evaluation and central lines set. Platelets above 50,000/mm^3, fibrinogen greater than 100mg/dL, prothrombin activity greater than 70% and normal PTTa/normal control ratio were maintained.

Bone marrow evaluation

Bone marrow samples and RT-PCR for *PML/RARA* were obtained after induction, after consolidation and at the end of the treatment. The absence of morphological or molecular response at the end of induction did not change the treatment, being evaluated only for investigative purposes. No periodic follow-up was performed during maintenance.

Definitions

Remission was considered as the presence of morphological (< 5% blasts) associated with molecular complete response (RT- PCR *PML/RARA* negative) at the end of consolidation. The refractory disease was defined as the persistence of positive *PML/RARA* after consolidation and the relapsed disease, as the presence of > 5% blasts in bone marrow or the presence of blasts in extramedullary sites after molecular remission. The early mortality was defined by death in the first 30 days of treatment. The differentiation syndrome was defined as the presence of 4 of the criteria: fever, dyspnea, weight gain > 10%, pleural or pericardial effusion, pulmonary infiltrate, hypotension or edema of the lower limbs.[7] The pseudotumor cerebri was defined as probable diagnosis by the Coombs criteria (based on the presence of papilledema, a normal neurologic exam except for cranial nerve abnormalities and normal neuroimaging, including normal meningeal enhancement on MRI or contrast-enhanced CT. No lumbar punction was performed).[8] The diagnosis of *DIC* was made according to the International Society on Thrombosis and Hemostasis criteria based on fibrinogen, prothrombin time, platelet count and D-dimer (available at https://www.thebloodproject.com/cases-archive/isth-dic-score/isth-dic-score).[9]. The overall survival

Table 1 – Demographics.

Characteristic	N (%)	Median (range)
No. of patients	32	
Male sex	18 (43.7%)	
Age, years		12 (1 - 17)
WBC counts/mm^3		5,100 (1,000 - 95,800)
< 10.000/mm^3	21 (65.7%)	
≥ 10.000/mm^3	11 (34.3%)	
Platelet count/mm^3		25,900 (1,000 - 295,000)
> 40.000/mm^3	5 (16.6%)	
≤ 40.000/mm^3	27 (84.4%)	
Risk group		
High risk	11 (34.3%)	
Intermediate risk	18 (56.3%)	
Low risk	3 (34.3%)	
Morphologic subtype		
M3	30 (93.8%)	
M3v	2 (6.2%)	
Cytogenetics		
t(15;17) alone	25 (78.1%)	
t(15;17) + others	3 (9.4%)	
Not available	4 (12.5%)	
Disseminated intravascular coagulation	10 (31.3%)	

(OS) was calculated between the time of diagnosis and death by all causes and the event-free survival (EFS), between the time of diagnosis and relapse or death by any cause.

Statistical analysis

The descriptive analysis of data of qualitative variables was expressed in absolute and relative frequency distribution and position and dispersion measurements were reported for quantitative variables. Survival curves were calculated by the Kaplan-Meier estimator and the log-rank test was used to compare the survival between groups. The level of significance adopted was 5% ($p < 0.05$).

Results

Thirty-two patients were analyzed, of whom 18 were females (56%). The APL corresponded to 27.5% of the cases of AML at our service. The median age of diagnosis was 12 years.

The median leukometry at diagnosis was 5,100/mm^3 and the platelet count was 25,900/mm^3. Most children (56%) were classified as intermediate risk and 34% were at high risk (> 10,000/mm^3 leukocytes). Ten children had DIC at diagnosis (31%) and 16% presented thromboembolic events.

The morphological evaluation revealed only two children with hypogranular variants. Three patients had another cytogenetic alteration in addition to the t(15;17): add(9)(p23), trisomy of 8 and +mar(9). None of the three cases evolved to death or relapse. Only 12 cases had the *FLT3* gene mutation evaluated and it was detected in 3 patients (25%). Pretreatment characteristics of study patients are listed in Table 1.

The median time for the introduction of anthracycline was seven days, with a median leukocyte count of 25,417/mm^3. Daunorubicin was administered in 74% of patients.

There were two early deaths (6%) due to central nervous system bleeding during the second week of treatment, one in 2001 and the other in 2012. One of them had the differentiation syndrome (DS).

Five children presented DS (16%), four with good response to corticosteroids and, in three of them, interruption of ATRA was also necessary. Six children were diagnosed with cerebral

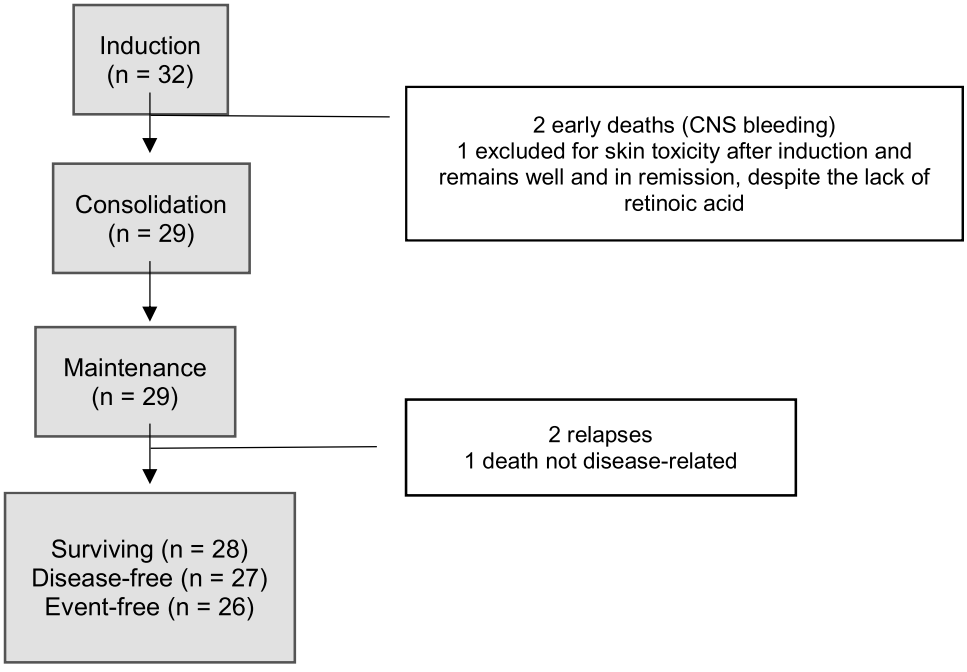


Figure 1 – Consort diagram.

pseudotumor (19%), all with resolution with acetazolamide treatment. One child was excluded due to skin toxicity and was analyzed until that moment. Figure 1 shows a consort diagram.

After the end of the consolidation, all patients presented molecular remission. There were two hematologic relapses at the end of the treatment (7%), both rescued with arsenic trioxide and bone marrow transplantation (one allogeneic and one autologous).

There was no refractory disease. One child died in remission, one year after the end of the therapy, due to a car accident. There were no deaths from toxicity.

Overall survival was 90% and event-free survival was 84% in 5 years. The only factor that had an impact on survival was the presence of DIC at diagnosis ($p = 0.03$). Survival data are shown in Figure 2. The median follow-up time was 90 months (7.5 years). The median duration of overall survival was 175 months (156 - 193 months).

Discussion

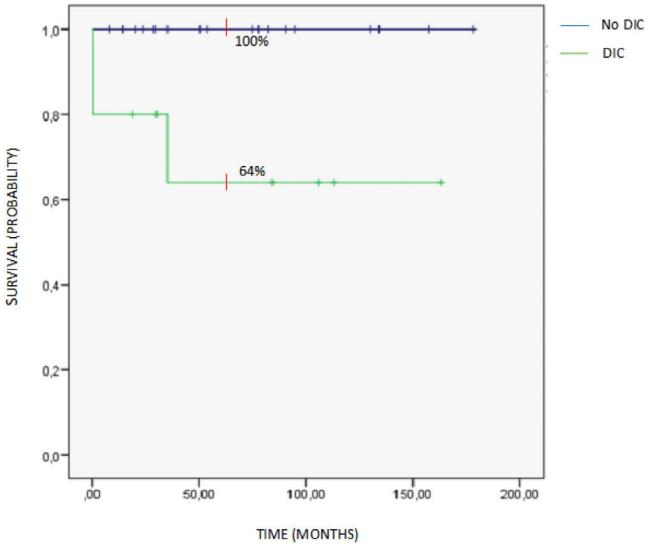
In our series, 27.5% of the cases of AML were APL, consistent with the highest number described in the literature in Brazil and other low-income countries. Demographic characteristics, such as gender, median age and high-risk features rates of patients, were also similar to those commonly seen.

Most pediatric series have response rates higher than 90%, when ATRA regimens combined with anthracycline are used, showing that treatment-resistant disease is very rare. In our study, all children achieved molecular remission after the consolidation phase, which is a known important good factor for the prognosis of APL.[10]

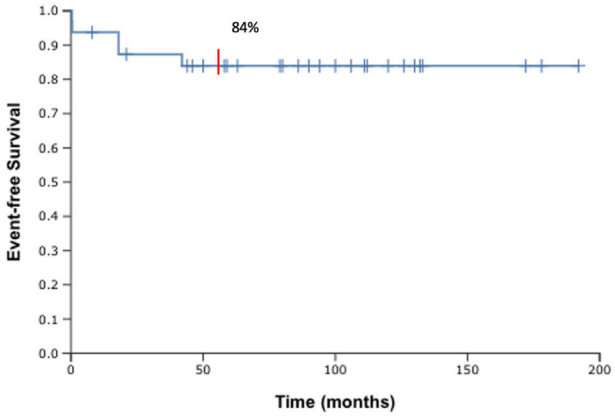
Also, it is now known that the periodic follow-up with RT-PCR for *PML/RARA* during maintenance therapy can detect relapses earlier and improve prognosis.[10] In pediatric patients, bone marrow evaluations are performed with sedation. Thus, risks of these sedated procedures must now be balanced with the benefit of such monitoring, particularly as patients are at a low risk for relapse. Although we did not perform this molecular analysis, our two children with relapsed disease are in continuous remission after salvage treatment, now for more than five years.

The major cause of mortality in APL continues to be early mortality due to bleeding/coagulopathy, differentiation syndrome and infection. Several pediatric groups report rates ranging from 3% to 13%. These numbers are independent of the type of treatment proposed and are also shown in the treatment with arsenic trioxide.[11] However, in Brazil and in low-income countries, early mortality rates as high as 32% have been described.[12] A survey conducted in a pediatric APL population of Recife showed an early mortality rate of 22%, while in Campinas, a rate of 13% was found.[13,14]

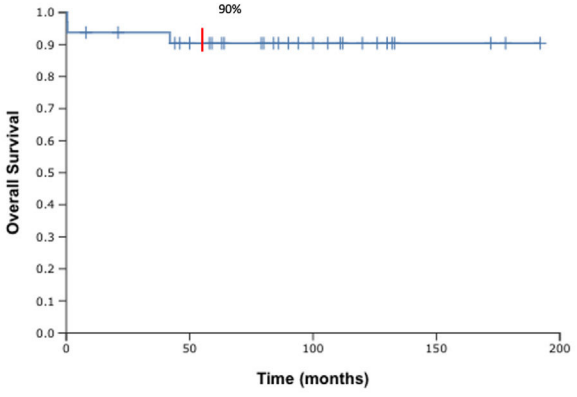
The rate found in this series of cases was 6%, being comparable to large multicenter studies. The two deaths found were secondary to coagulopathy and CNS bleeding, although one of them also had a diagnosis of differentiation syndrome. Both occurred more than 10 years ago, demonstrating our improvement in the management and support of these patients over the years.



a) Five-year event-free survival for all patients.



b) Five-year disease-free survival for all patients.



c) Five-year overall survival according to the presence of disseminated intravascular coagulation (Log rank $p = 0.03$).

Figure 2 – Survival (Kaplan-Meier curves). a). Five-year event-free survival for all patients.b). Five-year disease-free survival for all patients.c). Five-year overall survival according to the presence of disseminated intra-vascular coagulation (Log rank $p = 0.03$).

Most international protocols introduce anthracycline promptly in the first days of treatment, especially in those patients with leukocyte counts greater than 10,000/mm^3 at diagnosis, due to the risk of the differentiation syndrome. However, considering that coagulopathy mortality is the major cause of deaths in APL and that chemotherapy delivery in active leukemic promyelocytes can increase the risk of bleeding, our protocol proposes a delay in the onset of anthracycline. We believe that the promyelocytes already differentiated by the longer time of ATRA exposure can reduce this risk of bleeding, and thus we had a median start of chemotherapy after a mean of seven days. This approach may explain the lower rate of early mortality found in our service, when compared to other Brazilian centers.[13,14]

In our series, the only factor analyzed that had a negative impact on survival was the presence of DIC ($p = 0.03$). The DIC management is a challenging problem, especially in developing countries, in which insufficient supportive care and blood products are of real concern. This fact reinforces that bleeding is a major issue to be addressed to prevent early mortality and induction failure and thus, all efforts should be made to reduce this complication.

Our 5-years EFS and OS in 18 years of treatment were 84% and 90%, respectively. These results are comparable to great international collaborative protocols, such as AIDA, which showed 76% and 89% of EFS and OS, respectively.[15]

The results found are better than those reported by other small Brazilian groups and low-income countries, such as those from Recife (EFS 64%) and a collaborative study that included 12 Brazilian institutions (EFS 50%).[12,13]

We believe that the reduction of the maintenance period by one year caused no impairment of the results and that the non-use of cytarabine and postponing of the onset of anthracycline in induction may be a good strategy in low-income countries, where supportive therapy is limited, aiming to reduce early mortality rates. However, these treatment plans should be better analyzed and studied in a clinical trial setting.

This study presents some limitations because it is a retrospective study and limited to a single center, with a small sample size, causing limited statistical inferences.

Considering the benefits of the use of arsenic trioxide reported in the medical literature, despite our good results, we emphasize the strong urgency to seek socioeconomic alternatives that enable its use.

Conclusion

Our protocol proved to be feasible and possibly reproducible in resource-limited locations, while the use of less toxic and more efficient agents, such as the ATO, is not universally available.

Conflicts of interest

The authors declare that they have no conflicts of interest.

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