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Evolution of the Outcomes of Children with Acute Leukemia in Congo

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Abstract

Background: To lower the mori-mortality related to the aggressiveness of acute leukemia's chemotherapy regimens, we have implemented in 2017 two low toxicity chemotherapy regimens and new supportive care strategies. The aim of the study is to evaluate our new treatments. **Materials and Method:** A retrospective study was carried out from January 2014 to May 2021 in the hematology department of the teaching hospital in Brazzaville. The study concerned 47 children diagnosed with acute leukemia. Participants were divided into two groups: acute leukemia diagnosed before 2017 (group 1: 23 children) and after 2017 (group 2: 14 children). They were compared using the chi-square. **Results:** The median age was 10.0 ± 5.01 years. Features and outcomes of group 2 were better. The median duration of symptoms was shorter: 2.45 ± 2.87 months ($p = 0.036$). The Karnosky score was higher ($p = 0.002$) and white blood cell count lower ($p = 0.331$). Both groups started the treatment with a delay of 6 days. The induction treatment was completed in 69.6% before 2017 versus 93.3% after. The rate of relapse was more important for group 1: 85.7% versus 14.3% ($p = 0.01$). **Conclusion:** Trainings of professionals have improved the characteristics outcomes of our patients and should be pursued. Considering the high relapse rate, our protocol will need to be intensified.

Keywords

Childhood, Acute Leukemia, Outcomes

1. Introduction

The reported incidences of childhood cancers in Africa vary from 5% to 15% [1].

The survival of children is poor, related to the lack of capacity diagnosis, trained providers, and access to care. The distribution of malignant tumors throughout the continent differs depending on the country. In the Republic of Congo, for instance, acute leukemia stands as the most common malignant tumor in the child population [2] [3]. Its morbid-mortality rate is the highest among malignant hematological diseases and its outcome, the poorest [4]. The mobi-mortality is mainly associated with the agressiveness of western countries' chemotherapy regimens responsible for profound immunodeficiency [5]. The rate of complications in Congo is exacerbated by the poor hygiene standard of the hospital's environment, nonsustainability of blood products, and antibiotherapy.

In regard to that, we have taken multiple actions to improve the prognosis and quality of life of children with acute leukemia. We have implemented in 2017 new chemotherapy regimens trained our nurses on oncology care and increased our hygiene standards. These have led to a better management of both leukemia (lymphoblastic and myeloid) and have changed some features of childhood malignant.

The aim of our study is to review the clinical, biological and outcome features of patients with acute leukemia treated with low toxicity regimen chemotherapy.

2. Materials and Method

The study was conducted in compliance with the ethical standards of the responsible institution for human subjects as well as with the Helsinki Declaration.

We conducted a cross-sectional study during 7 years and 4 months in the hematology department in the University hospital in Brazzaville which is a tertiary and biggest healthcare facility in Congo.

We reviewed during the study period all records of children aged less than 21, diagnosed with acute leukemia and admitted in the hematology department. The diagnosis was made based on cytology studies of the bone marrow aspiration.

The period of study was divided into two subperiods: January 2014 to December 2016 (group 1) and from January 1, 2017 to May, 2021 (group 2).

The period from January 2014 to December 2016 was labelled before 2017 January, the one from January 2017 to May, 2021 was labelled after 2017.

All patients with acute leukemia (lymphoblastic and myeloid) admitted in the Hematology Department during the study period were included in the study.

For each patient we collected:
- epidemiological data: age, gender, and referral health facility;
- clinical features: length of medical history, health performance status; type of acute leukemia;
- Biological findings: Cell blood count;
- Treatment: type of chemotherapy, phase of treatment, toxicity related to chemotherapy and its delay;
- Outcome.

All information, epidemiological, clinical, biological, and outcome were extracted from participants' medical records.

Expenses including laboratory tests, chemotherapy, supportive therapy, and food are paid for by the patient's family. Chemotherapy for Acute lymphoblastic leukemia (ALL) consists of a low intensity regimen composed of vincristine, daunorubicin and dexamethasone, 6 mercaptopurine, methotrexate, intrathecal cytarabine, methotrexate and hydrocortisone for. It consists of a reduced dose of cytarabine arabinoside (CA) and daunorubicin for acute myeloid leukemia (AML). There are three different phases of treatment for ALL: Induction, consolidation, and maintenance while the treatment of AML has 3 phases: 2 induction, 2 consolidation, and maintenance.

Patients newly diagnosed with acute leukemia remain usually continuously admitted during induction and consolidation for ALL and 2 inductions and first consolidation for AML.

Patient loss of follow for a period of more than 6 months was recorded as dead.

Loss of follow refers to a patient that did not show up for a scheduled therapy up to 6 months.

The length of the medical history is defined as the period spanning from the onset of symptoms related to the acute malignancy to the admission to the hematology department.

Criteria for remission were less than 5% of blasts in the peripheral blood, no tumoral syndrome, absolute neutrophile ≥ 1 G/L, platelets ≥ 100 G/L. Relapse was defined as the recurrence of the disease after remission. The criteria were: recurrence of tumoral syndrome, leukocytosis and $\geq 5\%$ of blast in the peripheral blood.

Outcome is defined as the status of the patient at the end of the study period: December 31, 2016 for the participants in group 1 and May 30, 2021 for the participants in group 2.

3. Statistical Analysis

The data were analyzed by the software R version 4.0.0. The count data are presented as frequency (percentage) and the differences between groups were assessed using the chi square test. Quantitative were presented as the mean ± standard deviation.

4. Results

A total of 47 patients (32 in group1 and 15 in group 2) were included in the study.

The global median age was 10.0 ± 5.01 years.

There were 33 (70.2%) males and 14 females (29.8%).

The median duration of symptoms was longer before 2017: 4.88 ± 4.74 months versus 2.45 ± 2.87 months after 2017 (p = 0.036).

The median health performance status at admission was determined by the Karnosky score. Nine patients (19, 1%) scored 40 - 50 in group 1, while all patients had a score at 70 in group 2 (p = 0.002). Cell blood count showed that the white blood cell count was lower after 2017: 57.5 ± 51.2 G/L versus 76.2 ± 77.5 G/L before 2017 (p = 0.331). The median hemoglobin rate was 3.31.0 ± 1.41 g/dL before 2017 and 7.34 ± 2.22 g/dL after 2017. The platelet rate was respectively, 71.5 ± 43.5 and 78.49 ± 22.46 G/L in the group 1 and 2 (p = 0.201). The average follow-up time for both groups was 5.74 ± 9.91 months (Table 1).

During the study period, the median time to initiate treatment for each group was 6.36 ± 6.62 days. Thirty-seven out (37) of 47 (78.7%) have started chemotherapy. Among them, 69.6% in group 1 completed the first step of the treatment (69.6%) while 93.0% completed it in group 2.

The lethality rate was significantly lower in the group children (group 2) treated with low toxicity regimen: 50% versus 70.8% (p = 0.01).

The causes of death were: toxicity related to chemotherapy (94.12%) and relapse (5.88%) in group 1 versus relapse (85.71%) and toxicity related to chemotherapy (14.29%) in group 2 (p = 0.01) (Table 2).

Table 1. Patient characteristics.

	After 2017 (group 2)	Before 2017 (group 1)	Total	p-value
	N = 15	N = 32	N = 47	
AGE	10.9 ± 4.93	9.59 ± 5.06	10.0 ± 5.01	0.397
M n (%)	11 (73.3%)	22 (68.8%)	33 (70.2%)	
Referral health facility Tertiary hospital	7 (46.7%)	3	10	0.001
Secondary hospital	5 (33.3%)	28	33	
Private practice	3 (0.2%)	1	4	
F n (%)	4 (26.7%)	10 (31.2%)	14 (29.8%)	1.000
LAL	10 (6.67%)	28 (21.9%)	8 (17.0%)	0.065
LAM	5 (6.67%)	0 (0.00%)	1 (2.13%)	
Time since diagnosis (month)	2.45 ± 2.87	4.88 ± 4.74	4.10 ± 4.36	0.036
Karnosky score:				0.002
40 - 50	0 (0.00%)	11 (34.26%)	9 (19.1%)	
70	**15 (100%)**	**12 (37.5%)**	**27 (57.4%)**	
80 - 100	0 (0.00%)	9 (11.25%)	2 (4.26%)	
WBC (G/L) Moy ± sd	57.5 ± 51.2	76.2 ± 77.5	70.3 ± 70.2	0.331
Hb (G/L)	7.34 ± 2.22	3.31.0 ± 1.41	5.11.0 ± 3.21	
Platelet (G/L)	78.9 ± 22.5	71.5 ± 43.5	74.7 ± 33.5	
Follow up in month	5.92 ± 4.79	5.65 ± 11.6	5.74 ± 9.91	0.910

Table 2. Patients' treatment and outcome.

	After 2017	Before 2017	Total	p-value	N
	N = 14	N = 24	N = 38		
Time to initiate CT (day)	6.38 ± 8.25	6.35 ± 5.71	6.36 ± 6.62	0.989	37
Induction completed	14 (93.33%)	16 (69.56%)	30		
Consolidation completed	6 (40%)	7 (30.44%)			
Maintenance completed	1 (6.67%)	0 (00%)			
Outcome				0.001	
Alive	4 (33.30%)	0 (00%)	4		
Loss of follow	3 (19.97%)	7 (24.15%)	10		
Death	7 (50%)	17 (70.33%)	24		
Cause of death				0.01	
Relapse	6 (85.71%)	1 (5.88%)			
Toxicity of CT*	1 (14.29%)	16 (94.12%)			
Delay of toxicity	49.9 ± 35.9	11.0 ± 4.84	22.5 ± 26.3	0.018	
Delay of death	118 ± 106	38.3 ± 27.1	45.5 ± 41.8	0.047	

*Chemotherapy.

5. Discussion

Two -year survival rate of children with acute leukemia in Sub-Saharan Africa is very low [6]. It is due to the lack of diagnosis capacities, supportive therapies, low accessibility to cancer drugs, shortage of physicians, and nurses trained in oncology. Intensive therapy in conjunction with supportive therapy has increased survival rates more than 70% and 80% for ALL and AML in high resource countries [7] [8]. In low resource countries, like the Congo, myelosuppressive therapies are associated with a high rate of toxic death [5]. Taking into account our limitations and challenges to treat children with acute leukemia, we have offered training to professionals and implemented low toxicity protocols to increase the survival rate of our patients.

The Congo is located in Central Africa with a population of 5.2 million inhabitants. Most of the population is concentrated in its two largest cities, Brazzaville and Pointe Noire. Brazzaville has one teaching or university hospital established since 1999; it includes the department of hematology. In the last decade, the number of hematologists has increased from 2 to 7 for the whole country. Six of them have been appointed to the teaching hospital in Brazzaville. It has contributed to the reduction of the workload and creation. Since 2016, Brazzaville Medical School offers hematology education and training to residents. It has contributed to the reduction of the workload and the creation of a team that has carried out multiple reflections and innovations such as education. Training courses have made health providers more aware of acute leukemia, its symptoms, and treatment. In the present report, we are assessing our actions and new

strategy management of the malignant disease by comparing two periods: before and after 2017. The study was conducted in the COVID-19 context, which has significantly reduced the number of patients admitted in 2020 and 2021.

We did not find any difference in the average age at the onset of acute leukemia. It is a malignant hematology disease that affects most frequently children in their first decade [3] [9] [10]. Awareness sessions on the disease have significantly reduced the diagnostic time by nearly 2 and a half months after 2017 (p = 0.038). This resulted in a better clinical feature at the time of diagnosis. All patients scored 70% after 2017, while 34% had a score below 60% (p = 0.002) before that period. The prognosis was also more favorable as the peripheral white blood cell count was lower (p = 0.331). However, in both groups the number of leukocytes was over 50 giga/L. It is associated with the low survival rate [11] [12] [13].

We have implemented interprofessional consultations with government-owned peripheral hospitals that are geographically and financially more accessible to the population. The goal was to build hematology expertise in the secondary professional health facilities and decentralize the diagnostic point. As a result, after 2017, they became the first referral health facilities. Peripheral hospitals referred 87.5% suspected cases of acute leukemia to the university hospital versus 46% before 2017.

In average, the initiation time for acute leukemia treatment regimens is 6 days. The Congolese government does not subsidize treatment of cancer, nor does it offer a medical insurance program. Therefore, the cost of chemotherapy is the major obstacle to begin it. Most patients 'families cannot afford it or go into debt to purchase drugs for the first phase of treatment. They usually turned away for the second phase of it. The time to begin chemotherapy is also linked to the unavailability of certain cancer drugs such as L-Asparaginase, idarubicine, and etoposide. Therefore, considering these limited factors and the high morbi mortality related to chemotherapy, in 2016, we have implemented two low toxicity protocols to treat acute leukemia. All patients diagnosed with ALL were treated with the modified Hunger protocol without L-asparaginase [14]. All patients with AML were treated with adjusted doses of CA and daunorubicin. The reduced cost of the new regimens has increased the number of patients under treatment. Fourteen out of fifteen children (93.3%) have been able to start it versus 71.9% before 2017 with conventional treatment. However, long-term funding remains an issue. Indeed, if ninety 93.3% have completed the first phase of the treatment versus 69.3%, the rate dropped at 40% versus 30.4% for the second phase of treatment [p = 0.989]. Twenty percent of our patients were loss of follow which is slightly lower than what had been noticed before 2017 (p = 0.01). Treatment abandonment was relatively low in Tanzania (8%) and Rwanda (10%) probably because cancer drugs were donated to patients [6] [15]. Additional patient social support such as transportation and boosting consultation in the case of other malignant hematological have helped to reduce the rate of loss

of follow to 0.5% [10] [16].

The poor outcome observed in both groups after completion of the consolidation was related to factors that vary depending on the intensity of the regimen administered. As expected, the low toxicity protocol was associated with a high relapse rate: 85.5%, the highest reported. The lack of L-Asparaginase in our ALL's protocol may have worsened the prognosis since the drug is known to significantly increase the complete remission and survival rate [6]. Death related toxicity in group 1 accounted for 11.1%, which is lower when we compare with Kersen *et al.*, in Tanzania (26%) [6].

In the standard protocol group (group 2), death-related toxicities were without surprise, the major source of death: 88.9%. They occurred precociously during the treatment induction. In our unit, hospital-acquired infections are the main related toxicity treatment observed [5]. They increase substantially medical expenses and delay the initiation of the second phase of treatment which is source of relapse.

Our different interventions have improved the outcomes of children with acute leukemia. The survival rate at one year is very low in Africa [16] [17] [18]. Nevertheless, we have noticed a significant progress in the outcomes of our patients [6] [10]. The death delay has increased from 38.3 ± 27.1 to 118 ± 106 days (p = 0.047). At one year of follow-up, only 3 patients were alive. One was under complete remission (maintenance) and the other two under treatment consolidation.

Our study has some limits. The COVID-19 outbreak and confinement restrictions have reduced the number of patients admitted from March to September 2020. The high rate of loss of follow could have led to incomplete data and bias in our results.

Despite these limits, this first study describes the clinical, biological features, treatment, and outcomes of patients with acute leukemia. Many actions have been taken to improve the survival rate and quality of life of our patients. The delay of diagnosis has been reduced, patients have better feature, however the nutritional characteristics are some aspects we should have studied. The low toxicity regimen did not substantially improve the outcomes of our patients since the protocols were not complete. However, the progress was significant in other aspects such as treatment abandonment, delay of survival, and related toxicity deaths. Thus far, with limited resources at our disposal, we have been able to improve the care of children with acute leukemia. We are confident that with the help of our government and non-governmental organizations, significant results will be achieved.

6. Conclusion

The low chemotherapy regimens have improved the quality of life of children with acute leukemia but increased the rate of relapse, which advocates to gradually increase our treatment.

Consent

Written informed consent was obtained from the parents of the patients for publication of this study.

Data Availability

The data used to support the findings of this study are available from the corresponding author upon request.

Authors Contribution

Ngolet Lydie coordinated the field study and conducted the study and analyzed the data. Simo Josué Luokdom, Alexis Fortuné Bolenga Liboko, Firmine Olivia Galiba Atipo Tsiba, Alexis Elira Dokekias reviewed the draft. All authors read and approved the final manuscript.

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Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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