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Received: 23 April 2019 | Revised: 21 October 2019 | Accepted: 30 October 2019

DOI: 10.1002/pbc.28087

Pediatric Blood & Cancer | SIOP International Society of Paediatric Oncology | aspho The American Society of Pediatric Hematology/Oncology | WILEY

SPECIAL REPORT

SIOP PODC adapted risk stratification and treatment guidelines: Recommendations for acute myeloid leukemia in resource-limited settings

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Abstract

In low- and middle-income countries (LMICs), limited resources, suboptimal risk stratification, and disproportionate patient-to-infrastructure ratio result in low survival of patients with acute myeloid leukemia (AML). A high incidence of relapse, inherent to the biology, renders management arduous. The challenge of treating AML in LMICs is of balancing the intensity of myelosuppressive chemotherapy, which appears necessary for cure, with available supportive care, which influences treatment-related mortality. The recommendations outlined in this paper are based on published evidence and expert opinion. The principle of this adapted protocol is to tailor treatment to available resources, reduce preventable toxic death, and direct limited resources toward those children who are most likely to be cured.

KEYWORDS

acute myelogenous leukemia, acute nonlymphoblastic leukemia, chemotherapy, developing country, low and middle income, protocol, treatment

1 | INTRODUCTION

Acute myeloid leukemia (AML) accounts for 15% to 20% of all childhood leukemias, but it causes more than half of the disease-related deaths because of treatment toxicity and disease progression.[1] Each year, an estimated 15 000 to 20 000 children develop AML worldwide.[2,3] Treatment-related morbidity and treatment-related mortality (TRM) represents a significant challenge in pediatric AML worldwide. In low- and middle- income countries (LMICs), mortality associated with initial disease and treatment can be up to 50%.[4–6]

Abbreviations: 6-TG, 6-thioguanine; AML, acute myeloid leukemia; APML, acute promyelocytic leukemia; CNS, central nervous system; CR, complete response; CSF, cerebrospinal fluid; DA, daunorubicin and cytarabine; DAG, daunorubicin, cytarabine, and G-CSF; EFS, event-free survival; G-CSF, granulocyte colony-stimulating factor; HDAC, high-dose cytarabine; HIC, high-income country; HSCT, hematopoietic stem cell transplantation; i.v., intravenous; LMICs, low- and middle-income countries; MAG, mitoxantrone, cytarabine, and G-CSF; OS, overall survival; PODC, Pediatric Oncology in Developing Countries; PR, partial response; s.c., subcutaneous; SIOP, International Society of Pediatric Oncology; TIT, triple intrathecal chemotherapy; TLS, tumor lysis syndrome; TRM, treatment-related mortality; WBC, white blood count; WHO, World Health Organization.

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In a 3-year study from Tanzania, the 2-year event-free survival (EFS) for 25 children with AML was 0%.[7] In a report from Bangladesh, of 39 patients, a high abandonment (46%) and TRM (38%) compromised the outcome of children with AML.[6] The 5-year EFS was 30.8% in a retrospective cohort (2000-2014) of 154 children with AML from Brazil.[8] In contrast, in resource-rich countries, this mortality has been between 2% and 5% in recent years.[9–11] In a review of data from India, 50% to 80% of treated patients had experienced an adverse event (toxic death, refractory disease, or relapse).[12] In addition, many patients had opted not to start treatment.[12] In a 10-year follow-up survey of treatment abandonment of children with AML in Suzhou, China, 264 of the 474 (55.7%) cases examined abandoned therapy.[13] Pediatric AML has been described as "the final frontier with poor outcomes in the developing world.[14]" The treatment of AML comprises induction of remission followed by intensive consolidation therapy with the use of chemotherapy alone or in combination with allogeneic hematopoietic stem cell transplantation (HSCT).[15] Chemotherapy courses for remission induction and consolidation are typically accompanied by an extended period of myelosuppression during which there is significant morbidity and mortality.[16] High toxic death rates (with intensive chemotherapy protocols), high relapse rates (with less intense protocols), and treatment abandonment are substantial barriers to improving outcomes for pediatric AML in LMICs.[14]

We developed these recommendations for the adapted management of AML in children and adolescents younger than 18 years. The guidelines are based on the framework for tailored treatment regimens to manage pediatric cancer in LMICs that was established previously by the Pediatric Oncology in Developing Countries (PODC) Committee of the International Society of Pediatric Oncology (SIOP).[17] Obstacles to adapting treatment regimens to local conditions are multifactorial; they include (a) unwillingness to digress from published regimens used in high-income countries (HICs), for historical or cultural reasons, or the misconception that "more is better"; (b) a lack of published evidence about adapted regimens; (c) insufficient local data on which to base realistic adaptations because of a lack of hospital-based registries and regular audits of locally treated patients; (d) perceived ethical concerns about using a less intense regimen; (e) physicians in LMICs having insufficient time and expertise to adapt a regimen to local conditions; and (f) concern over inappropriate use of hospital resources, for example, having patients with relapsed disease occupying hospital beds while patients with low-risk malignant disease are kept on a waiting list.[17]

It is now well understood and accepted that if the relapse rate with a given therapy is excessive then the treatment may need intensification; however, if toxic death rates are too high, deintensification may save more lives, pending the enhancement of supportive care.[17] While drafting the guidelines, we faced the constant hurdle of a lack of evidence for adapted regimens for AML in LMICs. The difficulty regarding the lack of evidence has been well addressed by Howard et al.[17] It can be argued that using an adapted regimen that has not been validated by results from clinical trials represents a deviation from standard care and, therefore, will comprise research. However, applying a protocol developed and evaluated only in HICs without adaptation for LMICs is also a deviation from standard care, because the treatment setting is dissimilar and limitations on supportive care and specific treatment modalities in LMICs can render an HIC regimen inappropriate and unsafe.[17]

This document does not include guidelines for the management of acute promyelocytic leukemia (APML) or AML in children with Down syndrome. These are considered separate entities that require different treatment protocols.[18,19]

2 | METHODS

An AML writing group was established under the auspices of the Adapted Treatment Regimen Working Group of the SIOP PODC Committee. The writing group consisted of pediatric hemato-oncologists with experience in treating AML in LMICs and HICs. The group met online as well as face to face. Recommendations were circulated for peer review and were discussed at SIOP PODC meetings. This guideline has been ratified by the SIOP Scientific Committee. The recommendations of the PODC AML writing group are based on a review of the available published evidence for the management of AML reported from LMICs, which was assembled using PubMed search ranging 16 years (2003-2019). The PubMed search terms included "acute myeloid leukemia," "low-income country," "middle-income country," "limited resource setting," and "PODC." Individual country–specific searches using the names of known LMICs (as defined by the World Bank) and "AML" were also performed. Using this evidence, along with selected conference abstracts and expert opinion, the writing group developed the guideline for managing AML. The adapted treatment regimen framework established by the SIOP PODC Adapted Treatment Regimen Working Group was applied to define each treatment setting (Table 1). These guidelines are applicable mainly for level 2 settings. We do not recommend treating AML with curative intent in level 0 or level 1 settings, except in specific circumstances (in which case the current recommendations are applicable, particularly the prephase and low-dose induction regimen). The adapted regimen is not meant for use in level 3 or 4 settings. These guidelines outline recommendations based on the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) hierarchy criteria from Guyatt et al[20,21] (Table 2).

3 | TREATMENT GUIDELINES

3.1 | Diagnosis

A bone marrow examination is performed to confirm the diagnosis. It is a good practice to ensure safe hemoglobin (approximately ≥7-8 g/dL) before performing a bone marrow examination under general anesthesia. The condition of some patients with AML, particularly those presenting with hyperleukocytosis, may be too unstable for bone marrow evaluation; in such cases, the diagnosis can often be confirmed based on peripheral blood studies.[22] Morphology and flow cytometry are used for diagnosis. In the absence of flow cytometry, diagnosis is by morphology and cytochemistry. The World Health

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TABLE 1 Infrastructural and resource setting levels for selection of SIOP PODC adapted regimens for acute myeloid leukemia[14]

Service	Level 0	Level 1	Level 2	Level 3	Level 4
General description					
Pediatric cancer unit general description	Pilot project	Some basic oncology services	Established pediatric oncology program with most essential services and a few state-of-the-art services	Pediatric oncology program with all essential services and most state-of-the-art services	Pediatric oncology center of excellence with all state-of-the-art services and some highly specialized services (eg, access to phase I studies)
Typical settings	Centers in LICs in disadvantaged areas	Larger health care centers in LICs, disadvantaged areas in lower MICs	Larger health care centers in lower MICs, disadvantaged areas in upper MICs	Many centers in upper MICs, most centers in HICs	Some tertiary and quaternary care centers in HICs
Medical facilities					
Ward	No pediatric oncology unit	Basic pediatric oncology service available to some patients	Pediatric oncology unit available to most patients; isolation rooms usually available for infected patients	Pediatric oncology unit with a full complement of fixed staff and available to all patients; isolation rooms always available for infected patients	Specialized pediatric oncology units for particular groups of patients (eg, transplant, neuro-oncology, acute myeloid leukemia)
Intensive care availability	None	Intensive care unit present; limited equipment; personnel with limited pediatric experience; frequently delayed access	Mechanical ventilators, inotropes, central venous access; occasionally delayed access	Pediatric intensive care unit with all necessary equipment and personnel, readily accessible to all patients	Availability of extracorporeal membrane oxygenation
Outpatient facilities	None	Accessible to some patients sometimes	Outpatient area for chemotherapy and some emergency care available most of the time	Full-service outpatient care available 24 h/day for chemotherapy and emergencies, surgery, and diagnostic imaging	Outpatient satellite facilities available to provide care close to home
Diagnosis, risk-stratification, and therapeutic capabilities					
Hematopathology availability	None	Microscope, H&E staining, CSF cytology	Limited immunohistochemistry panel (disease specific), flow cytometry and cytogenetics available most of the time	Flow cytometry of high quality; minimal residual disease testing; molecular pathology and cytogenetics; pediatric expertise	Research diagnostics, whole-genome sequencing, molecular pathology for all diseases
Drug access	Dependent entirely on out-of-pocket payment or NGO support	Often dependent on out-of-pocket payment or NGO support	Basic drugs provided by the health system; more expensive drugs may depend on private insurance or NGO support	Most oncology drugs provided by the health system or private insurance available to most patients	Full access to all drugs by all patients
Venous access	Peripheral i.v. access	Mainly peripheral i.v. access; PICC available to some patients	Central venous access and a care plan for patients with a central line available to some patients	Central venous access and a care plan for patients with a central line available to all patients	
Blood product availability	Whole blood; frequent delays in access	Some blood products available sometimes for some patients; no irradiation/filtration possible	Red blood cells, platelets, cryoprecipitate, and fresh frozen plasma often available; irradiated/filtered blood products sometimes available	Ready availability of all blood products, including pheresed platelet units; routine access to irradiated/filtered blood products	

(Continues)

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TABLE 1 (Continued)

Service	Level 0	Level 1	Level 2	Level 3	Level 4
Personnel					
Nursing	No nurses with oncology training; no experience with oncology patients	Nurses with no specialized oncology training; some experience with cancer patients	Nurses with some dedicated oncology training and experience (eg, the ability to handle chemotherapy); oncology nurses not permanently assigned to the oncology unit; nurse educator available sometimes	Nurses with oncology training and experience who are permanently assigned to the pediatric cancer unit; nurse educators available	Highly specialized pediatric cancer nurses with disease-specific expertise
Pharmacists	None	Pharmacist in the hospital to dispense medications, but not available to prepare chemotherapy	Pharmacist available to prepare most chemotherapy	Dedicated oncology pharmacist with expertise preparing chemotherapy and monitoring drug safety	Highly specialized pediatric oncology pharmacists with expertise with specific patient groups

Abbreviations: CSF, cerebrospinal fluid; H&E, hematoxylin and eosin; HICs, high-income countries; LICs, low-income countries; MICs, middle-income countries; NGO, nongovernmental organization; PICC, peripherally inserted central line; PODC, Pediatric Oncology in Developed Countries.

TABLE 2 Grading of recommendations[20,21]

Grade of recommendation	Clarity of risk/benefit	Quality of supporting evidence	Implications
1A			
Strong recommendation, high-quality evidence	Benefits clearly outweigh risk and burdens, or vice versa	RCTs without important limitations or overwhelming evidence from observational studies	Strong recommendation, applies to most patients in most circumstances without reservation
1B			
Strong recommendation, moderate-quality evidence	Benefits clearly outweigh risk and burdens, or vice versa	RCTs with important limitations (inconsistent results, methodological flaws, indirect analyses or imprecise conclusions) or exceptionally strong evidence from observational studies	Strong recommendation, applies to most patients in most circumstances without reservation
1C			
Strong recommendation, low-quality or very low quality evidence	Benefits clearly outweigh risk and burdens, or vice versa	Observational studies or case series	Strong recommendation but subject to change when higher quality evidence becomes available
2A			
Weak recommendation, high-quality evidence	Benefits closely balanced with risks and burden	RCTs without important limitations or overwhelming evidence from observational studies	Weak recommendation, best action may differ depending on the patient, treatment circumstances, or social values
2B			
Weak recommendation, moderate-quality evidence	Benefits closely balanced with risks and burden	RCTs with important limitations (inconsistent results, methodological flaws, indirect or imprecise) or exceptionally strong evidence from observational studies	Weak recommendation, best action may differ depending on the patient, treatment circumstances, or social values
2C			
Weak recommendation, low-quality or very low quality evidence	Uncertainty in the estimates of benefits, risks, and burden; benefits, risk, and burden may be closely balanced	Observational studies or case series	Very weak recommendation; alternative treatments may be equally reasonable and merit consideration

Abbreviation: RCTs, randomized controlled trials.

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Organization (WHO) defines specific AML disease entities by cytogenetic and molecular genetic subgroups.[23] AML is a genetically and molecularly heterogeneous disease, as reflected in the 11 distinct entities that compose the WHO classification.[23,24] If APML is suspected by morphology or molecular characterization, treatment with all-trans retinoic acid and/or arsenic trioxide should be started, along with transfusion of blood products to avoid bleeding. APML is suspected if the following are present: >20% blasts being promyelocytes and myeloblasts, heavy granulation, prominent Auer rods, strong staining with myeloperoxidase, and immunophenotypic expression is CD34 negative/partial or weak positive, HLA-DR negative, CD13 and CD33 positive, CD11b negative, CD15 weak or negative, and CD117 weak/variable.[25] Cytogenetic confirmation of APML requires the demonstration of the t(15;17) translocation and/or PML/RARα fusion.

A lumbar puncture is performed only *after* prephase chemotherapy, at the beginning of induction course 1 (Recommendation 2 C). Cerebrospinal fluid (CSF) is submitted for cell count and morphology analysis (cytospin preparation) or flow cytometry. The extent of central nervous system (CNS) involvement is classified according to the standard definitions as CNS 1, 2, or 3, with CNS 3 indicating CNS disease.[26] Serum biochemistry (potassium, creatinine, calcium, phosphate, uric acid levels) is requested for evidence of tumor lysis syndrome (TLS).[27] Serologic evidence for human immunodeficiency virus, hepatitis B surface antigen, and anti-hepatitis C virus immunoglobulin is obtained. A chest X-ray is performed in patients to check for a mediastinal mass or pleural effusion that (a) indicates tumor load for risk of TLS, (b) forewarns for complications of airway and breathing during sedation for performing a bone marrow examination, or (c) to detect an infective focus particularly in a febrile patient. Incidental comorbid conditions, including malaria and tuberculosis, may be excluded depending on the local epidemiology.[28,29] Echocardiography at diagnosis is desirable but not mandatory.

3.2 | Risk stratification (Recommendation 1 C)

Cytogenetic characterization has widened the risk stratification of AML and has a significant bearing on the treatment. However, facilities for exploring genetic abnormalities in AML are limited in most centers in level 0, 1, or 2 settings. Also, centers in these settings are often unable to offer augmented therapy to most high-risk patients. If access to allogeneic HSCT is unlikely and the hospital infrastructure, supportive care, and financial resources for a second-line protocol are limited, performing a cytogenetic characterization may not be worthwhile.

3.3 | Management of AML in level 2 settings (Figure 1)

3.3.1 | Prephase chemotherapy (Recommendation 2 C)

We recommend a strategy of low-dose chemotherapy as a bridge to the standard treatment protocol. Beginning therapy "gently" is the standard of care in Burkitt lymphoma (prephase cyclophosphamide-vincristine-predniso(lo)ne) and acute lymphoblastic leukemia (steroid prephase). Physicians in level 2 settings may often have to deal with one or more of the following: (a) an active infection (bacterial, fungal, or undiagnosed) at diagnosis, rendering the patient unfit to tolerate standard chemotherapy; (b) noticeable mortality from febrile neutropenia, particularly after the first course of intensive chemotherapy[30]; (c) an undernourished patient; (d) a resource-constrained family; (e) the time required for arranging financial support from the government, a nongovernmental organization, or another resource; and (f) limited availability of hospital beds. Patients in such settings may have increased TRM if standard chemotherapy is administered upfront. However, the evidence supporting a metronomic approach to upfront chemotherapy in children with AML is limited.[31,32] In addition, there is concern regarding the development of resistance to chemotherapeutic drugs with the administration of low-dose chemotherapy. Nevertheless, it is anticipated that, in a level 2 setting, beginning treatment with inexpensive, low-intensity chemotherapy will result in reduced TRM and an overall improvement in survival. After the "prephase" chemotherapy, the bone marrow would be expected to be in partial remission, conceivably permitting the "standard" chemotherapy to be delivered more safely and with curative intent. The prephase can be administered on an outpatient basis. The additional time thus gained can be used to render the patient free from life-threatening infections (if any), to improve their nutrition and performance status, and to attain reasonable financial security for the family. In addition, it will help the family to make arrangements for a local stay, typically for an average of 4 to 6 months. This includes arranging accommodation near the treating center, settling job and leave concerns, and/or arranging for the care of the patient's siblings at home.

Two alternatives are listed for the prephase chemotherapy in this guideline. The reader may choose either option. The evidence regarding the optimal prephase treatment is limited; the authors urge colleagues working in LMICs to provide such evidence by first implementing a uniform protocol-based approach and then conducting randomized clinical trials. It is recommended to administer at least one cycle of either of the two options for the prephase chemotherapy before the start of induction course 1. Up to three cycles of prephase chemotherapy may be administered, based on an assessment of the clinical condition and socioeconomic circumstances of the patient.

Prephase chemotherapy: Option 1—PrET regimen (Recommendation 2 C)

This regimen has been reported by the Tata Memorial Hospital, Mumbai, India[31,32] (G. Narula, personal communication). It includes a combination of oral etoposide, 6-thioguanine (6-TG), and prednisolone as follows: (a) etoposide at 50 mg/m^2 orally once a day for 21 days, if oral preparation is unavailable, replace with intravenous (i.v.) etoposide at 50 mg/m^2 once a day for 7 days; (b) 6-TG at 40 mg/m^2 once a day for 21 days (if unavailable, replace with 6-mercaptopurine at 50 mg/m^2 once a day for 21 days); (c) prednisolone at 40 mg/m^2/day in two divided doses is added in the first 2 weeks (no tapering). If an invasive fungal infection is diagnosed, prednisolone is limited to 1 week. The cycle may be repeated after 1 week, for a total of up to three cycles, before starting standard chemotherapy, depending on the clinical or socioeconomic circumstances of the patient.

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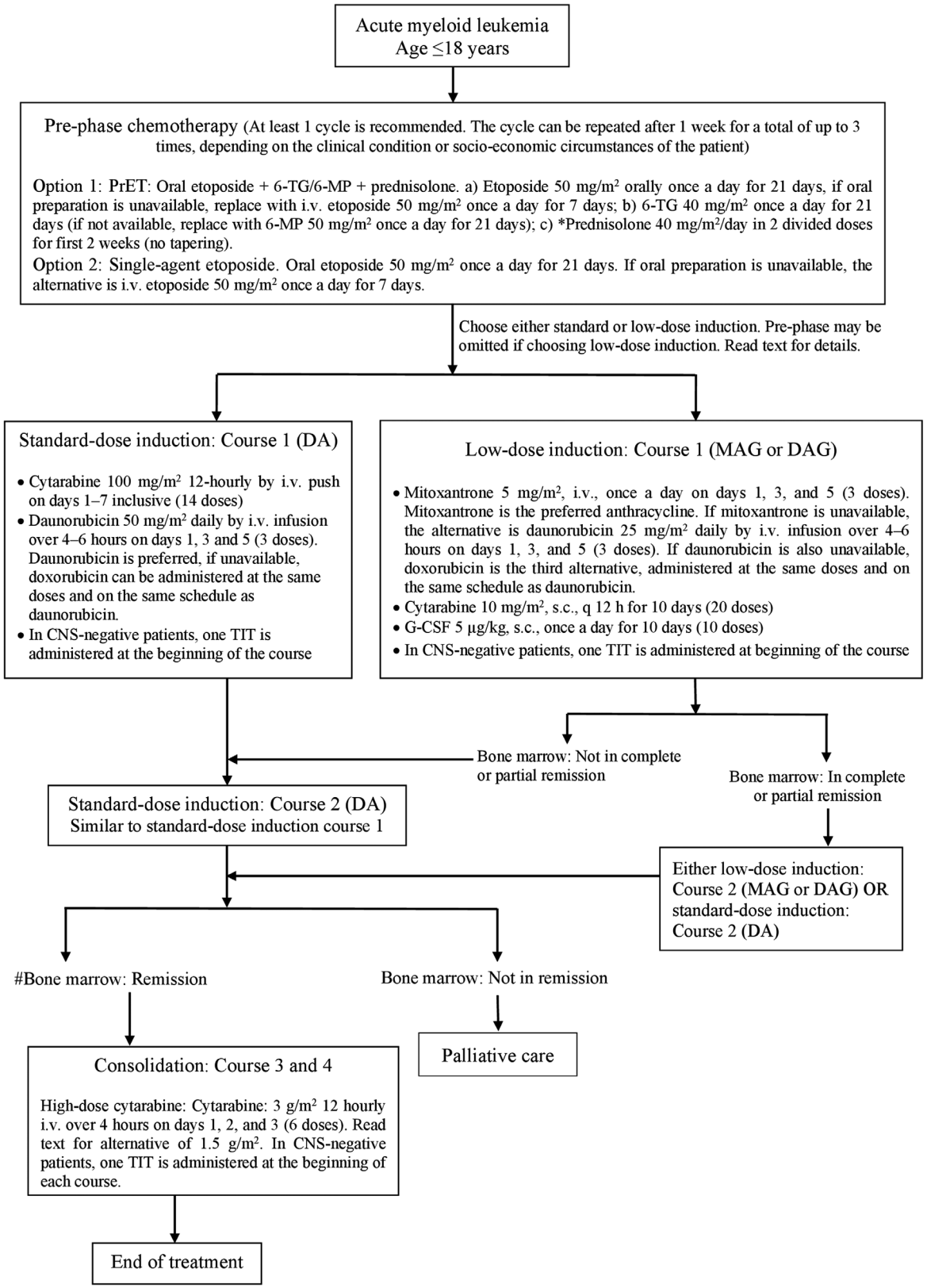

FIGURE 1 Flowchart of chemotherapy for acute myeloid leukemia in a level 2 setting

Note: See the text for details.

Abbreviation: TIT, triple intrathecal chemotherapy

*If an invasive fungal infection is diagnosed, the use of prednisolone is limited to 1 week

#Remission is defined as bone marrow with ≤5% blasts and with signs of normal regeneration; be aware of the possibility of normal regenerating blasts mimicking leukemic blasts

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Although steroids are typically not included in the armamentarium for AML, preclinical studies have demonstrated that glucocorticoids could be of considerable value in managing AML.[33–35] The development of cytarabine resistance in AML cells is associated with increased sensitivity to glucocorticoids.[34,35] Using a chemogenomic approach, Simon et al demonstrated that AML samples bearing inactivating *RUNX1* mutations are particularly sensitive to glucocorticoids.[36] Methylprednisolone has been reported to induce differentiation and apoptosis of myeloid leukemic cells in children with different subtypes,[37] although another in vitro study could not confirm this.[38] However, the latter study did demonstrate a glucocorticoid-induced proliferation of AML cells in a substantial subset of samples, suggesting a beneficial effect when combined with antiproliferative drugs.[38] More recently, in a French study, a short course of dexamethasone added to the induction chemotherapy for adult patients with AML and hyperleucocytosis resulted in improved survival ($P = .007$).[33]

Prephase chemotherapy: Option 2—Single-agent etoposide (Recommendation 2 C)

Etoposide is administered orally at 50 mg/m^2 once a day for 21 days. If oral preparation is unavailable, the alternative is to use i.v. preparation at 50 mg/m^2 i.v. once a day for 7 days. The cycle can be repeated after 1 week (for oral etoposide) or 2 weeks (for i.v. etoposide) for a total of up to three cycles before starting standard chemotherapy, depending on the clinical condition or socioeconomic circumstances of the patient.

Prevention of tumor lysis syndrome

Oral allopurinol is added for 1 week to the prephase chemotherapy. Intravenous hyperhydration is indicated for patients with hyperleucocytosis. TLS can often be prevented by encouraging the intake of oral fluids in children with AML with counts that are not "too high" ($<50 \times 10^9$/L).

Monitoring of blood counts

The patients' blood counts are monitored during the prephase chemotherapy and thereafter. The blood counts are monitored at 3- to 4-day intervals; the frequency of monitoring is tailored to the clinical condition of the individual patient. The hemoglobin is maintained above 8 g/dL during treatment. Bleeding is a significant cause of early death. Maintain the platelet count at more than 10×10^9/L in the first weeks, particularly if there is accompanying fever or sepsis.

3.3.2 | Induction chemotherapy

The induction includes two courses of chemotherapy.

Standard induction: Course 1 (Recommendation 1 C)

This includes daunorubicin plus cytarabine (DA).

1. Cytarabine at 100 mg/m^2 12-hourly by i.v. push on days 1 to 7 inclusive (14 doses in total).
2. Daunorubicin at 50 mg/m^2 daily by i.v. infusion over 4 to 6 h on days 1, 3, and 5 (three doses in total). For infants younger than 12 months or weighing ≤10 kg or with a body surface area (BSA) of <0.5 m^2, use daunorubicin at 1.67 mg/kg/dose, and cytarabine at 3.3 mg/kg/dose. Daunorubicin is preferred, however if unavailable, doxorubicin can be administered at the same doses and on the same schedule as daunorubicin.

Standard induction: Course 2 (Recommendation 1 C)

A bone marrow examination to check the status of remission after course 1 is not indicated in a level 2 setting as it will not influence the treatment plan. However, such an examination should be performed if there is nonrecovery of counts (neutrophil count of $<1.0 \times 10^9$/L and platelet count of $<75 \times 10^9$/L) by day 35 (the start of course 1 being counted as day 1). A nonrecovery of counts by day 35 could be due to an extended myelosuppressive effect of the chemotherapy, infection, or persistent leukemia. The bone marrow examination will reveal the marrow to be hypoplastic in the first two cases and infiltrated with a varying proportion of blast cells in the last case. Unless there is clear disease progression, it is recommended to proceed with course 2. It is essential to proceed with course 2 without delay, irrespective of the counts if the low counts are secondary to a nonattainment of remission by day 35. If the bone marrow is observed to be hypoplastic, but otherwise in remission, the counts are followed for recovery (neutrophil count of $>1.0 \times 10^9$/L and platelet count of $>75 \times 10^9$/L) for the administration of course 2. If the bone marrow is evaluated, one caveat is that there may be regeneration with normal blasts mimicking leukemic blasts. In such cases, repeat examination after 1 to 2 weeks may be useful. Course 2 of standard induction is similar to course 1 of standard induction (DA). Unequivocal disease progression after course 1 should lead to palliative care instead of intensive chemotherapy with curative intent.

Induction: Alternative low-dose protocol (MAG or DAG) (Recommendation 2 C)

The "standard" chemotherapy for AML induction has been noted to be associated with severe impairment of the normal bone marrow function, a high rate of toxic death, and a high economic burden for families in China.[39] The Children's Hospital of Soochow University, Suzhou, China, in collaboration with the Department of Oncology and Global Medicine, International Outreach Program, St. Jude Children's Research Hospital, Memphis, Tennessee, designed an alternative low-dose chemotherapy plus granulocyte colony-stimulating factor (G-CSF) induction protocol. The goal was to decrease TRM and treatment abandonment in patients with AML. The low-dose induction chemotherapy regimen included mitoxantrone, cytarabine, and G-CSF (MAG). G-CSF is intended to induce AML cell proliferation, rendering the cells more sensitive to antileukemic drugs. The EFS and TRM in patients treated with the MAG regimen ($n = 46$) were compared to those in patients receiving the standard-dose ($n = 94$) induction therapy followed by consolidation therapy. Allogeneic HSCT was included in the management of AML in high-risk patients. Patients treated with the MAG regimen experienced remission, and overall survival (OS)

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rates comparable to those of patients treated with the standard-dose therapy but with less toxicity and at a lower cost. In addition, the efficacy of the MAG regimen concerning molecular remission was similar to that of the standard-dose chemotherapy.[39,40] It was concluded that the MAG regimen represents a valuable alternative to standard induction chemotherapy.[39,40] However, the evidence supporting this conclusion is restricted to a small cohort of patients at a single center. Readers may choose to administer the low-dose (MAG) induction as an alternative to the standard-dose (DA) induction if the TRM and financial toxicity from the standard-dose protocol are expected to be a deterrent for a given patient. In addition, if the MAG regimen is chosen as induction course 1, the prephase may be omitted, depending on the general condition of the patient and other restraints as described above.

The low-dose induction (MAG) consists of the following:

1. Mitoxantrone at 5 mg/m^2, by i.v. infusion over 4 to 6 hours once a day on days 1, 3, and 5 (three doses in total). Mitoxantrone is the preferred anthracycline. If mitoxantrone is unavailable, the alternative is daunorubicin at 25 mg/m^2 daily by i.v. infusion over 4 to 6 h on days 1, 3, and 5 (three doses in total). If daunorubicin is also unavailable, doxorubicin is the third alternative, administered at the same dose and on the same schedule as daunorubicin.
2. Cytarabine at 10 mg/m^2, subcutaneous (s.c.), q 12 h for 10 days (20 doses in total).
3. G-CSF 5 μg/kg, s.c., once a day for 10 days (10 doses in total).

Induction course 2 in patients who receive MAG or DAG (Recommendation 2 C)

Patients who experience complete response (CR) (blast cells <5% by morphology in bone marrow with signs of normal regeneration) or partial response (PR) (5%-25% blasts in bone marrow) after receiving MAG or DAG as induction course 1 receive another course of MAG or DAG as induction course 2. Patients who do not experience CR or PR after receiving MAG or DAG receive the standard-dose regimen (DA) as induction course 2. It is also reasonable to administer the standard-dose regimen (DA) as induction course 2 in patients experiencing CR or PR after course 1 if the attending physician prefers this approach.

Patients who do not experience CR after course 2 of induction (Recommendation 1 C)

Most patients with AML in level 2 settings will not have access to HSCT. If CR is not attained after course 2 and HSCT is unavailable, the patient should receive palliative care, as a cure is not feasible with chemotherapy alone.

3.3.3 | Consolidation chemotherapy

A bone marrow examination is performed to check the status of remission upon count recovery (neutrophil count of >1.0 × 10^9/L and platelet count of >75 × 10^9/L) after course 2. It should nevertheless be performed by day 35, as nonrecovery of counts by day 35 could indicate nonattainment of remission. The bone marrow examination is unnecessary and should be avoided after course 2 if one was performed after course 1, and the patient had CR, provided a timely count recovery occurs. All patients who experience CR after course 2 of induction will receive consolidation (courses 3 and 4) chemotherapy. Course 3 should start on count recovery from course 2 (neutrophil count of >1.0 × 10^9/L and platelet count of >75 × 10^9/L) and when the patient is clinically well.

Consolidation: Courses 3 and 4: High-dose cytarabine (Recommendation 1 C)

Cytarabine: 3 g/m^2 12-hourly by i.v. infusion over 4 h on days 1, 2, and 3 (six doses in total). For infants younger than 12 months or weighing ≤10 kg or those with a BSA of <0.5 m^2: cytarabine: 100 mg/kg/dose. To prevent conjunctival and corneal pain, patients should receive prednisolone 0.5% eye drops (or dexamethasone 0.1% ophthalmic solution or a local equivalent) 2-hourly (one drop per eye) during high-dose cytarabine (HDAC) and for 2 days after the last dose of cytarabine. Course 4 consolidation should start on count recovery (neutrophil count of >1.0 × 10^9/L and platelet count of >75 × 10^9/L) from course 3 and when the patient is clinically well.

The German-Austrian AML Study Group compared a condensed HDAC regimen, 3 g/m^2 administered every 12 h on days 1, 2, and 3 (HDAC-123), with the commonly used HDAC regimen, 3 g/m^2 every 12 h on days 1, 3, and 5 (HDAC-135), in adult patients.[41] The time from the start of chemotherapy until hematologic recovery with a white blood cell (WBC) count of >1.0 × 10^9/L and a neutrophil count of >0.5 × 10^9/L was a median 4 days shorter in patients who received HDAC-123 compared to HDAC-135 ($P < .0001$ each). The rate of infections, days in hospital, and need for platelet transfusions were significantly lower for patients receiving HDAC-123 than for those receiving HDAC-135. Survival was not affected. The group concluded that a condensed schedule of HDAC on days 1, 2, and 3 for consolidation therapy in younger adult patients with AML appears to be preferable, resulting in faster hematologic recovery and fewer platelet transfusions, as well as a lower infection rate and fewer days in the hospital, without affecting the survival.[41] Also, HDAC-123 will help to reduce hospitalization by 2 days when compared to HDAC-135.

Alternative to cytarabine 3 g/m^2 for consolidation (Recommendation 2 C)

In the Medical Research Council AML15 trial, there were several randomization arms, including HDAC at 3 g/m^2 versus 1.5 g/m^2 for consolidation in adult patients with AML.[42] All children received HDAC at 3 g/m^2 and none was randomized to the 1.5 g/m^2 arm. A trend for a higher relapse risk in the 1.5 g/m^2 arm was observed, but the OS was not different. Considerably more supportive care and hospitalization were deployed in the 3 g/m^2 arm.[42] If the supportive care and resources are limited, and unacceptable morbidity and mortality with 3 g/m^2 of cytarabine is experienced or anticipated, the individual treating unit may consider administering cytarabine at 1.5 g/m^2 12-hourly by i.v. infusion over 4 h on days 1, 2, and 3 (a total of six doses) as an alternative to the conventional dose of 3 g/m^2.

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TABLE 3 Doses of intrathecal chemotherapy[46]

Age (years)	Methotrexate	Cytarabine	Hydrocortisone
<1	5 mg	15 mg	5 mg
1	7.5 mg	20 mg	7.5 mg
2	10 mg	25 mg	10 mg
>3 or over	12.5 mg	30 mg	12.5 mg

Note: Only preservative-free products and diluents are to be used for intrathecal administration. For intrathecal administration, dilute with 5 to 10 mL (or volume per institutional practice) preservative-free 0.9% sodium chloride injection or Ringer lactate injection. The volume of CSF removed should be equal to at least half the volume delivered.

3.3.4 | Management of CNS disease (Recommendation 1 C)

In children, CNS involvement at diagnosis has often not shown to worsen the prognosis.[26,43] However, a COG study of children with AML found that CNS involvement, particularly CNS3 status, was associated with inferior outcomes, including reductions in CR and EFS and an increased risk of CNS relapse.[44] CNS2 should not influence treatment, although the clearance of CSF should be documented at the next lumbar puncture. For most pediatric oncology groups, the treatment of CNS involvement includes triple intrathecal chemotherapy (TIT) combined with high-dose i.v. cytarabine.[43] However, treatment of the CNS with intrathecal medication has not yet been shown to contribute directly to an improvement in survival.[45] Neurologic deficits (such as cranial nerve palsy) and/or radiologic evidence of an intracranial or intradural mass consistent with a myeloid sarcoma are treated as CNS3.[46] TIT may be conveniently administered along with the bone marrow examination. The doses are illustrated in Table 3.[46]

Diagnostic CSF is performed at the start of induction course 1, *after* the prephase chemotherapy. Although a direct evidence to support delaying intrathecal chemotherapy is lacking, the authors suggest that performing CSF examination and administering intrathecal chemotherapy after the prephase chemotherapy is unlikely to worsen the survival, and instead may be beneficial in the setting of LMIC. In CNS-negative patients, one TIT is administered at the beginning of each of the four courses (for a total of four TITs). TIT includes the administration of age-appropriate doses of hydrocortisone, cytarabine, and methotrexate. If there is evidence of CNS3 disease, twice-a-week TIT is administered until the CSF is free of blast cells, with two additional TITs being administered after clearance. Subsequently, one TIT is administered at the beginning of courses 2, 3, and 4.

CNS irradiation is not necessary either as prophylaxis or for those patients presenting with CNS leukemia that clears with intrathecal and systemic chemotherapy.[45] CNS irradiation (24 Gy)[47] at the end of four cycles of chemotherapy is a reasonable alternative in older (>2 years) children if intensive administration of TIT is not considered feasible or if it was unsuccessful.

4 | SUPPORTIVE CARE

Metabolic, hemorrhagic, and infectious complications account for more than 80% of TRM. Progress in supportive care has been considered one of the most significant contributors to improved survival of pediatric AML in contemporary AML trials.[48] The components include prevention of infection, hand hygiene, antibiotic stewardship, antifungal and antibiotic prophylaxis, standard operating procedures for febrile neutropenia, nutrition, housing needs, in- versus outpatient management, venous access, social and financial support. A discussion of supportive care is beyond the scope of this report.

4.1 | Hyperleucocytosis

Hyperleukocytosis predisposes patients to the risk of mortality or serious complications due to leukostasis or hyperviscosity syndrome, coagulopathy, or TLS.[46] High-count leukemia is typically defined as a WBC of $>100 \times 10^9$/L except in monocytic AML (AML-M5), when a WBC of $>50 \times 10^9$/L may be problematic as the cells are large, tend to aggregate, and more readily result in coagulopathy.[46] A red cell transfusion may exacerbate leukostasis and should be avoided or limited until the WBC count has been reduced to a safe level. Hyperhydration, allopurinol, or, ideally, rasburicase, and monitoring of biochemistry are instituted in accordance with the local supportive care protocol. Patients are initiated on continuous i.v. hydration with potassium and calcium-free fluids (N/2 or N/4, 5% dextrose is appropriate), two to four times of normal maintenance. Typically, the fluids may be initiated at a rate that is twice the maintenance and can be increased in a symptomatic patient who persists to have a high WBC. The fluid rate depends on the tumor burden as well as the hemoglobin. If the hemoglobin is ≥7 g/dL, higher fluid volumes can be administered, while monitoring for fluid overload and urine output. If the hemoglobin is lower, fluid rate and volume should be decreased to avoid congestive heart failure.[49] Adequate urine output (≥2 mL/kg/h) should be ensured.[50]

The platelet count is maintained at $>50 \times 10^9$/L as long as hyperleukocytosis persists. Coagulopathy is corrected and fibrinogen is maintained at >1 g/L. A systematic review concluded that leukapheresis and low-dose chemotherapy do not reduce early mortality in AML.[51] Expertise and accessibility for leukapheresis may be limited in level 2 settings. In children with life-threatening anemia (eg, a hemoglobin level of < 5 g/dL) and hyperleucocytosis, exchange transfusion helps to increase hemoglobin safely.[49] In addition, exchange transfusion permits hyperhydration to be administered by ameliorating the risk of volume overload.

Hydroxyurea is frequently used in adult hematology practice before initiating the regular induction regimen to lower the tumor burden and reduce the risk of TLS.[52] However, there is no evidence that this approach is superior to immediate induction or that TLS can be prevented by a low-dose cytoreduction strategy.[52] Prompt initiation of cytoreductive treatment is mandatory and should not be delayed. We recommend the administration of prephase chemotherapy for the management of hyperleukocytosis as well. Frequent monitoring of counts, electrolytes, and renal function is done.

In a study from France, dexamethasone (10 mg b.i.d. for 3 days) was systematically added to induction chemotherapy for all adult patients with AML who had a WBC count of $>100 \times 10^9$/L or for patients with

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a WBC count of $>50 \times 10^9$/L and clinical symptoms of leukostasis.[33] Patients with APML were excluded from the study. There was no difference with respect to the induction death rate, response, and infections between the 60 patients in the dexamethasone group and the 100 patients in the no-dexamethasone group. Noticeably, multivariate analysis showed that dexamethasone was significantly associated with improved relapse incidence ($P = .001$), EFS ($P < .001$), and OS ($P = .007$).[33] Prospective randomized clinical trials are required to confirm the results of this study.

4.2 | Granulocyte colony-stimulating factor

Routine prophylactic use of G-CSF is not recommended for children with AML.[48] Contrasting results have been reported for its efficacy in preventing sepsis, but it does not affect survival.[53,54] There is a wide disparity in the prophylactic use of G-CSF for AML, but this practice is not uncommon, reflecting eager and desperate attempts to reduce the rate of infection in vulnerable patients.[55]

4.3 | Management of relapse and palliative care

A patient who experiences a relapse of AML in a level 2 setting is typically offered palliative care, with some individual exceptions. Management of pain and end-of-life care are the essential components of palliative care.

5 | CONCLUSION

We have provided treatment guidelines for pediatric AML that have been adjusted for level 2 centers operating in resource-limited settings. Given the virtual lack of evidence, these guidelines are mainly expert based. They do not apply to APML or myeloid leukemia in patients with Down syndrome. Because of the frequent need for bridge time, allowing more intensive treatment in hospitals in LMICs, we recommend a strategy of low-dose prephase chemotherapy. Because the available hospital beds are often limited, two different prephase regimens based on oral medication have been provided. There is insufficient evidence available to enable us to recommend one regimen over the other. After the prephase, more intensive—yet still adapted—induction therapy is indicated, and we have recommended conventional combinations of cytarabine with daunorubicin. However, there still may be a need to administer lower dose chemotherapy, and we have described such low-intensity induction chemotherapy as well. Depending on the treatment response, measured by morphologic bone marrow evaluation, consolidation therapy is administered in the form of two cycles of HDAC as a single agent. In total, patients will receive at least four cycles of chemotherapy, and most patients will have received prephase chemotherapy as well. Patients who have not experienced complete remission after induction treatment are considered incurable and are offered palliative care. Finally, we have also provided guidelines for treating CNS disease. To enable more evidence-based guidelines in the future, we urge colleagues working in LMICs to treat children and adolescents with AML according to a given protocol. This should then be followed by a systematic evaluation of the results and its publication in peer-reviewed journals such as this one. Resource-limited circumstances need not translate into less rigor in patient care and clinical research.[56,57] Pediatric AML is potentially curable with conventional chemotherapy in most patients. Our aim is for these treatment guidelines to contribute to improved outcomes for children and adolescents with AML in resource-limited settings.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

ACKNOWLEDGMENT

The authors thank Keith A. Laycock, PhD, ELS, for scientific editing of the manuscript.

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How to cite this article: Bansal D, Davidson A, Supriyadi E, Njuguna F, Ribeiro RC, Kaspers GJL. SIOP PODC adapted risk stratification and treatment guidelines: Recommendations for acute myeloid leukemia in resource-limited settings. *Pediatr Blood Cancer*. 2023;70:e28087. https://doi.org/10.1002/pbc.28087

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