Clinical characteristics and treatment outcome of paediatric non-Hodgkin's lymphoma at a tertiary care hospital in Pakistan
Juverya Naqvi1, Mir Ibrahim Sajid2, Saiqa Khan3, Zaib-un-Nisa Kamran4, Zehra Fadoo5

Abstract
Objective: To highlight the clinical characteristics of paediatric patients presenting with non-Hodgkin's lymphoma, treatment toxicities, and outcome.
Method: The retrospective study was conducted at the Aga Khan University Hospital, Karachi, and comprised data of all paediatric patients aged 0-18 years diagnosed with non-Hodgkin's lymphoma from 2010 to 2020. Demographic characteristics, presentation, treatment provided, complications, if any, and treatment outcome were recorded. Data was analysed using SPSS 21.
Results: Of the 92 patients, 69(75.0%) were males. The overall mean age was 14.35±5.80 years. The most common presenting complaint was pyrexia 42(45.7%), the most common diagnosis was Burkitt lymphoma 40(43.5%), the most common complication related to gastrointestinal issues 8(15.7%), and most toxicities were reported with the use of FAB-LMB96 (French American-British Mature B-Cell Lymphoma 96) for B-cell non-Hodgkin's lymphoma 23(45.1%). Mortality was the outcome in 17(18.5%) cases, while 19(20.7%) patients were lost to follow-up. PFS and OS was 60.4%, and OS 81.3% respectively at 10 years follow-up, median PFS was 17.5 months ([IQR]: 4.5-43.5 months) (p=0.011) and median OS was 33.5 months (IQR: 19.5-84 months) (p=0.007).
Conclusion: Early recognition of symptoms, specialist care, and proper planning can decrease treatment-related complications that result in abandonment.
Keywords: Child, Retrospective studies, Progression-free survival, Burkitt lymphoma. (JPMA 72: 2161; 2023)
DOI: https://doi.org/10.47391/JPMA.6901
Submission completion date: 18-08-2022 - Acceptance date: 22-05-2023

Introduction
Among the commonly diagnosed malignant tumours, lymphomas, including Hodgkin's lymphoma (HL) and non-Hodgkin's lymphoma (NHL), follow leukaemia and brain tumours in paediatric age. Mature B-cell NHL (B-NHL) constitutes the most prevalent entity encountered in NHL, and is considered to be aggressive compared to HL in children. The incidence of NHL is steadily increasing in both low- and middle-income countries (LMICs) and high-income countries (HICs). A variety of factors, including environmental, chemical and infectious exposures, such as drugs, pesticide, solvents, hair dyes, viruses, may contribute. In HICs, the advances in diagnosis, intensification of chemotherapy, including control of central nervous system disease (CNS) and proper psychosocial and logistic support, have significantly improved overall survival (OS) because of newer research and immunological therapies. Unfortunately, in LMICs, the outcome remains dismal, with event-free survival (EFS) around 30% which is mostly due to deferred diagnosis, abandonment of treatment and deaths due to chemotherapy-induced complications.

The current study was planned to highlight the characteristics of NHL patients who presented to a tertiary care centre, treatment toxicities, and outcome.

Materials and Methods
The retrospective study was conducted from December 1, 2020, to June 30, 2021, at the Aga Khan University Hospital (AKUH), Karachi, and comprised data of all paediatric patients diagnosed with NHL between 2010 and 2020. Inclusion criterion was all patients aged <18 years with a confirmed NHL diagnosis who were diagnosed and treated at AKUH and had not taken any chemotherapy before presenting to AKUH. Exclusion criterion was patients with unconfirmed pathological diagnosis or those who presented with relapsed disease. Patients with missing data were also excluded.

After exemption from the institutional ethics review board, files of patients diagnosed with NHL were retrieved using International Classification of Diseases-10 (ICD-10) coding from hospital medical records. Data, extracted on a
proforma, included age, gender, clinical presentation, pathological and radiological investigations, treatment received, reported toxicities, and outcome.

Data was analysed using SPSS 21. Quantitative variables were presented as mean and standard deviations, while qualitative data was presented as frequencies and percentages. Progression-free survival (PFS) and OS were calculated using Kaplan-Meier curves.

**Results**

Of the 92 patients, 69 (75.0%) were males. The overall mean age was 14.35±5.80 years. The most common presenting complaint was pyrexia 42 (45.7%), followed by breathlessness 20 (22%) and pain in abdomen 17 (18.5%) (Table 1).

The most common region involved was abdomen-pelvis 43 (46.7%), followed by mediastinum 23 (25%) and head-and-neck 17 (18.5%) (Table 2).

Burkitt lymphoma (BL) was diagnosed in 40 (43.5%) patients; stage II-group B 17 (42.5%) and stage IV-group C 12 (30%). The second most common diagnosis was T-cell NHL (T-NHL) 17 (18.5%), followed by diffuse large B-cell lymphoma (DLBCL) 14 (15.2%) patients; stage III 8 (57.1%), stage 2-group B 2 (14.3%), stage IV-group C 2 (14.3%).

Haematological parameters showed bi-cytopenia in 28 (30.4%), and pancytopenia in 8 (8.7%) patients. Burkitt translocation (t8;14) by fluorescent in-situ hybridisation (FISH) was detected in 19 (20.7%) patients. Cerebrospinal fluid (CSF) involvement (cytology positive) was found in 14 (15.2%) patients; 7 (50%) had underlying BL diagnosis, 3 (21%) had ALCL (Anaplastic Large Cell Lymphoma), 2 (14%) had T-cell lymphoma and 1 (7%) each had DLBCL (diffuse large B-cell Lymphoma) and B-cell lymphoblastic lymphoma (BLL). Chest X-ray revealed a mediastinal mass in 8 (8.7%) patients.

The three most common findings on computed tomography (CT) scan were multiple enlarged lymph nodes (LNs) in 21 (22.8%) patients, followed by mediastinal mass 12 (13%) and hepatosplenomegaly 6 (6.5%).

All mature B-cell NHL (B-NHL) 41 (44.6%) were treated based on the FAB-LMB96 protocol, and T-NHL patients were treated with BFM-based (Berlin-Frankfurt-Münster) Children Oncology Group COG AALL0434 20 (21.7%), and ALCL-99 11 (12%).

Treatment-related toxicities were reported in 51 (55.4%) patients. Episodes of febrile neutropenia requiring stay in hospital/intravenous (IV) antibiotics were most commonly observed 36 (39%) followed by gastrointestinal issues 8 (8.7%) and neurological toxicity 5 (5.4%) (Table 3).

Concerning the treatment outcome, 52 (56.5%) patients completed the treatment as planned, 19 (20.7%) were lost to follow-up, and 17 (18.5%) died. The relapse rate was 2 (2.2%). At 10-year follow-up, PFS and OS was 60.4%, and OS 81.3% respectively, median PFS was 17.5 months (IQR: 4.5-43.5 months) (p=0.011) (Figure 1), and median OS was 33.5 months (IQR: 19.5-84 months) (p=0.007) (Figure 2).
NHLs carry a malignant potential to other organs of the body. These neoplasms have a distinct biological and cytotoxic behaviour and are very responsive to therapy. The incidence of NHL increases with age and carries a multifactorial aetiology. Among the most widely recognised causes are the Epstein-Barr virus (EBV), human immunodeficiency virus (HIV) and lymphomas secondary to immunosuppressive disorders. Other infectious agents responsible for development of lymphomas are human herpesvirus 8, T-lymphotropic virus type 1 and hepatitis B and C viruses.

Most of the patients present with painless lymphadenopathy, night sweats, unexplained significant weight-loss and fever. Since clinical presentation can be indistinct and vary on a large spectrum, the diagnosis is made on tissue biopsy, according to the World Health Organisation (WHO) classification of lymphoid neoplasms, and staging is mainly done clinically. Staging includes physical examination (primary site and tumour load), complete blood count (CBC) with morphology and bone marrow detailed examination, CSF analyses, ultrasonography, X-ray, CT and/or magnetic resonance imaging (MRI), skeletal scintigraphy and serum lactate dehydrogenase (LDH) levels.

In the current study, among the NHL tumour subtypes, BL was the topmost histological diagnosis, followed by T-NHL and DLBCL. A similar study comprising 2,084 patients reported 48% BL, followed by LL 21% and DLBCL 2%. The current study had 15.2% DLBCL. Age distribution of various types of NHL was also similar with patients <15 years primarily having BL, T-NHL and ALCL, and those 15 years and above frequently presenting with DLBCL, T-NHL and BL. The current findings were similar. BFM group had a male-female ratio of 2.7:1, which was almost identical to the current cohort; 3:1. Also, a low CNS and bone marrow involvement was reported at 5% and 19% respectively.

Another study from Pakistan reported almost similar gender distribution.

There have been major advances in the treatment of paediatric NHL patients. Historically, BL was one of the first cancers treated successfully with chemotherapy alone. Studies from LMICs reported that children present with advanced stages of BL with comorbidities have low survival rates compared to the children in HICs. Multiple studies have reported 3- or 5-year EFS at 70-90% in mature B-NHL, 75-85% in T-NHL, and 65%-75% in ALCLs. A study reported the treatment of 749 patients with a 5-year OS and EFS of 89% and 84% respectively. The current study showed similar parameters.

Treatment abandonment, which is 4 weeks or more of missed appointments all through the treatment, is a foremost concern facing LMIC settings, whereas the relapsed aggressive mature B-NHLs are even harder to salvage. Hence, continuity of treatment perhaps is the key to preventing adverse outcomes. In the current limited cohort, 5% abandonment was noted. A study in Malawi found that the most significant pointer for treatment abandonment was lack of care-giver education and travel time greater than four hours. Another study found that the primary reason for treatment abandonment were financial constraints, followed by belief of incurability, serious side effects and apprehensions over late complications. Although the current study did not formally interview those who abandoned, but financial aspect and risk of toxicity were felt to be the major driving forces for abandonment.

Hence, it is important to educate patients, especially their parents/guardians, on the importance of continuity of treatment once initiated and to ensure prompt follow-ups.

The current regimen of high-dose chemotherapy comprising commonly accessible and mostly inexpensive generic drugs are administered according to the patient’s risk group. However, as dose intensity increases, so does the rate of toxic deaths, which in literature have been reported to be up to 10.8%. The most dangerous acute toxicities include severe oro-intestinal mucositis, produced predominantly but not exclusively by high-dose methotrexate, and severe neutropenia, together causing serious infections. The risk in the early days of treatment has decreased due to the cytoreductive pre-phase, which consists of corticosteroids, low-dose cyclophosphamide, and urate oxidase to prevent or treat tumour lysis syndrome.

The current study has limitations, like a small sample and retrospective design with limited follow-up. Also, there...
were many patients who had been lost to follow-up. Prospective studies with larger representative samples are needed to confirm the findings.

**Conclusion**
The paediatric NHL patient's cohort showed characteristics comparable to those reported from other developing countries. A thorough understanding of clinical characteristics, together with demographics, will help hospitals formulate better guidelines and allocate sufficient resources, especially for meticulous supportive care and logistic support to decrease the abandonments and toxic deaths. Only after addressing such factors that an LMIC healthcare system can achieve better PFS and OS.

**Acknowledgment:** We are grateful to Mr Salman Soomar for statistical assistance.

**Disclaimer:** None.

**Conflict of Interest:** None.

**Source of Funding:** None.

**References**