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Case Report

Childhood cancer care beyond the 'six common and curable types': A comparative case series on acute myeloid leukemia in Kenya and the Netherlands

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ABSTRACT

Annually, over 400,000 children develop cancer, with the majority living in low- and middle-income countries (LMICs). Survival rates in high-income countries (HICs; ≥ 75%–80%) significantly exceed those in LMICs (< 30%). Acute myeloid leukemia (AML) is a childhood cancer with high mortality rates in LMICs and is not included in the World Health Organization (WHO)'s 'six common and curable types of cancer'. This case report explores two pediatric AML cases in Kenya (LMIC) and the Netherlands (HIC), highlighting differences and similarities in both patient journeys. The first case is a 15-year-old Kenyan boy who initially experienced dizziness and fatigue. After repeated blood transfusions without a definitive diagnosis, AML was confirmed via bone marrow aspiration (BMA) 63 days later, and treatment followed the SIOP PODC AML guidelines for LMICs. The second case is a 6-year-old Dutch boy with fatigue and malaise. Initially diagnosed with post-viral bone marrow failure, a BMA performed 61 days after symptom onset revealed AML, and treatment followed the NOPHO-DBH AML-2012 protocol. Both patients faced frequent febrile neutropenia, managed per local guidelines, illustrating the balance between anti-cancer treatment and supportive care. Despite challenges, both boys completed treatment and are in complete remission. This case series highlights the potential for effective AML treatment in resource-constrained settings and underscores the need to address cancers beyond the 'six common and curable types'.

Introduction

Cancer is the most common cause of death by a non-communicable disease in children globally.[1] Worldwide 429,000 children are estimated to develop cancer each year.[1] Around 90% of children affected by cancer live in low- and middle-income countries (LMICs).[1,2] Chances of survival in LMICs are significantly lower (< 30%)[3] compared to those in high income countries (HICs), where survival rates exceed 75%.[2,4] To reduce the inequity in childhood cancer survival, the World Health Organization (WHO) launched the Global Childhood Cancer Initiative in 2018.[2] The aim of this initiative is to improve childhood cancer survival rates globally to at least 60% for the six common and curable types of cancer. These cancers include: acute lymphoblastic leukemia (ALL), Burkitt lymphoma, Hodgkin lymphoma, retinoblastoma, nephroblastoma and low-grade glioma.[3] What does this imply for the many other forms of childhood cancer in LMICs?

Acute myeloid leukemia (AML) accounts for 15% to 20% of acute leukemia in children[5] and is not included in the six common and curable types of cancer.[2] Worldwide, yearly about 20,000 children develop AML,[5] and survival rates of pediatric AML are currently nearly 80%,[4] whereas survival rates in LMICs often fall below 30%, mainly caused by high toxic death rates.[6] AML is a heterogeneous disease, characterized by uncontrolled clonal proliferation of myeloid blasts.[7] Development of normal blood cell lines is hampered, causing clinical symptoms such as

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petechiae (indicating thrombopenia), pallor and fatigue (indicating anemia), and frequent episodes of fever (indicating leukopenia, or caused by the leukemia itself). In addition, patients can present with (sub) cutaneous manifestations, and other extramedullary deposits of myeloid cells, known as chloromas. Timely diagnosis of AML is vital; however, this can be challenging, as atypical symptoms can mimic symptoms of common childhood diseases.[5] Additionally, comprehensive AML treatment itself is challenging, both in LMICs and HICs, as it represents the delicate balance between anti-cancer treatment and adequate supportive care measures.[6,7] The lack of adequate supportive care in LMICs poses a major limitation to favorable outcomes of AML.[6] To improve outcomes, SIOP Pediatric Oncology in Developing Countries (PODC; now the Global Health Network) published an adapted treatment guideline for AML in LMICs in 2019 which, among other things, includes a low-dose etoposide pre-phase prior to starting induction chemotherapy.[8]

Although the Global Childhood Cancer Initiative focuses primarily on improving the survival of children with curable cancers, childhood cancers beyond the 'six common and curable types,' such as AML, should not be overlooked. Several international collaborations aim to contribute to this Global Childhood Cancer Initiative. The Princess Máxima Center for pediatric oncology in the Netherlands collaborates with the Moi Teaching and Referral Hospital (MTRH) in Kenya through a so-called Twinning Program. The Netherlands is a HIC in North-Western Europe, with a population of 18 million. In the Netherlands, all 600 newly diagnosed pediatric oncology patients are treated at the Princess Máxima Center, a specialized pediatric oncology hospital. Kenya is a LMIC in sub-Saharan Africa with a current population of approximately 55 million. MTRH is one of the two academic public hospitals in Kenya offering comprehensive pediatric oncology care. Approximately 300 pediatric oncology patients are diagnosed annually at MTRH. Treatment of AML has been perceived as extremely challenging by LMIC colleagues within the Twinning Program. A recent study was conducted at MTRH to evaluate the implementation of the SIOP PODC adapted treatment guideline for AML. This showed that treating AML in a LMIC is not a lost cause: even though numbers were low, curing AML seemed possible (2-year overall survival [OS] 16%), while highlighting high early death (ED) rates mostly due to infections.[8,9] This drove us to explore similarities, differences and challenges during the patient journeys of two AML cases: one from Kenya (LMIC) and one from Netherlands (HIC).

Case presentation

Case 1 – A fifteen-year-old Kenyan boy with AML

Case 1 involves a fifteen-year-old Kenyan boy originating from Nyandarua county, a region within Kenya. The boy, along with his twin, is the last-born child in a family of nine children and a widowed father. His mother passed away when he was four years old. His father retired in 2018. The boy initially had complaints of dizziness and he fainted in class on May 29th 2021. This prompted his brother to take the boy to a local hospital for assessment. Upon assessment by the clinician the boy was pale but otherwise in fair condition. No other abnormalities were reported upon physical examination. Laboratory investigations showed a hemoglobin (Hb) of 4.4 g/dL for which the boy received a blood transfusion. No causes of the anemia were investigated. The family history did not reveal hematological disorders or cancer at a young age. However, considering these findings, several diagnoses such as Malaria and other hematological conditions could have been investigated. As the physical examination did not mention any jaundice, hemolytic diseases such as sickle cell's disease or G6PD deficiency were unlikely. Since the past medical history of the child was normal, hereditary causes also seemed unlikely. Additionally, iron deficiency anemia, commonly caused by helminthiasis in this area, was not ruled out. Finally, transient erythroblastopenia of childhood (TEC) could have been ruled out sooner if a full hemogram was done. One month later the boy was taken to Nakuru hospital for follow-up of the anemia. The laboratory results revealed a Hb of 9.8 g/dL, thrombocytes of 1×10^9/L, and a white blood cell count (WBC) of 5.94×10^9/L. Therefore, another blood transfusion was given, and a bone marrow aspiration (BMA) was planned to investigate malignant causes of the anemia and thrombocytopenia. On July 27th, the BMA (using Grunwald Giemsa staining) showed 88% myeloid blasts, morphologically typical of FAB M2. Hence, 49 days after symptom onset, the diagnosis AML was confirmed. The boy and his brother went back to the hospital on August 3rd where they received the diagnosis. After this the boy was referred to MTRH and admitted on the 8th of August. At admission, he looked ill, was vomiting, had petechiae on his tongue and a hepatosplenomegaly. Table 1 shows additional patient characteristics.

AML treatment was initiated on August 10th, 14 days after diagnosis. In MTRH, treatment is given according to the SIOP PODC AML-specific expert-opinion based treatment guideline, which was developed specifically for level 2 settings in LMICs[8,10] (Fig. 1). The aim of this guideline is to tailor treatment to available resources, to decrease treatment-related mortality (TRM), and to distribute limited resources to those children who are most likely to be cured.[8] In 2019, this guideline was implemented in MTRH. Supportive care measures included antimicrobial prophylaxis (ciprofloxacin, co-trimoxazole, fluconazole), oral care (sodium bicarbonate mouth gurgles) nutritional care (nasogastric tube [NGT]),

Table 1
Overview of case characteristics.

	Case 1	Case 2
General characteristics		
Sex	Male	Male
Age	15 years	6 years
Weight	44.8 kg	28.7 kg
Height	140 cm	123 cm
BMI	15.4 kg/m^2	18.97 kg/m^2
Z-score	0 SD	2 SD
Diagnosis	AML	AML
Country of origin	Kenya	The Netherlands
Income classification Worldbank	Lower middle income country	High-income country
Parent occupation	Retired (mother) / deceased (father)	Social worker (mother) and outdoor hospitality (father)
Access to care		
Distance to pediatric oncology care facility	253 km	100 km
Health insurance active	Yes	Yes
Diagnostic services available		
Laboratory services	Yes	Yes
BMA equipment	Yes	Yes
Pathology services	Yes	Yes
Therapeutic services available		
Chemotherapy	Yes	Yes
Hematopoietic stem cell transplantation	No	Yes
Radiotherapy	Yes	Yes
Treatment protocol	AML treatment protocol version 1: 2019	NOPHO-DBH AML-2012
Delays[a]		
Patient delay	0 days	42 days
Physician delay	49 days	19 days
Diagnosis delay	49 days	60 days
Treatment delay	14 days	1 day
Health system delay	63 days	19 days
Total delay	63 days	61 days
Supportive care		
Antibiotic prophylaxis	Yes	Yes
Nutritional support	Naso-gastric tube	Naso-gastric tube
Blood products	Yes	Yes
Febrile neutropenia	Yes	Yes
- Episodes	5	6
- Antibiotics	Yes	Yes
- Blood cultures	Not always	Yes
Outcome	Alive	Alive
Follow-up	Remission	Remission

BMI, body mass index; AML, acute myeloid leukemia; BMA, bone marrow aspiration.

[a] See Fig. 3 for visual explanation of delay definitions.

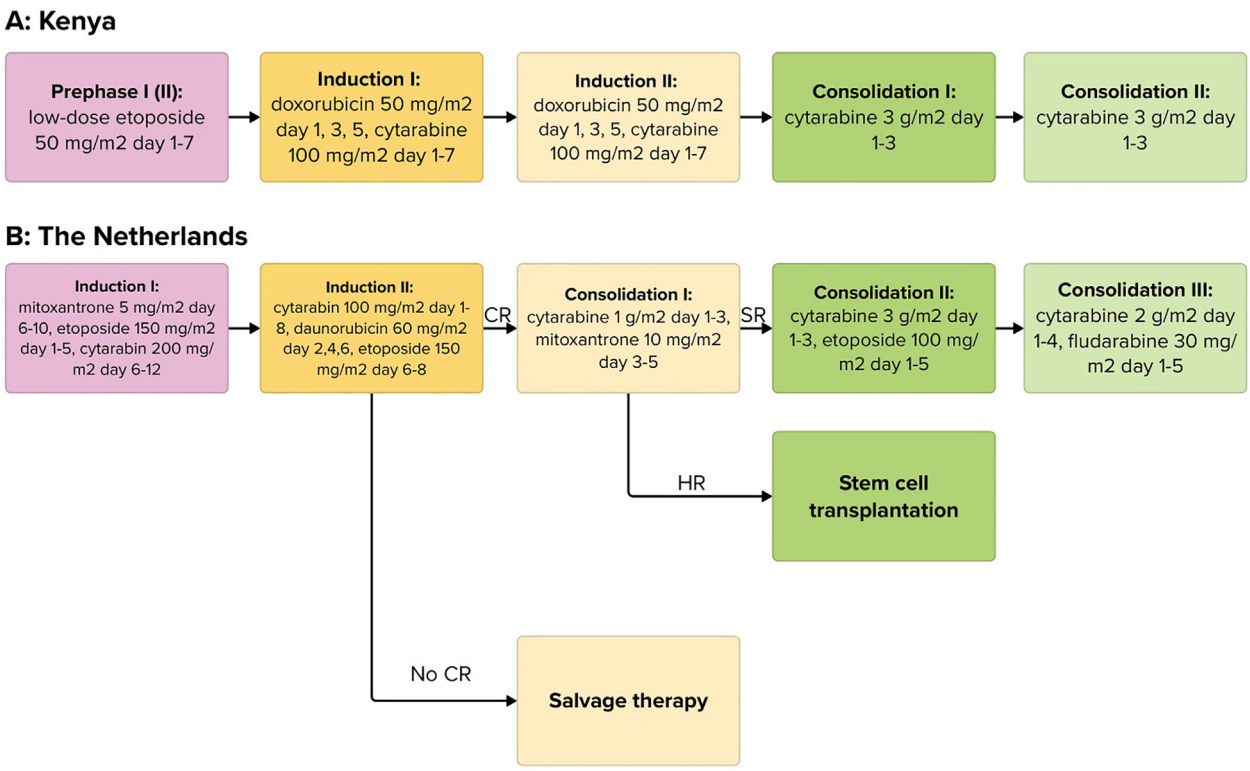

Fig. 1. General treatment overview of pediatric acute myeloid leukemia treatment at (A) Moi Teaching and Referral Hospital and (B) The Princess Máxima Center for pediatric oncology. CR, complete remission; SR, spontaneous remission; HR, histological remission.

antiemetic therapy (ondansetron), blood transfusions, and steroid eye-drops, according to the local supportive care guideline at the ward.

During the course of the treatment, several episodes of febrile neutropenia (FN) occurred (Fig. 2A). Neutropenia is defined as ANC of $< 0.5 \times 10^9$/L or $< 500/m^3$. All episodes were managed according to local guidelines including broad-spectrum antibiotics; however, blood cultures were not always routinely taken. We highlight the second episode of FN, which occurred after induction cycle 1. The boy was initially treated with meropenem and amikacin while awaiting the blood culture result; however, this culture did not show any bacterial growth after 48 hours. Meanwhile, the boy's clinical condition did not improve and therefore amphotericin B was added to the treatment plan. The fever persisted and the boy was suffering from severe mucositis. To ensure caloric intake, the boy was fed through a NGT. Eight days after onset of fever the boy was still febrile, suffering from mucositis, coughing and conjunctival hemorrhage. Amikacin was stopped, and levofloxacin was added to the treatment plan. One day after this new treatment plan, the boy's COVID-19 rapid test turned positive. However, as the boy's FN episode persisted, amphotericin B was stopped and fluconazole was started. In addition, a second blood culture was taken. This culture showed a Staphylococcus haemolyticus and an Enterococcus faecium. Meropenem was therefore changed to clindamycin and vancomycin based on the susceptibility results. Finally, 20 days after onset of this FN episode, the boy's clinical condition improved, as he recovered from neutropenia.

After the two induction courses, a BMA was performed, which showed morphological remission on 29th October 2021. The boy was in continuous complete remission (CR) after completing the treatment, and returned to school to sit for his primary examination. The last date the boy of follow-up was July 12, 2024. The boy was still in CR and is in fine condition.

Case 2 – A six-year-old Dutch boy with AML

Case 2 involves a six-year-old Dutch boy originating from the Netherlands. The boy lives with both his parents and younger sister. On 17th of August 2021, the boy developed symptoms of fatigue and malaise. On 28th September 2021, the boy presented at his general practitioner with fever, accompanied by a cough and ear pain. Physical examination revealed a bilateral otitis and was otherwise normal. The prolonged history of fever prompted the general practitioner to request laboratory investigations of the blood. The blood tests revealed severe leukopenia and anemia, for which the boy was referred to a local hospital on 29th September 2021. There was no family history of hematological disorders or early-onset cancer. The differentials included benign conditions such as post-viral bone marrow failure, other rare bone marrow failure syndromes, and malignant diseases. Therefore, morphological and flow cytometric evaluation of the peripheral blood was prompted at the pediatric oncology hospital, which did not reveal leukemia. Consequently, post-viral bone marrow failure was concluded. Follow-up blood count showed stability; however, on October 12th, the boy presented at the emergency department, with severe abdominal pain, vomiting, and pancytopenia, leading to a referral to the pediatric oncology hospital. Upon physical examination, the boy now appeared pale and had several hematomas on his legs. The total blood count showed a Hb of 6.0 g/dL, thrombocytes of 224×10^9/L and a WBC of 1.7×10^9/L (differential count: basophils $< 0.10 \times 10^9$/L, eosinophils $< 0.10 \times 10^9$/L, lymphocytes 1.52×10^9/L, monocytes $< 0.10 \times 10^9$/L). Additional blood tests showed prolonged clotting times (PT of 16.9 sec, APTT of 35 sec), and a D-dimer of 0.72 mg/L. An abdominal ultrasound did not show hepatosplenomegaly. Morphological examination (using Grunwald Giemsa staining) indicated no blasts in the peripheral blood but revealed 92% blasts in the bone marrow, which were described as typical for

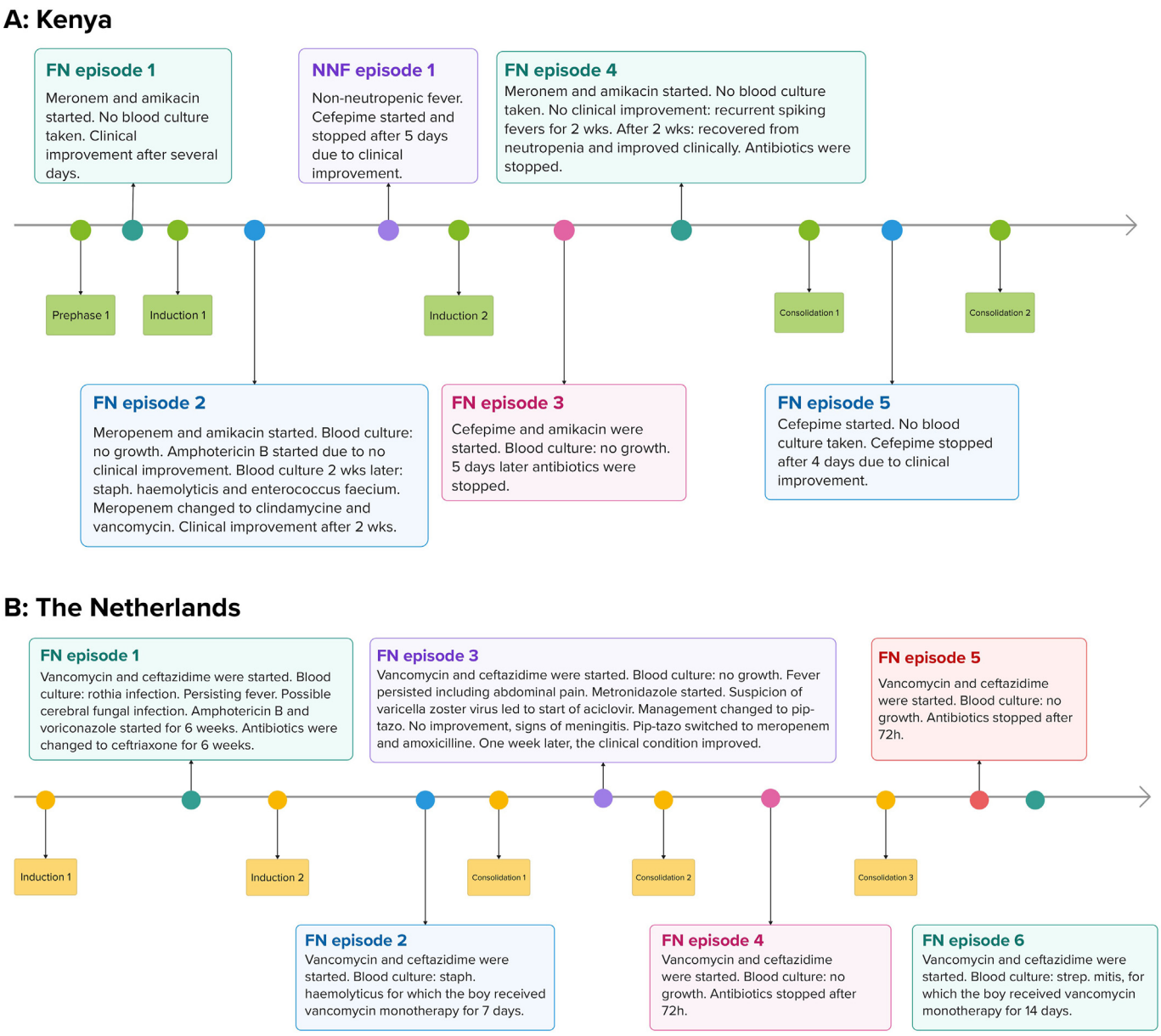

Fig. 2. Overview of FN episodes for the Kenyan boy (A) and the Dutch boy (B). FN, febrile neutropenia; NNF, non-neutropenic fever.

monoblastic leukemia (FAB type M5). Flow cytometry investigation showed the markers CD4, CD15, CD33, CD34, CD38, CD45, CD56, CD64, CD117 (dim), and HLA-DR to be positive. Cerebrospinal fluid was negative for blasts. A KMT2A-MLLT10 fusion was detected only with RNAseq. Further cytogenetic analysis did not reveal any abnormalities. Hence, on 16th October, 61 days after symptom onset, the diagnosis AML was confirmed. Treatment was initiated on 17th October (Fig. 1).

In the Netherlands, AML patients at this time were treated according to the NOPHO-DBH AML-2012 treatment protocol, which was considered the best available evidence-based treatment protocol within the consortium. Standard AML treatment consists of five chemotherapy cycles. Patients with refractory disease, i.e., patients not achieving CR after two induction courses, receive salvage treatment, followed by hematopoietic stem cell transplantation (HSCT). High risk patients proceed to HSCT after three chemotherapy courses (Fig. 1). Supportive care measures include antimicrobial prophylaxis (ciprofloxacin, cotrimoxazole, itraconazole), nutritional support (NGT), antiemetic therapy (granisetron), blood transfusions, oral care, and psychosocial support according to local supportive care guidelines.

During the course of treatment, several episodes of FN occurred (Fig. 2B). All episodes were managed according to local guidelines including broad-spectrum antibiotics and blood cultures. We highlight the first FN episode, which occurred one day after the first chemotherapy course was completed. Vancomycin and ceftazidime were started, and the blood culture showed a penicillin resistant Rothia mucilaginosa. Despite these antibiotics, the boy's fever persisted, prompting fungal diagnostics. A computed tomography (CT)-thorax did not show features of a fungal infection; however, an MRI of the cerebrum revealed lesions, potentially indicative of intracerebral fungal involvement or caused by the Rhotia infection. Therefore, amphotericin B and voriconazole were started for six weeks, and vancomycin and ceftazidime were changed to ceftriaxone for six weeks to treat a possible intracerebral Rhotia infection. A follow-up MRI of the cerebrum demonstrated improvement. After these six weeks, voriconazole monotherapy was continued as secondary prophylaxis.

A BMA 22 days after the start of treatment showed molecular remission. Treatment was completed in April 2022. After clinical recovery, the boy successfully returned to school. The date of last follow-up is July 12, 2024, and the boy is still in CR.

Discussion

The continuous CR in both cases illustrate that curing AML is also possible in LMICs, suggesting cancers beyond the 'six common and curable types' should not be overlooked. Nonetheless, it also highlights the delays in the patient journey and supportive care challenges associated with AML treatment, marked by multiple neutropenic fever episodes, regardless of setting.

Timely access to adequate childhood cancer care is crucial in optimizing outcomes for children with cancer. Different delays illustrate the challenges in access to care, that were observed in both patient journeys (Fig. 3). Firstly, the patient delay in both cases (Kenya vs. Netherlands: 0 vs. 42 days) reflects that recognizing symptoms of childhood cancer and seeking care can be difficult for families.[11] In addition, the Kenyan family shared that they sought for care immediately after the boy fainted; however, the symptoms might have been present for a longer period of time. Secondly, physician delay in both cases highlights the difficulty for physicians to timely recognize cancer and refer the patient, as signs and symptoms of childhood cancer can mimic other diseases.[5] The patient from Kenya presented with anemia for which he received two blood transfusions. The Dutch patient was firstly suspected of a post-viral bone marrow failure, instead of leukemia, based on the absence of blasts in the peripheral blood, which delayed the AML diagnosis. Despite timely discussions with the pediatric oncology team of the tertiary care facility for the Dutch patient, the diagnosis was confirmed 61 days after onset of symptoms. Thirdly, in both cases the treatment delay was relatively short (Kenya vs. Netherlands: 14 days vs. 1 day), suggesting that as soon as the diagnosis was confirmed, access to adequate treatment could be ensured. However, the longer treatment delay for the Kenyan boy could be attributed to the referral from the local hospital to MTRH, which was more than 200 km away from the Kenyan family's residence. It indicates that families might encounter challenges in accessing treatment after the diagnosis has been confirmed elsewhere. Many LMICs face challenges in accessing treatment in a timely manner. Although the WHO essential medicine list contributes to adequate availability of chemotherapeutic drugs, stock outs are still frequently reported.[12] Finally, the total delay was similar for both cases (Kenya vs. Netherlands: 63 vs. 61 days). However, median total delay over 90 days has been reported in other African settings.[11] Our findings suggest that delays in access to care can be similar between HIC and LMIC settings in individual patients. However, in practice, access to care is often more challenging in LMICs, frequently resulting in underdiagnosis or late presentation of children with cancer.[13] The similar total delay in this case series can be attributed to the atypical presentation of AML in both cases. In both settings, physicians were misled to consider other conditions over AML.

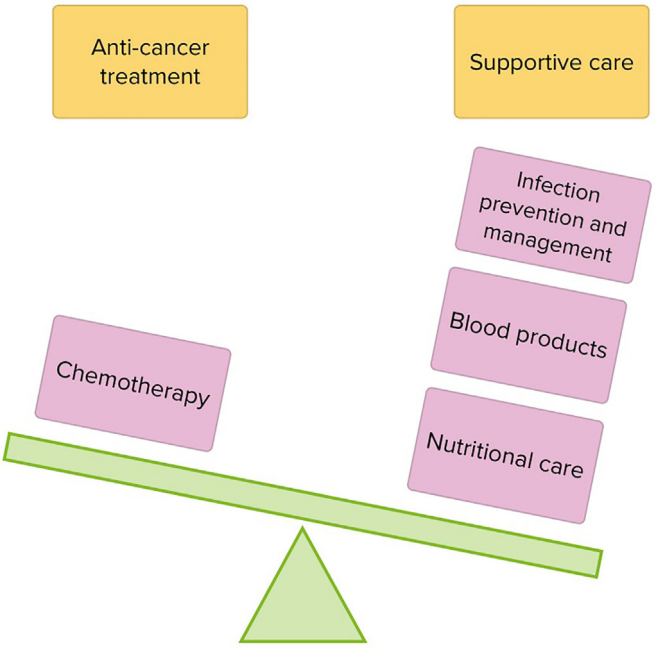

Fig. 4. Balance between anti-cancer treatment and supportive care.

Both cases underline the challenging balance between intensive AML treatment, and adequate supportive care (Fig. 4). Adequate prophylactic measures were taken prior to the start of chemotherapy for both patients. During the courses of treatment, several episodes of FN occurred; however, management of FN episodes differed per setting. Adequate FN management includes timely recognition of FN, taking blood cultures, and starting antibiotics within 60 minutes (golden hour) after onset of fever, since infections in these patients progress rapidly.[14] Managing FN appropriately is important as the mortality of this condition is very high, especially in LMICs, where bacterial and fungal infections during FN episodes are the main cause of mortality.[5,14,15] In the Kenyan hospital, blood cultures were not taken routinely for FN episodes; hence, the causative pathogens often remained unidentified. Similarly, a multicenter observational cohort study in five African countries reported that in merely 15% of all FN episodes a blood culture was obtained.[16] Moreover, in only 10% of the FN episodes in that study antibiotics were started within one hour.[16] In addition, extensive diagnostic work-up was limited in the Kenyan setting. Empiric treatment was therefore mostly adjusted based on the clinical condition, potentially leading to prolonged and unnecessary antibiotic exposure. Studies from other resource limited

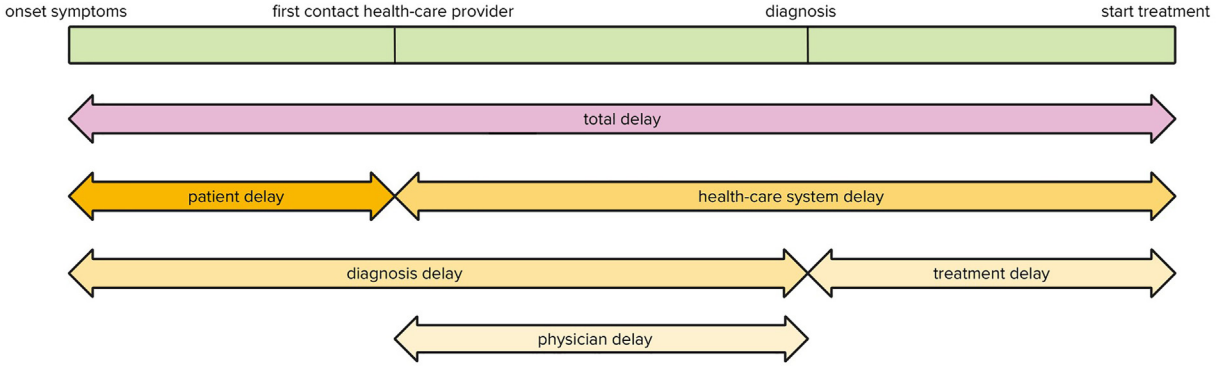

Fig. 3. Delays in access to care (*adapted from Njuguna et al.*).[11]

settings report high infection related mortality during the course of AML treatment.[15,16] A systematic review on outcomes of AML in LMICs reported high ED and TRM rates, mainly attributable to high infection rates and suboptimal supportive care.[6] In addition, studies suggest the usefulness of anti-fungal prophylaxis in LMICs as well to reduce morbidity and mortality as a consequence of fungal infections that are frequently seen during AML treatment.[17,18]

In the Dutch setting, the *shared care* concept, wherein pediatric oncology patients can receive their cancer care in a nearby hospital with a maximum 45-min drive, generally ensured timely administration of antibiotics within one hour after detecting the fever. Moreover, the Dutch patient received extensive work-up in diagnosing a fungal brain infection when clinical improvement was lacking. Nevertheless, despite the current nearly 80% OS rates of AML in HICs,[4] even in HIC settings treating AML is challenging; ED and TRM remain important causes of treatment failure, appearing in 5% to 10% of patients.[19,20] Also in HICs, often this is due to infections, as 60% to 70% of AML patients experience at least one culture proven bloodstream infection during AML treatment.[21–23]

In the Kenyan hospital, blood product availability has become more stable over the past years, due to active recruitment of blood donors. However, timely thrombocyte transfusions remain challenging. In the Dutch hospital, blood product availability is ensured through a national blood bank system. A non-profit organization (Sanquin) collects, processes and distributes blood products.

Nutritional support and oral care were started in both cases. This is a key element of supportive care and influences treatment tolerance, survival and quality of life.[24] Undernutrition prevalence is high amongst children with cancer.[24] In both cases a NGT was provided to assure adequate feeding. In addition, both patients received anti-emetics to reduce side effects of chemotherapy such as loss of loss of appetite which could further deteriorate nutritional status.

A high infection risk due to poor hygiene and overcrowding, and malnutrition often cause high treatment-related mortality in LMICs, underlining the importance of supportive care.[9] In a study on pediatric AML in a LMIC setting, enhancement of supportive care significantly reduced mortality rates that were caused by infections from 41% to 29%.[25] These findings suggest that supportive care might be the low-hanging fruit in improving outcomes. Previous recommendations on supportive care by SIOP PODC[26] are currently being updated through efforts such as the Adapted Resource and Implementation Application (ARIA) guide, initiated by St. Jude Global and SIOP, aiming to create resource-stratified, evidence-based guidelines to ensure adequate childhood cancer diagnosis and treatment all over the world.

Strengths and limitations

This case series provides a unique comparison between a HIC and LMIC setting. It emphasizes the challenging journey of treating AML regardless of setting. However, several limitations apply to this case series. Firstly, for the Kenyan boy, not all clinical data were available. For example, results of several laboratory investigations could not be retrieved from the patient file. Moreover, this case series solely describes one AML case from a resource limited setting that has achieved CR. This is not representative of all AML cases in LMICs as the majority still does not survive. Finally, treatment protocols for both cases were different, however the backbone of AML treatment and approach of the management was mostly similar.

Conclusions

In conclusion, childhood cancer holds promise for curability, extending beyond the recognized 'six curable types of cancer' such as AML in this case series. Survival rates in LMICs are increasing, and it is imperative to focus on timely access to comprehensive childhood cancer care including supportive care, to further improve outcomes and contribute to the global endeavor of curing all children with cancer. We therefore recommend physicians treating AML in low-resource settings to endorse usage of adapted treatment guidelines for AML and to focus strongly on implementing adequate supportive care measures. Moreover, we recommend to raise awareness amongst health care professionals on AML as a disease to ensure timely recognition and referral.

CRediT authorship contribution statement

Study design, data retrieval, writing manuscript (NW, LK). Critically reviewing the manuscript (AG, LA, FN, KK, MH, BG, SM, GK). All authors were granted complete access to all the data in the study, with the corresponding author bearing the final responsibility for the decision to submit for publication. The corresponding authors affirm that all listed authors fulfill the authorship criteria and that no others meeting the criteria have been omitted.

Ethics statement

Ethical approval for collection of retrospective data was obtained for both patients. For both patients, written informed consent was obtained for publication of the case reports.

Declaration of competing interest

The authors declare no conflict of interest.

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Data availability statement

The data that support the findings of this study are available from the corresponding authors, Noa Wijnen and Larissa Klootwijk, upon reasonable request.

Declaration of generative AI and AI-assisted technologies in the writing process

No AI tools/services were used during the preparation of this work.

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