Adverse effects of chemotherapy and their management in Paediatric patients with Non-Hodgkin's Lymphoma in Kenya: A descriptive, situation analysis study

Abstract

Background

Chemotherapy-related side effects and their management in patients with Non-Hodgkin's Lymphoma (NHL) are not well defined in developing countries, including Kenya. This needs addressing considering the high number of patients with cancer in these countries. Consequently, we sought to determine the common side effects of chemotherapy used to treat NHL in pediatric patients. and its implications.

Methods

Observational study conducted at the Kenyatta National Hospital in patients aged ≤15 years. Some data was collected by reviewing patients' records admitted to the pediatric oncology ward, December-2016 to May-2017; and additional data was collected retrospectively (review of patients' records with NHL, January-2014 to May-2017). Data were analyzed descriptively.

Results

Overall, out of the identified NHL patients (n=85), 93% (n=79) had chemotherapy-related side effects. The majority of patients suffered from side effects were managed; apart from 23% and 24% of the documented anemia and hypersensitivity, respectively..

Conclusions

Whilst the majority of the reported side-effects were being managed, the lack of management of some side effects raises real concerns since this indicates either failure to manage or failure to document their management in patients' records, both of which should be addressed appropriately to improve future care.

Key words

Chemotherapy; side effects; Non-Hodgkin Lymphoma; Developing countries; Kenya

1 Introduction

Childhood cancers are a continual concern worldwide as they are a major cause of death in children (1). This includes Kenya where childhood cancers accounted for 15% of all cancer admissions between 1998-2008 (2). Furthermore, only one in ten children survive their cancer in Kenya compared to seven out of ten or more in developed countries (3,4). Even if children do survive their cancer, there are concerns with chemotherapy-related adverse events which compromises patients' health related quality of life when compared to children without cancer (4).

Among childhood cancers, lymphomas are among the most common cancers originating from cells of the immune system. They are divided into Hodgkin's and Non-Hodgkin's Lymphomas (NHL). NHL is more prevalent in children than in adults, and characterized by the presence of malignant white blood cells. NHL consists of 3 types; B-cell, T-cell and natural killer lymphocyte lymphomas (5). In a recent study in the Republic of Congo, the authors observed a higher proportion of B-cell non-Hodgkin's lymphoma, BL and bcl-2 expression cancers among identified NHL patients (6).

NHL is the third most common cancer in children after leukemia and brain tumors; accounting for approximately 7% of all cancers in children below the age of 20 years in high income countries (7). Overall, over 90% of NHLs occur in lower and middle income countries (LMICs) (7), with BL appearing particularly prevalent in sub-Sahara Africa with prevalence rates 10 to 20 times higher than seen in the US (8). This can be of particular concern as healthcare resources are more limited in LMICs versus western countries (9). Furthermore, there are certain risk factors for cancers that are more prevalent in LMICs, which include infections such as HIV/AIDS (10). HIV/ AIDs is a particular issue in sub-Sahara Africa, with rates as high as 24% in some African countries (11,12) although there are ongoing plans to eliminate HIV from infants born to infective mothers (13). The HIV prevalence in Kenya, is approximately 4.9% (14). According to the Canadian Cancer Society, males are more susceptible to NHL than females because of mutations on X-linked immune system genes which cause a syndrome called Wiskott-Aldrich that predisposes them to NHL (15). Females have two X-chromosomes; consequently, the likelihood of being affected is typically lower (16). Chemotherapy is the most common mode of treatment for NHL with treatment undertaken in three phases: induction, consolidation and maintenance. There are various combinations of medicines that can be used to treat NHL. These include

cyclophosphamide, doxorubicin hydrochloride (Adriamycin), vincristine and prednisolone (CHOPP). Prednisolone is given to delay the onset of chemotherapy-induced emesis. Sometimes patients are also given granulocyte colony stimulating factor (G-CSF) to accelerate bone marrow production of white blood cells (5). Rituximab is also increasingly used to improve patient outcomes, particularly in higher income countries (7,18). The number of medicines, their dosages and duration of treatment depends on the type and stage of lymphoma. with chemotherapy typically given in cycles followed by a resting period. Generally, each cycle lasts for several weeks (19).

Despite their benefits, the various chemotherapy combinations, including CHOP, have acute and chronic side-effects. The most common side-effects include alopecia, nausea and vomiting, bone marrow suppression and a general reduction in patient's quality of life. Some of these side effects are dose dependent and vary from one child to another, whilst others are common among all pediatric patients. The presence and severity of side effects also depends on patients' ages, weight, body surface area and type of the chemotherapy. Consequently, there is often a need for dose adjustments during prescribing (20,21). We are also aware that chemotherapy causes a reduction in white blood cell count, especially neutrophils, which makes patients susceptible to secondary infections during their nadir period (22). This needs to be carefully monitored. Pain can also occur as a consequence of tissue destruction and invasion by cancerous cells, and it may also be a side effect of chemotherapy. Typically pain is managed using analgesics in line with the WHO pain ladder (23).

There are adverse effects with chemotherapy; however, their appropriate management can subsequent the morbidity and mortality (5, 24). Having said that, to date, very few studies have been undertaken regarding chemotherapy-associated side effects in paediatric patients with NHL in sub-Sahara Africa including Kenya. This is important given the extent of NHL in these countries and concerns with issues of affordability and availability of medicines to adequately diagnose and treat these patients as well as the side-effects of any chemotherapy. Consequently, we sought to determine the prevalence and types of chemotherapy-related side effects, and their management, among paediatric patients admitted to a leading public tertiary care hospital in Kenya, which typically manages these patients from across Kenya, to provide future guidance in Kenya and elsewhere across sub-Sahara Africa.

2 Patients and methods.

2.1 Study site, design, and data collection

This observational study was carried out at Kenyatta National Hospital (KNH), the largest national referral hospital in Kenya, which has a bed capacity of 1800 beds and has a specialized paediatric oncology unit where patients from across Kenya with NHL are diagnosed and treated. Data was collected using two approaches; firstly, a review of patients' records who were admitted to the pediatric oncology ward from December-2016 to May-2017; secondly, a retrospective review of patients' records with NHL from the Records Department of the KNH hospital from January-2014 to May-2017, using a universal sampling technique involving all patients who had been diagnosed for NHL and had received chemotherapy.

2.2 Study population, inclusion and exclusion criteria

The inclusion criterion was all children aged ≤15 years, diagnosed and treated for NHL. Children with other comorbidities were excluded to ensure that the side effects recorded were mainly due to the administered chemotherapy.

2.3 Outcome measures, study variables and sample size

Predesigned data collection forms were used to obtain information from patients' records diagnosed and treated for NHL. These forms were pre-tested to enhance the robustness of data collection. Data from the patients' records admitted in the wards, was used to estimate the prevalence of NHL; whereas, data on the management of NHL patients (including adverse effects of chemotherapy and their management) was collected from all NHL patients identified through both approaches. The collected information included patients' biological data, age, weight, height and sex, time of diagnosis, drugs/regimen used, the side effects and any interventions made. The sample size was calculated using the following formula proposed by Cochran (25).

$$N=\frac{Z^2P(1-P)}{C^2}$$

Where N=sample size

Z= 1.96

C= Confidence interval

P=Prevalence

$$\text{Thus } N=\frac{1.96^2 * 0.07(1-0.07)}{0.05^2}$$

=99.93636, Consequently we sought to analyse 100 patients with, as mentioned, a universal sampling approach adopted.

2.4 Data Analysis

Descriptive statistics, mean and standard deviation for normally distributed continuous variables and frequencies and proportions for categorical variables, were used to describe patients' characteristics and study outcomes. Data was presented using frequency distribution tables, graphs and pie charts as appropriate. The prevalence was represented as proportions of patients with NHL to that of other cancers. Microsoft Excel and SPSS programs were used to analyze the data.

2.5 Ethical Approval

Ethical approval was sought from the KNH /University of Nairobi ethics and research review committee with a reference number UP898/11/2016. Patients' identities were not revealed and code numbers were used instead. Files were not taken out of the records department. The data collection forms were placed under lock and key, and the key was only accessed by the principal investigator. Data entered in Microsoft Excel and SPSS data was password protected.

3 Results

3.1 General

Data collection was affected by nationwide doctors' strike which took a period of 100 days from December 2016 to March 2017. As a result, patients were discharged to private hospitals resulting in very few patients in the paediatric oncology wards during the study period. This led to the initial sample size of (n=100) not being achieved. Consequently, two approaches were used for data collection: review patients currently in the ward (n=12) and a retrospective review of patients' records from the records department (n=73); with both approaches identified a total of 85 patients.

3.2 Prevalence of Non-Hodgkin's lymphoma and patient demographics

A total of 85 paediatric patients with NHL were identified and reviewed out of which , the majority were male (79%) and aged 6-10 years old. The average weight of patients in the study was 23 kg (SD:±8.14) (Table 1). Out of the total number of children admitted to the

pediatric oncology wards at the time of data collection (n=73), 17% (n=12) had NHL while leukemia was the most common type of cancer with 33% (n=24). (Table 1).

3.3 Clinical characteristics of the NHL paediatric patients

The majority of the NHL patients (98%) were diagnosed both clinically (based on symptoms) and objectively (via the clinical investigations such as x-rays, CT scans and biopsies). The remaining 2% were diagnosed using laboratory assessment only consisting of complete blood counts, level of inflammatory markers and lactate dehydrogenase levels. All the patients went through the induction phase of treatment and out of these, 39% were still on the induction phase at the time of the study, 4% had finished induction and were in the consolidation phase while 57% had completed induction and consolidation and were on the maintenance phase. All the patients had gone through or were still in the first cycle of chemotherapy; 61% of patients were still in the consolidation phase together with those who had completed it, while 56.5% were in the maintenance phase. The majority of the patients suffered from Non-Burkitts lymphoma (52%) (Table 2).

3.4 Management of Non-Hodgkin's Lymphoma

The various drug combinations that were used for the induction phase included 6 cycles of cyclophosphamide, vincristine, doxorubicin, prednisolone and procarbazine (CHOPP). Other drug combinations included CHOP+M (Cyclophosphamide, Vincristine, doxorubicin, methotrexate and prednisolone). For the consolidation phase, cyclophosphamide, cytarabine and doxorubicin were administered in two cycles. Much higher doses were typically used for the consolidation phase compared to the induction phase. Cyclophosphamide, doxorubicin, vincristine, methotrexate (both oral and intrathecal) and 6- mercaptopurine were used for the maintenance phase in 16 cycles. The various dosages of the medicines were adjusted according to the BSA (body surface area) of the children calculated using their weights and heights. This reduced their side effects due to body surface area variations (Appendix 1).

For the relapse of BL, patients were treated with methotrexate, 6-mercaptopurine, vincristine and cytarabine. For the relapse of non-Burkitts lymphoma, patients were treated with methotrexate, doxorubicin and vincristine (Appendix 1). In two cases, patients were unresponsive to CHOP+M and were given vincristine, adriamycin, cytarabine and cisplatin (VAC-CIS) instead (26).

3.5 Side effects of cytotoxics used for treatment of NHL

The most common side effects experienced by patients were vomiting (93%, n=79), followed by anaemia (<11.0g/dl) (88%, n=75), loss of appetite and weight (86%, n=73), pain (84%, n=71) and leucopenia (72%, n=61) (Figure 1). All these side effects were confirmed from patients' files as related to the administered chemotherapy.

3.6 Management of side effects of chemotherapy for paediatric patients with NHL

The majority of patients who suffered from the chemotherapy-related side effects were receiving treatment (Table 3). All patients who suffered from loss of appetite, mucositis, diarrhea and hyperacidity were managed. It was noted that a number of patients who suffered from anemia and allergies were not treated for these side-effects. The specific management for each side effect is displayed in Table 4.

The proportion of patients who were managed for pain was 94%, which was addressed using analgesics including opioids (morphine (14%), dihydrocodeine (25%), and tramadol (2%) as well as simple analgesics including paracetamol (47%), and NSAIDs: ibuprofen (9%) and diclofenac (1%).

Leucopenia was experienced in 61 patients of whom 80% were managed using filgrastim administered within 24-72 hours post chemotherapy. However, details for the remaining 20% was not indicated in their files. Patients may experience fever, which is a sign of infection accompanied with mucositis. In the study, 82% of the patients who had fever (Table 3) were given paracetamol and ibuprofen , (Table4).

Various chemotherapy agents were withdrawn from the children due to the different side effects. Cyclophosphamide was withdrawn from one patient due to pleural effusion, doxorubicin due to cardiomyopathy shown on x-ray, vincristine due to an allergic reaction in one patient, 6- mercaptopurine and methotrexate due to anemia in two patients, adriamycin due to pancytopenias in two patients and in one case the dosages of 6- mercaptopurine and methotrexate were reduced due to anaemia. In another case, cytarabine was used instead of methotrexate due to an allergic reaction which developed after administration. Generally, the allergic reactions were not specified in the patient files.

4 Discussion

From our study findings, NHL was the second most common cancer in the pediatric oncology ward with a prevalence of 17% (Table 1). NHL was more common in male children than females in our study, which is similar to data from the American Cancer society which indicates that NHL is 2-3 times more common in boys than girls(27,28,). In Sub-Saharan Africa, higher incidences of lymphomas have also been reported in males than females at 16 and 10.8 per 100,000 children, respectively (29). As mentioned, this is perhaps a reflection of the mutation of the X-linked immune system genes (30). However, more research needs to be undertaken before we can say anything with certainty.

Our study had more patients with Non-Burkitts Lymphoma than Burkitts lymphoma. This is different though to the majority of published studies which showed BL is more common in Sub-Saharan Africa due to presence of Epstein Barr virus responsible for its etiology (31), with an overall prevalence of 29.2 % in Kenya (32). However, this could be due to the small sample size of this study.

The study findings indicated an appropriate and accurate diagnosis of NHL since the majority of patients were diagnosed clinically then confirmed via further investigations. In addition, the regimens used for the management of NHL is consistent with other settings (19). This indicates that children are getting standard care, which is encouraging. The top three side effects of chemotherapy seen in our study were vomiting (93%), anemia (88%) and a loss of appetite (86%). This is similar to published figures from the American Cancer Society, where the most common side effects of chemotherapy in children are nausea and vomiting, hair loss, mouth sores, loss of appetite, diarrhea or constipation, low blood cell count and an increased risk of infection (26).

Additionally, our findings showed that the interventions being given to the patients with the side effects were appropriate in line with published studies and standards (1,2,33), which is again encouraging considering the limited resources available in LMIC countries such as Kenya to adequately treat patients with cancer (34). There have been concerns whether G-CSF should be given prophylactically rather than after chemotherapy. However, more recent data suggests that giving G-CSF 24 to 72 hours after chemotherapy is effective in line with administration times in our study (35). All patients who had loss of appetite, mucositis, diarrhoea and acidity as side effects were managed appropriately for these (Table 4),

including nutritional supplementation, nutritional counseling to the mothers and nasogastric tubes to administer foods to patients who are unable to feed. However, not all of the patients who suffered from some other side effects including allergic reactions, anemia, leucopenia, fever, pain, dehydration, vomiting, hyponatremia and constipation, were subsequently managed appropriately. This could perhaps be either due to a lack of documentation although the intervention was given since the information was retrieved from the records and this was not recorded; alternatively, the intervention was not given at all. Failure to manage the side effects of chemotherapy for mainly pancytopenia can lead to death due to excessive bleeding and infections. Consequently, this needs to be looked at further in this hospital to improve future care. Vomiting and diarrhea can lead to loss of fluids and electrolytes and patients may die due to hypovolemic shock. Consequently, it is also important to manage these side effects and record any interventions made (5). These concerns are now being followed up in the hospital, and will be the subject of future research.

In our study, 94% of the patients with pain were managed using opioids: morphine, dihydrocodeine, as well as non-opioids: paracetamol, ibuprofen and diclofenac (Table 4). This finding is comparable to another study where the majority of the patients were treated effectively by non-opioid analgesics while others with bone and neuropathic pain were referred to specialists where pain was alleviated using strong opioid analgesics (36). The choice of analgesics was made according to the WHO pain ladder.

Encouragingly, 80% of patients with leukopenia were managed with filgrastim in line with standard guidance (Table 4). This is encouraging as there can be concerns with the availability and affordability of medicines in countries such as Kenya generally as well as for medicines to treat patients with cancer (9,34,37).

Overall, we believe this study contributes information on the management of NHL in children from low income settings such as Kenya. Encouragingly, the findings have shown that diagnosis and management of NHL in children is generally undertaken according to the agreed standards and is consistent with care for NHL in children in other settings. KNH has cancer treatment guidelines that are consistent with international guidelines for treatment of different types of cancer. This is welcomed and encourages the hospital management team that the patients in KNH with NHL are getting good care, although there is still a need to strengthen some aspects of care to further improve patients' outcomes. This includes patients

suffering from allergy, anemia, leucopenia and fever, and will be the subject of future research projects to address this

The study had several limitations. Firstly, data collection was affected by a nationwide doctor's strike which took place from December-2016 to March-2017. This led to fewer patients in the ward than expected and hence most patient details were retrieved retrospectively from the Records Department. Consequently, a sampling error due chance cannot be ruled out.

Secondly, given the use of secondary information, some information may have been left out of patients' notes such as other side effects including alopecia as well as the psychological effects of treatment including mood changes, anxiety, fatigue, and memory changes, which could not be observed. In addition, some of the information could not be obtained regarding the management of the side effects in some patients since it was not recorded in the files. The side effects might have been managed but not recorded in the files of patients. Furthermore, although classic methods of evaluating adverse events usually include "grading" of these events, this data was not been included in this study as the grading information was typically not recorded in patients' file only the occurrence of adverse events. Long term side-effects of chemotherapy were also not observed for example any adverse effect on sexual and reproduction issues as well as adverse effects on heart, brain, lungs, liver and kidneys. This was due to the limited period of study, and will be the subject of future research. Thirdly, the study was only conducted in one hospital in Kenya. However, this is the leading hospital in Kenya treating children from across Kenya with NHL. Despite these limitations, we believe our findings are valid and show concerns with the level of detail recorded in patients' notes, which is now being followed up.

5 Conclusions

Non-Hodgkin lymphoma accounted for 17% of the total number of children admitted in pediatric oncology wards of a leading public tertiary care hospital in Kenya. Diagnosis and management of NHL were encouraging, given the issues of affordability and accessibility in the developing countries such as Kenya. The majority of the patients suffered from acute side effects of chemotherapy. Loss of appetite, mucositis, diarrhea and acidity were well managed. However, the management of anaemia and allergic reactions needs to be improved for the

patients to respond well to treatment and have better outcomes. Documentation should be emphasized and addressed in order to improve patients' clinical outcome, including a greater focus on grading system for these events rather than just reporting their occurrence. A prospective large sample sized study is now being undertaken in KNH to corroborate our study findings and follow up on the outcomes of adverse events of chemotherapy on patients' rate of hospitalization as well as potentially also mortality. The findings and their learnings can be used to further improve the management of NHL in this hospital including greater recognition and management of the side-effects of chemotherapy .

6 Authors' contribution

LO, MM and SO were involved in the conception, design, analysis and interpretation of the data; BG and AK were involved in the analysis and interpretation of the results. All the authors participated in the drafting of the paper, and critically revising it following comments from the reviewers. All authors approved of the final version of the paper and all authors agreed to be accountable for all aspects of the work.

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None

8 References

1. Mazzucco W, Cusimano R, Mazzola S. Childhood and adolescence cancers in the Palermo Province (Southern Italy):Ten years (2003-2012) of epidemiological surveillance. Int J Environ Res Public Health. 2018;15(7):1344

2. Cancer Network organization K. Kenya Cancer Statistics & National Strategies [Internet]. 2016 . Available from: https://kenyacancernetwork.wordpress.com/. Accessed 14th June 2018.

3. Mutuma G, Korir A. The burden of childhood cancers in nairobi, kenya (2000-2006) – pattern, trends, risk factors and epidemiology. Afr J Health Sci . 2011 ;19(3.4).

4. Philips S, Padgett L, Leisenring W, Stratton K, Bishop K, Krull K. Survivors of childhood cancer in the United States: prevalence and burden of morbidity. Cancer epidemiology, biomarkers & prevention : a publication of the American Association for Cancer Research, cosponsored by the American Society of Preventive Oncology. Am Soc Prev Oncol. 2015;24(4):653–63.

5. Lymphoma society L and Non-Hodgkin Lymphoma . 2013. 56 p. Available from: https://www.lls.org/sites/default/files/file_assets/nhl.pdf. Accessed 14th February 2018

6. Budiongo A, Ngiyulu R, Lebwaze B, Gini-Ehungu J, Mafuta E, Ekulu P. Pediatric non-Hodgkin lymphomas: first report from Central Africa. Pediatr Hematol Oncol. 2015;32(4):239–49.

7. Gross T T, Biondi andrea. Paediatric non-Hodgkin lymphoma in low and middle income countries. Br J Haematol. 2016 ;173(4):651–4.

8. AKa P, Kawira E, Masalu N, Emmanuel B, Brubaker G, Magatti J. Incidence and trends in Burkitt lymphoma in northern Tanzaniz from 2000 to 2009. Pediatr Blood Cancer. 2012 ;59(7):1234–8.

9. Omondi M, Opanga S, Martin A, Kurdi A, Goodman B. Pilot study assessing the direct medical cost of treating patients with cancer in Kenya; findings and implications for the future. J Med Econ. 2018;21(9):878–87.

10. Epeldegui M, Vendrame E, Martínez-Maza O. HIV-associated immune dysfunction and viral infection: role in the pathogenesis of AIDS-related lymphoma. J Immunol Res. 2010 ;48(0):72–83.

11. UNDP. UNDP on Botswana HIV [Internet]. Available from: http://www.bw.undp.org/content/botswana/en/home/ourwork/hiv_aids/overview.html. Accessed 10th January 2018.

12. Wang H, Wolock T, Nguyen G, Kyu H, Gakidou E, Hay S. Estimates of global,regional and national incidence,prevalence and mortality of HIV,1980-2015: the Global Burden of disease study 2015. Lancet HIV. 2016 ;3(8):361–87.

13. Ngambi P, Kalungia A, Law M, Kalemeera F, Goodman B, Munkombwe D. Evidence on the cost-effectiveness of lifelong antiretroviral therapy for prevention of mother to child transmission of HIV:Implications for resource-limited countries in sub-saharan Africa. Expert Rev Pharmacoeconomics Outcomes Res. 2017 ;17(5):459–67.

14. National AIDS Control Council. Kenya HIV estimates- Report 2018. 2018. Available at:https://nacc.or.ke/wp-content/uploads/2018/12/HIV-estimates-report-Kenya-20182.pdf. Accessed 1st April 2019.

15. Canadian Cancer Society. 2019, Risk factors for non-Hodgkin lymphoma.Available at: http://www.cancer.ca/en/cancer-information/cancer-type/non-hodgkin-lymphoma/risks/?region=on. Accessed 1st April 2019.

16. Mbulaiteye S, Bhatia K, Biggar R, Linet M, Devesa S. Sporadic Burkitt lymphoma incidence in the United states during 1992-2005. Pediatr Blood Cancer. 2009 ;53(3):366–70.

17. Huang H, Hsiao F, Chen L, Chen H, KO B. Women with Diffuse Large B cell Lymphoma Benefit from Rituximab-Containing Chemotherapy. J Womenens Health . 2018 Jun 20; Available from: https://visualizinghealthdata.idv.tw/?route=article/thesis&id=29924676. Accessed 20th July 2018.

18. Griffin M, Morley N. Rituximab in the treatment of non-Hodgkin's lymphoma--a critical evaluation of randomized controlled trials. Expert Opin Biol Ther. 2013;13(5):803–11.

19. American Cancer Society. Chemotherapy for Non-Hodgkin Lymphoma. . Available from: https://www.cancer.org/cancer/non-hodgkin-lymphoma/treating/chemotherapy.html. Accessed 14th June 2018

20. Zeltzer P, LeBaron S, Zeltzer L. Chemotherapy side effects in pediatric oncology patients: drugs, age, and sex as risk factors. Med Paediatr Oncol. 1988;16(4):263–8.

21. Fleishman B S. Understanding and managing chemotherapy side effects. Cancer care. 2018. Available from: https://media.cancercare.org/publications/original/24-ccc_chemo_side_effects.pdf. Accessed 25th July 2018.

22. Hamilton S. low blood counts-Managing side effects [Internet]. Chemocare. 2002 . Available from: http://chemocare.com/chemotherapy/side-effects/low-blood-counts. Accessed 14th June 2018.

23. WHO. WHO Guidelines on Pharmacological treatment of Persisting Pain in children with medical illnesses . 2012 p. 84. Available from: http://apps.who.int/iris/bitstream/handle/10665/44540/9789241548120_Guidelines.pdf;jsessionid=825223873BCC30B417A8D3887219D506?sequence=1. Accessed 5th October 2018.

24. Gotti, M, Fiaccadori, V, Bono, E, Landini, B, Varettoni, M, Arcaini, L, et al. Therapy-related late adverse events in Hodgkin's lymphoma. Lymphoma 2013;2013:1-7.

25. Cochran G, W. Sampling Techniques [Internet]. third. John Willey and Sons; 1977. Available from: https://hwbdocuments.env.nm.gov/Los%20Alamos%20National%20Labs/General/14447.pdf . Accessed 20th July 2018.

26. American Cancer Society. No Titlechemotherapy for non Hodking lymphoma . Available from: https://www.cancer.org/cancer/non-hodgkin-lymphoma/treating/chemotherapy.html. Accessed 29th June 2017.

27. American Cancer Society. About Non-Hodgkin Lymphoma in Children What Are the Differences Between Cancers in Adults and Children?2016 . Available from: https://www.cancer.org/content/dam/CRC/PDF/Public/8723.00.pdf. Accessed 29th June 2017.
28. National Cancer Institute. Childhood Non-Hodgkin Lymphoma Treatment (PDQ®): Health Professional Version. PDQ Cancer Information Summaries. 2017 . Available from: http://www.ncbi.nlm.nih.gov/pubmed/26389181. Accessed 29th June 2017.
29. Ministry of Health K. National Guidelines for Cancer Management Kenya August, 2013. 2013;22.
30. Dorak MT, Ebru K. Gender differences in cancer susceptibility: an inadequately addressed issue. Front Genet. 2012;3:1–11.
31. Muller AM., Ihorst G, Mertelsmann R, Engelhardt M. Epidemiology of non-Hodgkin's lymphoma (NHL): trends, geographic distribution, and etiology. Ann Hematol. 2005 ;84(1):1–12.
32. Masakhwe C, Ochanda H, Nyakoe N, Ochiel D, Waitumbi J. Frequency of Epstein - Barr Virus in Patients Presenting with Acute Febrile Illness in Kenya. PLoS ONE. 2016;11(5):1–14.
33. Scholten W. WHO Persisting Pediatric Pain Guidelines: A Research Agenda [Internet]. Powerpoint presented at: Third Partners Meeting on Better Medicines for Children; 2011; Geneva,Switzerland. Available from: http://www.who.int/childmedicines/partners/ScholtenW_Partners.pdf. Accessed 14th June 2018.
34. Atieno OM, Opanga S, Martin A, Kurdi A, Godman B. Pilot study assessing the direct medical cost of treating patients with cancer in Kenya; findings and implications for the future. Journal of medical economics. 2018;21(9):878-87
35. Ludwig, H, Gascón, P, Bokemeyer, C, Aapro, M, Boccadoro, M, Denhaerynck, K, et al. Outcomes of chemotherapy-induced (febrile) neutropenia prophylaxis with biosimilar filgrastim (Zarzio®) initiated "same-day"(< 24 h),"per-guidelines"(24–72 h), and "late"(> 72 h): findings from the MONITOR-GCSF study. Support Care Cancer 2018;1-12.
36. Geeta MG, Ajithkumar VT, Krishnakumar P ML et al. management of pain in leukemic children using WHO analgesic ladder. Indian J Pediatr (2010) 77: 665
37. Mbui J, Oluka M, Guantai E, Sinei K, Achieng' L, Baker A, et al. Prescription patterns and adequacy of blood pressure control among adult hypertensive patients in Kenya;Findings and implications. Expert Rev Clin Pharmacol. 2017 ;10(11):1263–71.

Tables

Table 1a: Prevalence of NHL in the paediatric ward at the time of data collection

Type of cancer	**Number of patients(n=72) n(%)**
Hodgkin's lymphoma	6 (8%)
Non –Hodgkin's lymphoma	12 (17%)
Leukemia	24 (33%)
Neuroblastoma	7 (10%)
Wilm's tumor	6 (8%)
Nasal pharyngeal cancer	4 (6%)
Rhabdomyosarcoma	4 (6%)
Osteogenic sarcoma	7 (10%)
Brain stem glioma	2 (3%)

Table 1b: Demographic characteristics of paediatric patients with Non-Hodgkin lymphoma (n=85).

Variable	Description	Frequency n=85	Percent (%)
Age(years)	< 5	29	34.1
	6-10	39	45.9
	11-15	17	20
	Mean(SD)	7.3(2.99)	
	Range(min, max)	10(3,13)	
Sex	Male	67	78.8
	Female	18	21.2
Weight(kg)	Mean(SD)	23.03(8.136)	
	Range(min, max)	44(10, 54)	
Height(cm)	Mean(SD)	118.11(16.666)	
	Range(min ,max)	73(75,148)	

Table 2: Clinical characteristics of paediatric patients with Non-Hodgkin Lymphoma at the Kenyatta National Hospital in Kenya.

Variable	Category/classification/description	Frequency n=85	Percent (%)
Type of Lymphoma	Burkitts Lymphoma	39	45.9
	Non Burkitts Lymphoma	44	51.8
	Burkitts relapse	1	1.2
	Non Burkitts Relapse	1	1.2
Diagnosis Methods	Clinical and Laboratory assessment	83	97.6
	Laboratory assessment Only	2	2.4
Treatment Phases	Induction	85	100.0
	Consolidation	52	61.2
	Maintenance	48	56.5
Treatment Phases Combined	Induction/Consolidation/maintenance	48	56.5
	Induction and Consolidation	4	4.7
	Induction Only	33	38.8

Table3: Comparison between the numbers of patients who experienced side effects of treatment versus those whose side effects were managed

Side effect	No. of patients experiencing having side effects (n=85)	No. of patients whose side effects were managed	Percentage of patients managed
Vomiting	79	75	95
Anaemia	75	58	77
Loss of appetite	73	73	100
Pain	71	67	94
Leucopenia	61	49	80
Dehydration	45	41	91
Mucositis	44	44	100
Hyponatremia	32	29	91
Constipation	29	28	97
Fever	28	23	82
Diarrhea	21	21	100
Acidity	18	18	100
Allergic reactions	17	13	76

Table 4: Intervention given for the management of side effects of chemotherapy for Non-Hodgkin Lymphoma in paediatric patients at a Public tertiary care hospital in Kenya

Side effect	Intervention
Vomiting	Ondansetron or granisetron, metoclopramide and dexamethasone
Anaemia	Ranferon and blood transfusion of packed red cells
Loss of appetite	Multivitamin syrup, counseling on high protein and lipid diet, predisure, ensure, vitalipid supplements and use of gastric tubes for those not able to feed properly.
Pain	Morphine, dihydrocodeine, paracetamol, ibuprofen and diclofenac
Leucopenia	Neupogen
Dehydration	Normal saline
Mucositis	Betadine mouth wash and miconazole gel
Hyponatremia	Normal saline
Constipation	Lactulose
Fever	Paracetamol tablets and syrup, ibuprofen
Diarrhea	ORS , zinc sulphate and loperamide
Hyperacidity	Omeprazole, esomeprazole and ulgel
Cystitis	Mesna
Secondary infections -chicken pox	Acyclovir and calamine lotion
Respiratory infections	Amoxicillin Clavulanate
Tinea capitis	Clotrimazole cream
Oral thrush	Nystatin
Insomnia	Midazolam

9 Appendix 1: Dose regimens used for management of Non-Hodgkin Lymphoma in Paediatrics at KNH.

A. CHOP REGIMEN-currently protocol of choice for induction of remission in Burkitt's Lymphoma at the KNH

(i) INDUCTION

DRUG	DOSAGE
Cyclophosphamide	500mg/m^2 IV on day 1 and weekly x6
Adriamycin/Doxorubicin	50mg/m^2 IV on day 1, 21, and 43
Vincristine	1.4mg/m^2 IV on day 1 and weekly X 6
Prednisone	40mg/m^2 orally daily for 4 weeks tail off to zero from week 5
Methotrexate	12.5mg/m^2 IT twice weekly during induction and consolidation

Consolidation starts 10-14 days after completing induction

(ii) CONSOLIDATION

DRUG	DOSAGE
Cyclophosphamide	1200mg/m^2 IV in saline over 8 hours on day 1 and 8
Adriamycin/Doxorubicin	60mg/m^2 IV on day 1
Cytarabine	75mg/m^2 SC days 1-4,22-25, 29-32

*Second course is given after 7 to 10 days of day 8. This does not include Adriamycin

Maintenance (24 months) starts 4 weeks after completing consolidation and is still remission

(III) MAINTENANCE

DRUG	DOSAGE
6-Mercaptopurine	75mg/m^2/ day ,PO on daily for 24 months
Methotrexate	25mg/m^2/week, PO weekly for 24 months. Rest period for two weeks in case of cytopenias for both 6MP and methotrexate
Vincristine	1.5mg/m^2 IV on day 1 and monthly for 24 months
IT MTX	Every 8 weeks for 1st year for those without CNS disease
Adriamycin	25mg/m^2 every three months for 24 months
Cyclophosphamide	300mg/m^2 every three months 24 months

In disease free events (continuing remission) this maintenance is continued for 24 months

B. CHOP-BLEO

DRUG	DOSAGE
Cyclophosphamide	1000mg/m^2 IV on day 1 and weekly x 6
Doxorubicin	50mg/m^2 IV on day 1, 21, and 43
Vincristine	2mg/m^2 IV on days 1 and 5 and weekly x 6
Prednisone	40mg/m^2 orally daily for 4 weeks tail off to zero from week 5
Bleomycin	15 units IV on days 1 and 5 during induction and consolidation
Methotrexate	12.5mg/m^2 IT twice weekly during induction and consolidation

1. Recurrent NHL before reaching maintenance may be re-induced using option B
2. Older children 8-15 years with Non-Burkitt's Non-Hodgkin's Lymphoma are better suited for this option (B)
   If indeed remission is achieved, consolidation and maintenance should be as Acute Lymphocytic Leukemia.