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OUTCOMES AND CLINICAL FEATURES OF PEDIATRIC AML AT ADDIS ABABA TERTIARY HOSPITAL: A RETROSPECTIVE CROSS-SECTIONAL STUDY

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Abstract
Acute Myeloid Leukemia (AML) in pediatric populations accounts for 15-20% of all acute leukemias, with recent studies from African cancer registries indicating a prevalence of 20-25% (de Rooij et al., 2015; Molyneux et al., 2017; Kassahun et al., 2020). However, comprehensive data on pediatric AML incidence in Ethiopia remains limited. AML's etiology involves a combination of genetic and acquired/environmental risk factors, though the exact age at presentation varies. A review of literature shows a median presentation age of 7.4 years, with ranges from 8 months to 15.8 years (Viana et al., 2003), and variations in mean and median ages across studies (Ghafoor et al., 2020; Van Weelderen et al., 2021). Clinical characteristics, such as malnutrition prevalence, initial white blood cell counts, and morphological subtypes, also vary widely. For instance, a Brazilian study reported a malnutrition rate of 29.4%, with a median initial white blood cell count of 23.3×10^3/mm^3, and the most frequent morphologies being M2 (35%) and M3 (22%) (Viana et al., 2003). This study aims to fill the gap by evaluating the clinical features and induction outcomes of pediatric AML patients at a tertiary referral hospital in Addis Ababa, Ethiopia, using a retrospective cross-sectional approach.

INTRODUCTION

Among pediatric acute leukemias, 15 to 20% was acute cancer registries from African hospitals showed 20 to myeloid leukemias (de Rooij et al., 2015). Reports from 25% were acute myeloid leukemias (Molyneux et al., 2017; Kassahun et al., 2020) and in Ethiopia the incidinece in children was not studied. Risk factors for its development are genetic and acquired/environmental. Several risk factors have been described in literature (Pizzo et al., 2016). The approximate age at presentation remains to be determined as data's are pausing on this matter. A single institution study showed the median of age at presentation was 7.4 years (range from 8 months to 15.8 years); and of these 19.3% were greater than 12 years (Viana et al., 2003). Others report the mean and median age at diagnosis of 6.30 ± 3.66 years and 5.5 months to 13 years respectively (Ghafoor et al., 2020; Van Weelderen

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et al., 2021). Symptoms, signs and laboratory values reported in different studies were also divergent. A 15-years' experience in a single institution in Brazil reports a total of 83 pediatric AML patients with the following clinical characteristics: malnutrition prevalence of 29.4% using Mora method, initial WBC count of $23.3\times10^3/mm^3$ and the most common morphology being M2 FAB class (35%) and M3 FAB class (22%) (Viana et al., 2003). In a children's cancer group study (2013), from a total of 498 patients, splenomegaly, hepatomegaly and chloroma were present in 193 (39%), 190 (38%) and 30 (6%) respectively. The most common FAB morphology was M2 (27%) and M4 (26%); and 84% of patients had WBC $<100,000\times10^3/mm^3$, 48% had Hgb <8g/dl and 82 % had platelet count of $>20,000/mm^3$ (Wells et al., 2002). A report by Tariq et al, found that pallor, fever and bleeding/bruising were the presenting symptoms in descending order of frequency; and similarly on physical examination pallor, organomegaly and proptosis were the most detectable findings in that order of frequency. In the study, mean WBC, Hgb and platelet counts were $53.28\pm68.27\times10^3/mm^3$, $7.66\pm2.55g/dl$, $58.41\pm81.68\times10^3/mm^3$ respectively. The M2 and M4 morphology were the most common FAB sub-types in the study (Ghafoor et al., 2020) Figure 1. The induction outcomes observed, including complications of treatment, across setups were far worse in low- and middle-income countries (Van Weelderen et al., 2021). According to Nicole A. McNeer et al, induction failure occurred in 10-15% of cases and of whom 33% achieved remission upon re-induction (McNeer et al., 2019). Lower complete remissions were documented in those with platelet count of $< 20,000/mm^3$, palpable liver, FAB M5 morphology, male gender (Wells et al., 2002). Experience from developing countries showed failed induction was associated with presence of malnutrition, elevated white blood cell counts of $>50,000/mm^3$, FAB M0 and adding etoposide in induction regimen, but other variables like platelet count were not associated with failed induction (Viana et al., 2003; Ghafoor et al., 2020). Death during or after induction is the main challenge and it is highly associated with poor supportive care with transfusion, administration of anti-infective medications, and lack of ICU care. Such practices are widely and specifically available in high income countries and have profound effect on induction mortality (Gupta et al., 2012). For many reasons low-income countries have a high rate of induction mortality (Van Weelderen et al., 2021).

METHODOLOGY

Study area

The study was conducted at Tikur Anbessa Specialized Hospital, School of Medicine, College of Health Sciences, Addis Ababa University and is the largest referral hospital in Ethiopia. It was established in 1964, and is now the main teaching center for both clinical and preclinical training of most disciplines. It is also an institution where specialized clinical services that are not available in other public or private institutions are rendered to the whole nation. It serves as the only tertiary hospital where pediatric AML patients are being treated with Haemato-oncologist till recently.

Study design and patient selection

A retrospective study was conducted from July 2016 to August 2020 and data was collected cross-sectionally from June to September 2021. A total of 38 pediatric AML patients were included in this study and the included patients were bone marrow-confirmed pediatric AML patients aged 0 to 15 years who took induction chemotherapy and had post induction bone marrow aspiration results. Patients who were not commenced on induction chemotherapy were excluded from the study. Bone marrow aspirations were done to examine the presence of myeloblasts and myeloblasts with Auer rods and azurophilic granules confirming the presence of AML. Patients who had myeloblasts greater than 20% were classified further using FAB morphological classifications. Flow cytometry and cytogenetic studies were not available during the study period. Upon confirmation of the diagnosis, patients were put on induction regimen with: Cytarabine 100 mg/m^2 daily as intravenous infusion for 07 days and Doxorubicin 50 mg/m^2 daily as intravenous infusion for 03 days (7+3

protocol) or Cytarabine 100mg/m2 IV twice daily as intravenous infusion from Days 1 to 10, Doxorubicin 50mg/m2 IV infusion on Days 1, 3 and 5 and Etoposide 100mg/m2 IV infusion from Day1 to 5 (ADE protocol). For acute promyelocytic (APML) patients: ATRA (All Trans Retinoic Acid) 25 mg/m^2 per day in two divided doses, Doxorubicin 50 mg/m^2 IV push on each of days 3 through 6 (four days) and Cytarabine 200 mg/m^2 daily as a continuous infusion for days 3 through 9 (seven days) was used as induction regimen. Supportive medications given were ciprofloxacin, cotrimoxazole, acyclovir and fluconazole. Transfusion with blood (whole or packed), platelet and fresh frozen plasma were also administered whenever indicated. No separate ICU care was available while induction treatment. Response was assessed after repeat bone marrow done one month after the beginning of the protocol; and if blasts in the bone marrow have decreased by more than 95% or blasts <5%, and for APML: in addition to the above, absence of Auer rods in blasts, then the patient was considered to have complete response (CR).

Data collection

Individual patient charts were retrieved from card room after getting names and medical record numbers from inpatient registry. Data were collected using structured form that contained socio demographic and clinical characteristics, induction chemotherapy outcomes (including remission status, morbidity and mortality). Variables included in the data collection form were obtained after extensive literature search of similar studies. Socio-demographic and clinical characteristics included were patients age, sex, address, duration of symptom, patient reported symptoms, and physical examination findings with focus on hepatomegaly, splenomegaly and chloromas. Laboratory data collected were leukemic morphology using FAB classification and patients initial white blood cell (WBC), platelet and hemoglobin values. Type of protocol used for induction chemotherapy and co-morbidities (infection and nutritional status) were also extracted. Post induction remission status and post induction mortality and morbidities (like infection and tumor lysis syndrome) were also included in the data collection process.

Table 1. Socio-demographic characteristics of the patient admitted to TASH Haemato-Oncology unit with AML, 2016 – 2020.

Variables		Frequency	%
Sex	Male	21	55.3
	Female	17	44.7
	Total	38	100
Age (years)	0-2	4	10.5
	2-10	23	60.5
	10-20	11	28.9
	Total	38	100
Region	Oromia	14	36.8
	Amhara	11	28.9
	Addis Ababa	7	18.4
	SNNPR	4	10.5
	Somali	2	5.3
	Total	38	100

Table 2. Clinical characteristics of the patient in admitted to TASH HaematoOncology unit with AML 2016 to 2020.

Variables		**Frequency**	**%**
	<10,000	13	34.2
	10,000-99,000	15	39.5
WBC count	>100,000	10	26.3
	Total	38	100
	<20,000	14	36.8
Platelet count	>20,000	24	63.2
	Total	38	100
	Fatigue	29	76.3
	Nasal bleeding	1	2.6
Initial symptoms	Orbital swelling	6	15.8
	Abdominal swelling	2	5.3
	Total	38	100
	Yes No	15	39.5
Palpable liver		23	60.5
	Total	38	100
	Yea No	12	31.6
Palpable spleen		26	68.4
	Total	38	100
	Yea No	6	15.8
Chloroma		32	84.2
	Total	38	100
	Mo	1	2.6
	M1	5	13.2
	M2	12	31.6
FAB	M3	5	13.2
	M4	12	31.6
	M5	3	7.9

	Total	38	100
	Normal	31	81.6
	MAM SAM	2	5.3
Malnutrition		5	13.2
	Total	38	100
	Infection	25	65.8
Infection or death	Dead	5	13.2
before induction	No	8	21.1
	Total	38	100

Table 3. Pediatric AML induction outcome, Ethiopia, 2016-2020.

Variables		**Frequency**	**%**
	>5%	11	33.3
OUTCOME-Remission	<5%	22	66.7
	Total	33	100
	Infection	20	60.6
Treatment related morbidity or death after	Died	10	30.3
induction	TLS	2	6.1
	No	1	3.0
	Total	33	100
		28	84.8
PROTOCOL	7+3 APML	4	12.1
	ADE	1	3.1
	Total	33	100

WBC-white blood cell, PLT-platelet, HGB- hemoglobin, DUR-duration of illness OUT- induction outcome FAB=French American British, NUTR- nutrition, LIV- liver, SPL- spleen, CHL- chloroma.

Data analysis

Data was cleaned and entered into Epi data version 3.1 and exported to SPSS version 25 for analysis. Output data were reported as mean, median standard deviation for continuous data and percentage was used for categorical one. Association between independent and dependent variables was assessed with P-value less than 0.05.

Ethical issue

The research was conducted after obtaining approval from the Ethical Review Board of the Institution. Data was collected from secondary sources which were the patients' charts; and the issue of consent from patients and /or parents was not needed. Data were collected based on declaration of Helsinki excluding patient card number and names and ensuring strict confidentiality.

Table 4. Correlation between various variables and pediatric AML induction outcomes, 2016-2020.

Induction outcome	
AGE	0.10237
WBC	-0.10812
HGB	0.102104
PLT	0.18132574
DUR	0.210793
FAB	0.249149
NUTR	0.170717
LIV	-0.18365
SPL	-0.17148
CHL	0.076932
SEX	0.16855

RESULTS

Socio-demographic characteristic of pediatric AML patients treated at Tikur Anbessa Specialized Hospital

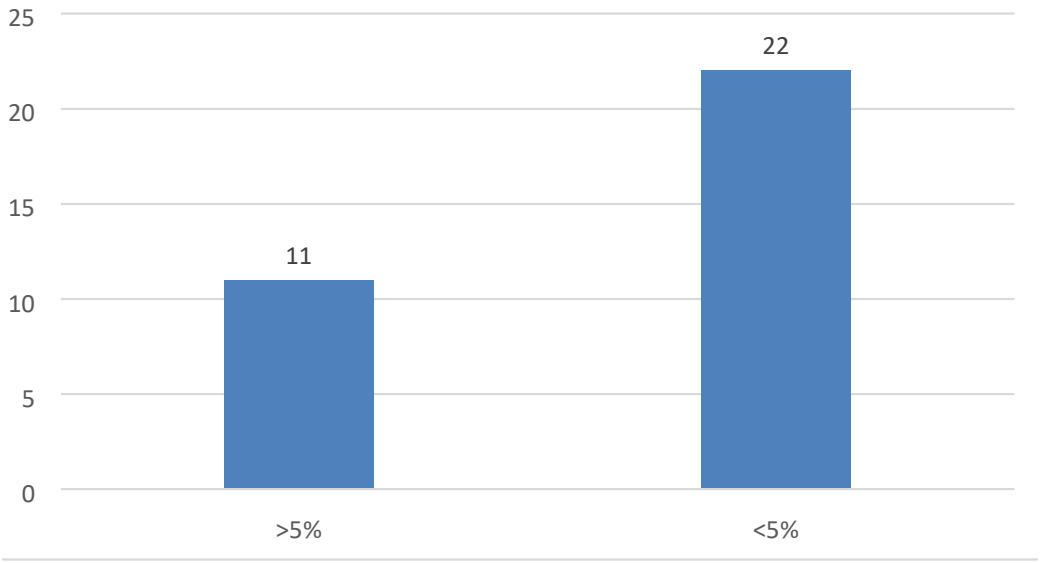
A total 38 pediatrics AML patients were included in this study; 21 (55.3%) were males with a male to female ratio of 1.23:1. The mean age of the patients at diagnosis was 8.003 ±3.76 years with the range of 8 months to -15 years old. Most of the children came from Oromia region, accounted for 36.8% of children and 28.9 % of children were from Amhara region (Table 1).

Clinical Characteristics of pediatrics AML patients

The median duration of illness was 30 days and ranged from 20.75 to 90 days. Majority of patients presented with fatigue, accounted for 29 (76.3%), the other presentations were orbital swelling in 6 (15.8%), abdominal swelling in 2 (5.3%) and nasal bleeding in 1 (2.6%). Physical examination revealed hepatomegaly in 15 (39.5%), splenomegaly in 12 (31.6%) and chloroma in 6 (15.8%) cases. Severe acute malnutrition (SAM) was observed in 5 (13.2%) and Moderate Acute Malnutrition (MAM) in 2(5.3%).The median WBC count was 39.2 $\times 10^3/mm^3$ ranged from 6.05 to 79.7 $\times$ $10^3/mm^3$. White blood cell count above 50,000/mm^3 was observed in 15 (39.5%) patients. The median hemoglobin was 6.65 g/dL, ranging from 4.67-8.82 g/dl. The median platelets count was 25.5$\times$ $10^3/mm^3$, ranging from 16.25 $\times 10^3$ - 66.25$\times 10^3$ /mm^3. Initial platelet count of less than 20×10^3 /mm^3 was observed in 36.8% of patients. Regarding the FAB morphology 12 patients had M2 (31.6%) and M4 (31.6%) morphology, followed by M3 in 5 (13.2%), M1 in 5 (13.2), M5 in 3 (7.9%) and M0 in 1(2.6%) (Table 2).

Induction outcome of children with AML

For all patients, 7+3 protocol chemotherapy was started for 28 (84.8%), Acute promyelocytleukemia protocol to 4 (12.1%) and ADE to 1(3.1%) case. Induction mortality occurred in 10 (30.3%) of pediatrics AML patients (Tables 3 and 4). Bone marrow aspiration done at 1 month of induction showed 22 (66.7%) patients achieved morphological complete remission and 33.3% patients had failed remission. Infection occurred in 20/33(60.6%) of patients, tumor lysis syndrome (clinical and lab) occurred in 2/33 (6.1%) (Figure 1).



REMISSION

Figure 1. Outcome of AML patients after induction in TASH Haemato-Oncology unit, 2016-2020.

Correlation

In this study, we found a weak negative correlation between WBC count, hepatomegaly, splenomegaly and outcome of induction. In subsequent regression model, no variable was statistically significant. Similarly, there was a weak positive correlation between platelet count, FAB morphology, nutritional status, age, hemoglobin concentration, and induction outcome. With multiple logistic regression model, the variables were not statistically significant.

DISCUSSION

Data on pediatric AML is lacking in Ethiopia. Reports from systematic review of literature and Pakistanian study showed median and mean age of 5.5-13 years and 6.3±3.66 years respectively. These reports are consistent with the current study where we found mean age range from 8.003± 3.76 years with the range of 7 months to 15 years with little effect on the outcome of induction chemotherapy as described in their study (Ghafoor et al., 2020; Weelderen et al., 2021). The disease affects more males with no much effect on treatment outcomes like other studies (Viana et al., 2003; Ghafoor et al., 2020; Weelderen et al., 2021). Late presentation to the cancer treatment center was observed in the current study but the effect was not significant in terms of induction outcome or treatment related mortality. The most common presenting symptom reported was fatigue followed by abdominal swelling and bleeding, which was consistent with available literatures (Wells et al., 2002). In the study we have found that the median WBC count was 39.2 x 10^3 /mm^3 with IQR of 6.05 x 10^3-79.7 x 10^3 which was consistent with other studies (Viana et al., 2003; Ghafoor et al., 2020; Gupta et al., 2012; Inaba et al., 2008). Severe anemia is frequently observed (hemoglobin of 3.6g/dl) with median hemoglobin of 6.65g/dl (IQR 4.678.82g/dl), which is in line with previously published reports that shows being anemic is not a predictor of induction outcome, rather a predictor of treatment-related mortality and morbidity (Gupta et al., 2012; Inaba et al., 2008).

In our study we have found that 24/38 (63.2%) patients have platelet count of >20x10^3 /ul and 14/38(36.8%) have <20x10^3/ul and most studies report higher platelet count. (Ghafoor et al., 2020; Wells et al., 2002; Gupta et al., 2012) FAB M2 and M4 morphological sub-types were the commonest subtype identified in this study which is similar to other studies (Weelderen et al., 2021; Wells et al., 2002; Gupta et al., 2012; Rasche et al., 2018; Rubnitz et al., 2004; Molgaard-Hansen et al., 2010; Slats et al., 2005; Draga et al., 2006; Testi, 2005; Stéphane et al., 2004; Ortega et al., 2005; Kutny et al., 2017). In our study, complete morphologic remission rate was 66.7%, this is

much lower as compared to developed countries (Barbara et al., 2019; Tierens et al., 2016; Rubnitz et al., 2010) owing to the presence of high quality supportive care in these countries,but it is the same as low middle income countries (Van Weelderen et al., 2021) and even higher than sub-saharan African countries (Kersten et al., 2013; Weelderen et al., 2021; Nzamu et al., 2020) which can be explained by the enhanced supportive care given ,though not readily available, with anti-infective medications and transfusion services. Post induction death (30.3%) and Infectious morbidity (60.6%) were very high as compared to other studies (Viana et al., 2003; Wells et al., 2002; Ghafoor et al., 2020; Van Weelderen et al., 2021; McNeer et al., 2019; Gupta et al., 2012.), this is attributed to the lack of isolated ward and unavailability of isolated ICU care. Studies showed high initial WBC count, low platelet count, presence of malnutrition and FAB M5 morphology were associated with failed remission (Viana et al., 2003; Ghafoor et al., 2020; Wells et al., 2002). In our study we found no statistically significant association for the above variables, and this might be due to the small sample size studied and the retrospective nature of the study. Although it was not the scope of the current study, we encourage further prospective cohort studies to explore variables that significantly affect induction outcome.

CONCLUSION AND RECOMMENDATION

The median duration of illness in children with AML was 30 days and presented to haemato-oncology center as late as 90 days. Primary health care professionals should be vigilant of any abnormal blood values and should refer them for appropriate diagnosis and care. The mortality rate in pediatric patients with AML is high and is mainly attributed to infection; hence isolated care is highly recommended and effective interventions have to be practiced to prevent infections and subsequent deaths. Low platelet count at presentation resulted in failed induction. Optimizing blood product transfusion practices is crucial for preventing bleeding outcomes and to achieve a successful remission induction.

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CONFLICT OF INTERESTS

The authors have not declared any conflict of interests.

REFERENCES

Barbara De M, , Reedijk A, De Bock GH, Lammens T, de Haas V, Denys B, Dedeken L, van den Heuvel_Eibrink MM, Te Loo M, Uyttebroeck A, Van Damme A (2019). Response_guided chemotherapy for pediatric acute myeloid leukemia without hematopoietic stem cell transplantation in first complete remission: results from protocol DB AML_01. Pediatric blood and cancer 66(5):e27605-e27605. de Rooij J, Zwaan C, van den Heuvel-Eibrink M (2015). Pediatric AML: From Biology to Clinical Management. Journal of Clinical Medicine 4(1):127-149.

Draga B, Alonzo TA, Gerbing RB, Soheil M, Heerema NA, Barnard D, Lange BJ, Woods WG, Arceci RJ, Smith FO (2006). Minimally differentiated acute myeloid leukemia (FAB AML-M0) is associated with an adverse outcome in children: a report from the Children's

Oncology Group, studies CCG-2891 and CCG-2961. Blood 109(6):2314-2321.

Ghafoor T, Khalil S, Farah T, Ahmed S, Sharif I (2020). Prognostic Factors in Childhood Acute Myeloid Leukemia; Experience from a Developing Country. Cancer Reports 3(5).

Gupta S, Bonilla M, Valverde P, Fu L, Howard SC, Ribeiro RC, Sung L (2012). Treatment-related mortality in children with acute myeloid leukaemia in Central America: incidence, timing and predictors. European Journal of Cancer (Oxford, England: 1990) 48(9):13631369.

Inaba H, Fan Y, Pounds S, Geiger TL, Rubnitz JE, Ribeiro RC, ChingHon P, Razzouk BI (2008). Clinical and biologic features and treatment outcome of children with newly diagnosed acute myeloid leukemia and hyperleukocytosis. Cancer: Interdisciplinary International Journal of the American Cancer Society 113(3):522-529.

Kersten E, Scanlan P, DuBois SG, Matthay KK (2013). Current treatment and outcome for childhood acute leukemia in Tanzania. British Journal of Haematology 60(12):2047-2053.

Kutny MA, Alonzo TA, Gerbing RB, Yi CW, Raimondi SC, Hirsch BA, Fu C, Soheil M, Gamis AS, Feusner J, Gregory J (2017). Arsenic Trioxide Consolidation Allows Anthracycline Dose Reduction for Pediatric Patients With Acute Promyelocytic Leukemia: Report From the Children's Oncology Group Phase III Historically Controlled Trial AAML0631. Journal of Clinical Oncology 35(26):3021.

McNeer NA, Philip J, Geiger H, Ries RE, Lavallée V-P, Walsh M, Shah M, Arora K, Emde A-K, Robine N, Alonzo TA, Kolb EA, Gamis AS, Smith M, Gerhard DS, Guidry-Auvil J, Meshinchi S, Kentsis A (2019). Genetic mechanisms of primary chemotherapy resistance in pediatric acute myeloid leukemia. Leukemia 33(8):1934-1943.

Molgaard-Hansen L, Möttönen M, Glosli H, Jónmundsson GK, Abrahamsson J, Hasle H (2010). Early and treatment-related deaths in childhood acute myeloid leukaemia in the Nordic countries: 19842003. British Journal of Haematology 151(5):447-459.

Molyneux E, Scanlan T, Chagaluka G, Renner L (2017). Haematological cancers in African children: progress and challenges. British Journal of Haematology 177(6):971-978. Kassahun W, Tesfaye G, Bimerew LG, Fufa D, Adissu W, Yemane T (2020). Prevalence of Leukemia and Associated Factors among Patients with Abnormal Hematological Parameters in Jimma Medical Center, Southwest Ethiopia: A CrossSectional Study. Advances in Hematology 2020:1-7.

Nzamu I, Ssenyondwa J, Naitala R, Akullo A, Ankunda S, Kashaigili H, Omeddo D, Nakiddu N, Namazzi R, Munube D, Kasirye P,

Bakulumpagi D, Naturinda E, Lubega J, Wasswa P (2020). Feasibility of evidence-based treatment of childhood acute myeloid leukemia in a Sub-Sahara Africa center. Journal of Clinical Oncology 38(15_suppl):e22508-e22508.

Ortega JJ, Madero L, Martín G, Verdeguer A, García P, Parody R, Fuster J, Molines A, Novo A, Debén G, Rodríguez A, Conde E, de la Serna J, Allegue MJ, Capote FJ, González JD, Bolufer P, González M, Sanz MA (2005). Treatment with All-Trans Retinoic Acid and Anthracycline Monochemotherapy for Children

with Acute Promyelocytic Leukemia: A Multicenter Study by the PETHEMA Group. Journal of Clinical Oncology 23(30):7632-7640.

Pizzo PA, Poplack DG, Adamson PC, Blaney SM, Helman L (2016). Principles and practice of pediatric oncology. Wolters Kluwer.

Rasche M, Zimmermann M, Borschel L, Bourquin J-P, Dworzak M, Klingebiel T, Lehrnbecher T, Creutzig U, Klusmann J-H, Reinhardt D (2018). Successes and challenges in the treatment of pediatric acute myeloid leukemia: a retrospective analysis of the AML-BFM trials from 1987 to 2012. Leukemia *32*(10):2167-2177.

Rubnitz JE, Inaba H, Dahl GV, Ribeiro RC, Bowman WP, Taub JW, Pounds S, Razzouk BI, Lacayo NJ, Cao X, Soheil M, Degar BA, Gladstone A, Raimondi SC, Mihaela O, Coustan-Smith E, Downing JR, Leung W, Ching-Hon P, Campana D (2010). Minimal residual disease-directed therapy for childhood acute myeloid leukaemia: results of the AML02 multicentre trial. Lancet Oncology 11(6):543552.

Rubnitz JE, Lensing S, Zhou Y, Sandlund JT, Razzouk BI, Ribeiro RC, Ching-Hon Pui. (2004). Death during induction therapy and first remission of acute leukemia in childhood. 101(7):1677-1684.

Slats AM, Egeler RM, van der Does-van den Berg A, Korbijn C, Hählen K, Kamps WA, Veerman AJP, Zwaan CM (2005). Causes of death – other than progressive leukemia – in childhood acute lymphoblastic (ALL) and myeloid leukemia (AML): the Dutch Childhood Oncology Group experience. Leukemia 19(4):537-544.

Stéphane de B, Valérie C, Chevret S, Rayon C, Vilmer E, Sanz MA, Javier P, André BN, Leverger G, Robert A, Miguel CE, Sotto J-J, Bron D, Fegueux N, Fey MF, Parry A, Chomienne C, Laurent D (2004). Outcome of Childhood Acute Promyelocytic Leukemia with All-Trans-Retinoic Acid and Chemotherapy. Journal of clinical oncology 22(8):1404-1412.

Testi AM (2005). GIMEMA-AIEOPAIDA protocol for the treatment of newly diagnosed acute promyelocytic leukemia (APL) in children. Blood 106(2):447-453.

Tierens A, Bjørklund E, Sanna S, Hanne VM, Gitte W-J, Tarja-Terttu P, Forestier E, Henrik H, Kirsi J, Lausen B, Jonsson OG, Palle J, Zeller B, Fogelstrand L, Abrahamsson J (2016). Residual disease detected by flow cytometry is an independent predictor of survival in childhood acute myeloid leukaemia; results of the NOPHO-AML 2004 study. British Journal of Haematology 174(4):600-609.

Van Weelderen RE, Klein K, Natawidjaja MD, De Vries R, Kaspers GJ (2021). Outcome of pediatric acute myeloid leukemia (AML) in low- and middle-income countries: a systematic review of the literature. Expert Review of Anticancer Therapy 21(7):765-780. van Weelderen RE, Njuguna F, Klein K, Mostert S, Langat S, Vik TA, Olbara G, Kipng'etich M, Kaspers GJL (2021). Outcomes of pediatric acute myeloid leukemia treatment in Western Kenya. Cancer Reports 5(10).

Viana MB, Cunha KCCMS, Ramos G, Murao M (2003). Acute myeloid leukemia in childhood: fifteen-year experience in a single institution. Jornal de Pediatria 79(6):489-496.

Wells RJ, Arthur DC, Srivastava AK, Heerema NA, Michelle LB, Alonzo TA, Buxton A, Woods WG, Howells WB, Benjamin DR, Betcher DL, Buckley JD, Feig SA, Kim T, Odom LF, Ruymann FB, Smithson WA, Tannous R, Kenneth JW, Wolff LJ (2002). Prognostic variables in newly diagnosed children and adolescents with acute myeloid leukemia. Children's Cancer Group Study 213. Leukemia 16(4):601607.