ORIGINAL ARTICLE

Pediatric Lymphoma among Immigrant Children in Saudi Arabia

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Abstract

Little is known regarding the clinical presentation and treatment outcomes of childhood lymphoma among children of international workers and unauthorized immigrants in Saudi Arabia. A retrospective chart review was performed for all immigrant children (< 15 years in age) who had been diagnosed with lymphoma and managed at King Abdulaziz University Hospital from December 2015 to February 2020. Descriptive statistics using SPSS were conducted to evaluate the clinical characteristics of the patients. Event-free survival and overall survival were calculated using Kaplan–Meier survival analysis. A total of 15 children with lymphoma were included in the study period: 10 children as Non-Hodgkin lymphoma and five children as Hodgkin lymphoma cases. A medium follow-up of 36 months was conducted for all patients. The three-year event free and overall survivals were 90% for Non-Hodgkin lymphoma while were 100% for Hodgkin lymphoma. Significantly advanced disease and initial severe side effects were encountered, which mandated individualized treatment approaches to mitigate such risk factors and complications. An individualized treatment approach for unique, vulnerable children with lymphoma is feasible and critical.

Keywords

Non-Hodgkin lymphoma; Hodgkin lymphoma; Immigrants; Children

Introduction

Lymphoma is the third most common form of childhood cancer worldwide[1]. Lymphoma should be suspected when a child presents with persistent lymphadenopathy, fever, and weight loss[2]. Moreover, lymphoma needs a high index of suspension since it can present aggressively with life-threatening features[2]. Lymphoma is broadly classified into two main types: Hodgkin's and non-Hodgkin's lymphoma (NHL)[2]. Hodgkin's lymphoma (HL) can be further subdivided into Classic HL (CHL) and Nodular Lymphocyte Predominant (NLP). The vast majority of pediatric NHL is comprised of four main types: Burkitt Lymphoma (BL), Diffuse Large B Cell Lymphoma (DLBCL), Anaplastic Large Cell Lymphoma (ALCL), and Lymphoblastic Lymphoma (LL)[2].

Socioeconomic status and access to care are factors that affect patient outcomes[3]. The health care system in Saudi Arabia is free for citizens and insured patients[4]. However, there are approximately 13 million immigrants living in Saudi Arabia as per the most recent United Nation 2019 Report[5]. Although the exact number is not known, some of those immigrants

may lack either legal papers or comprehensive medical insurance. Those people and their families face significant obstacles when dealing with medical issues, including language barriers, fear of deportation, financial barriers, and socio-cultural barriers.

Located in the Western Province of Saudi Arabia, King Abdulaziz University Hospital (KAUH) is a non-profit organization that provides free-of-charge services for children with cancer regardless of nationality or insurance status, in contrast to the above-mentioned health system features. King Abdulaziz University Hospital is the only hospital in the region capable of providing free and comprehensive care for non-Saudi children with cancer. To our knowledge, no previous studies of this unique and vulnerable population in our country have been conducted. Therefore, the objective of this study was to report the clinical characteristics and outcome data of childhood pediatric lymphoma associated with this distinct and vulnerable group.

Methods

Data collection and analysis

Retrospective chart review was done for consecutive children (1-14 years) with childhood lymphoma, who were diagnosed and managed at KAUH from December 2015 to February 2020. Demographic, clinical, laboratory, and outcomes data were captured and analyzed using the IBM SPSS Statistics for Windows, Version 24 (IBM Corp., Armonk, NY USA). Event-free survival (EFS) was computed from the date of diagnosis to the date of the event, which defined as relapse, progression, or death. Overall survival (OS) was calculated from the date of diagnosis to the date of death or last follow-up. Kaplan-Meier analysis was used to calculate EFS and OS. The institutional research ethics committee approved the study.

Diagnosis and treatment protocols

All patients were diagnosed and subsequently managed based on pre-defined institutional procedures and protocols. Once the diagnoses were confirmed, pre-treatment diagnostic tests and staging workup were conducted; which typically included comprehensive laboratory workup, diagnostic pan computed tomography (CT) scan, bone marrow aspirate and biopsy, flow cytometry, cytogenetic and molecular testing, lumbar puncture (for NHL), baseline echocardiogram, and chest radiograph. After the staging workup was completed, a final staging and risk assignment was performed. For HL, the Ann Arber staging system was used while for NHL, the St. Jude System (Murphy Staging System) was typically used[6]. Hodgkin's lymphoma and NHL patients were treated with risk-adapted and response-based approaches. Subsequently, HL and NHL patients were managed per the institutional pre-selected standard of care protocol (See Table 1). Nonetheless, in the best interests of the patients, individualized management approaches were always considered.

Results

Clinical characteristics

A total of 15 newly diagnosed children with lymphoma were included in the study period. Clinical characteristics are shown in Table 2. The median age at diagnosis was five years (1 - 13). Nine (60%) patients were female, and six (40%) were male. The majority of lymphoma subjects had NHL (10 cases; 67%), and 33% of the subjects had HL.

Of the NHL cases, 60% were mature B cell lymphoma (BL and DLBCL), 20% were LL, and the remaining 20% were ALCL. The clinical presentations

Table 1. Institutional standard of care protocols

Disease	Protocol	Drugs
Hodgkin's lymphoma		
Classic HL	ABVD	A, Adriamycin; B, bleomycin; V, vinblastine; D, Dacarbazine
NLP HL	R-CHOP	R: Rituximab; C: Cyclophosphamide; H: Hydroxydaunorubicin; O: Vincristine sulfate (Oncovin); P: Prednisone
Non-Hodgkin's lymphoma		
Mature B cell	**ANHL1131**	Different cycles of chemotherapy
ALCL	ALCL - 99 protocol	Different cycles of chemotherapy
T cell LL	Treated as acute lymphoblastic leukemia	Different cycles of chemotherapy

HL: Hodgkin's lymphoma; ABVD: (A: Adriamycin; B: bleomycin; V: vinblastine; D: Dacarbazine); NLP: Nodular lymphocyte predominant; ANHL1131: Intergroup Trial for Children or Adolescents with B-cell NHL or B-AL; ALCL: Anaplastic large cell lymphoma; LL: Lymphoblastic lymphoma

Table 2. **Patients' chrematistics**

Item	N	%
Age (years)		
< 5	2	20
5 - 10	4	40
> 10	4	40
Gender		
Male	6	40
Female	9	60
Type		
Hodgkin's lymphoma	5	33
Non-Hodgkin's lymphoma	10	67
Hodgkin's lymphoma		
Classic Hodgkin's lymphoma	3	60
Nodular lymphocyte predominant	2	40
Non-Hodgkin's lymphoma		
Mature B cell	6	60
Lymphoblastic lymphoma	2	20
Anaplastic large cell lymphoma	2	20
Hodgkin's lymphoma stage		
I/II	2	40
III/IV	3	60
Non-Hodgkin's lymphoma stage		
I/II	2	20
III/IV	8	80

of NHL varied according to the disease type. However, NHL patients commonly (80% of cases) presented with systemic symptoms, including fever, unexplained weight loss, and local symptoms at the involved site(s). The majority of mature B cell lymphomas (80%) originated in the abdomen, while T cell LL presented primarily as mediastinal masses in all patients. One case of ALCL presented as primary bony lymphoma, and another case originated in the head and neck area. The majority of NHL cases had progressed to the advanced stage (III/IV), as shown in Table 2. Of note, a severely malnourished macerated child with advance end-stage renal failure presented with BL at an advanced stage very late (one-year from initial surgery). Unfortunately, this patient died shortly after admission before receiving any chemotherapy.

Of the HL cases, two were NLP HL, and three were CHL. The NLP cases all presented as persistent cervical lymphadenopathy, which was confirmed to be NLP HL based on excisional biopsies. Both cases of NLP were stage IIA. CHL cases presented with more systemic symptoms (fever, weight loss) and more advanced lymphadenopathy. Interestingly, one CHL case presented with severe autoimmune hemolytic anemia, with a Hb value of 2 g/dl. Another CHL case presented with heart failure-like symptoms due to long-standing HL; echocardiography confirmed a reduced ejection fraction of 25%.

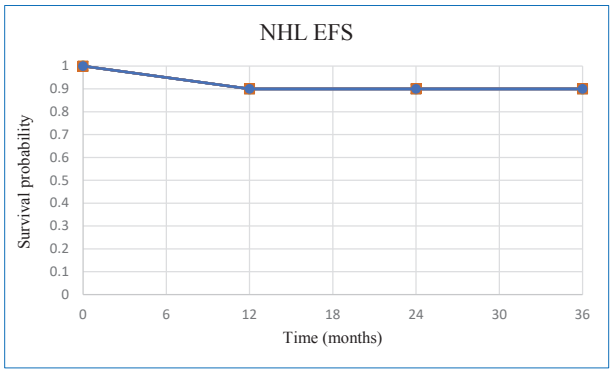
Treatment response and outcome

Non-Hodgkin's lymphoma patients

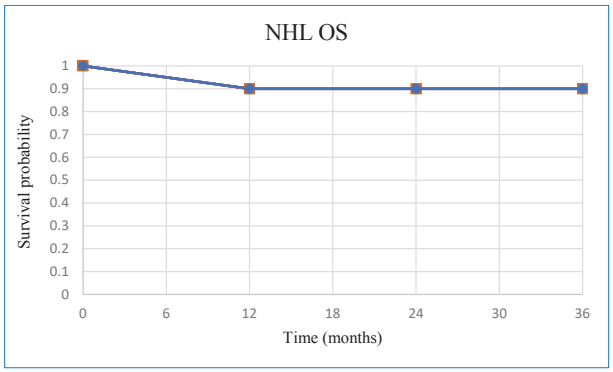
Except for one case, all cases received and completed the intended treatment protocols. Most of the patients had a difficult time starting the initial chemotherapy as a whole which led to individualization of the treatment. Tumor lysis syndrome was encountered in 50% of the cases, which required aggressive electrolyte management, including dialysis in three cases and active cardiac shock in two cases. Critical airway obstruction was encountered in the two cases of T cell LL, which mandated steroid pre-biopsy to mitigate the risk of anesthesia and diagnostic procedures. Such serious complications are mandated by the protocols to extend the initial light phase of chemotherapy known as CVP (low dose cyclophosphamide, vincristine and prednisolone) in order to mitigate the expected risks and complications of the upcoming aggressive courses of chemotherapy. The median follow-up time for NHL patients was 33 months (range 14 - 50 months). Follow-up data were available for all patients. As depicted in Figure 1, the three-year OS for all patients was 90%, and the three-year EFS was 90%. Although it maybe too early to comment on the long-term follow up, the survived patients are doing so far well at last time seen in the follow up clinic (average of three years).

Hodgkin's lymphoma patients

All five HL patients received the intended course of therapy. Most patients tolerated chemotherapy with the expected side effects, including febrile neutropenia, mucositis, hypertension and tumor lysis syndrome. Two NLP HL cases presented as stage IIA and were managed with three cycles of rituximab + CHOP (C: Cyclophosphamide; H: Hydroxydaunorubicin; O: Vincristine sulfate (Oncovin); P: Prednisone) without radiotherapy. Both achieved complete remission and continue to do well to date and had complete immunological recovery post-rituximab at six months' post-therapy. Three CHL cases presented at an advanced stage III or IV and were managed with individualized protocols; one protocol used EBVD (E: Etoposide; B: bleomycin; V: vinblastine; D: Dacarbazine) instead of ABVD (A: Adriamycin; B: bleomycin; V: vinblastine; D: Dacarbazine); *i.e.,* avoidance of anthracycline because of reduced cardiac function. Such protocol used etoposide instead of Adriamycin. Another patient required pre-steroid therapy for severe life-threatening autoimmune hemolytic anemia. Interim response evaluations (positron emission tomography or gallium



A. Event-free survival



B. Overall survival

Figure 1. A). Event-free survival and B). Overall survival of Non-Hodgkin's lymphoma.

scan) indicated good partial response, necessitating complementary radiotherapy to residual sites. The median follow-up time for study patients was 30 months (range 12 - 48 months). Follow-up data were available for all HL patients. The three-year OS for all patients was 100%, and the three-year EFS was 100%. Of note, all paraneoplastic phenomena (hemolytic anemia and reduced cardiac function) entirely resolved by treating the HL.

Discussion

Access to care and education levels play essential roles in early diagnosis and management of health-related issues[7]. Cancer care is very complex and requires dedicated and expedited access and time to enable such care. Such features are not always available to specific groups of people. Roughly 13 million non-Saudi workers or inhabitants live in Saudi Arabia and some of them may lack either without legal papers or with limited health insurance coverage[5]. Such obstacles may place such people in awkward positions when seeking health care. Also, language barriers and fear of deportation can worsen the situation. Collectively, these factors may prevent or significantly delay cancer care. Affected children may die before reaching a health care center or may present with an advanced stage of the disease, as shown in our cohort.

In agreement with previous reports, vulnerable groups of patients are faced with a number of health-related issues including, but not limited to presenting with an advanced stage of the disease, and concurrent malnourishment and steroid pre-treatment in cases of hematological malignancies such as leukemia or lymphoma, which may jeopardize the efficacy of treatment due to chemotherapy resistance[8]. In addition, line access, which is an essential part of cancer therapy, is difficult in situations of severe malnourishment and advanced disease stage. In addition, there is a psychosocial burden on an already impoverished family that must care for a child with cancer.

Recognizing the above issues and barriers, multiple levels of support have been used to facilitate and manage patients and families. First, at a higher administration level, various attempts have been made to keep cancer patients exempt from any financial charges, irrespective of their health insurance status. Besides, such patients should be fast-tracked by expediting their file opening and admission at the initial visit. Second, building a comprehensive childhood cancer care (4C), including medical (specialized physicians, nurses, dietitians, pharmacists, and others) and psychosocial teams that help patients and their families. Third, translation services are readily available through the hospital or by using volunteer families who speak the same language. Forth, financial support was successful at our center due to fundraising parties as well as joining dedicated charity societies that provide accommodations, travel expenses, and support funds for patients and their families.

Despite all of the obstacles facing the families and the oncology team, treatment outcomes are approaching those reported in Western Countries[9-11]. These results were accomplished because of aggressive supportive care as well as tailoring/individualizing treatment protocols based on the needs of each patient. We managed to safely deliver high-intensity chemotherapy to our cohort with zero incidences of treatment related mortality. Another lesson learned, is the conservative use of the central lines in our setting due to recurrent serious infections in such patients.

Our study has several drawbacks; these include the retrospective design, small sample size, and relatively short follow-up periods.

Conflict of Interest

The author declared that there is no conflict of interest that is related to this study and this article.

Disclosure

The author did not receive any type of commercial support either in the form of compensation or financial support for this case report. The author has no financial interest in any of the products, devices, or drugs mentioned in this article.

Ethical Approval

The study was approved by the Ethics Committee of the KAUH in Jeddah, Kingdom of Saudi Arabia, also known as the Institutional Review Board of Hospitals.

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سرطان الغدد الليمفاوية بين الأطفال المهاجرين في المملكة العربية السعودية

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المستخلص. لا يُعرف الكثير عن الاعراض السريرية ونتائج علاج سرطان الغدد الليمفاوية لدى الأطفال بين أطفال العمال الدوليين والمهاجرين غير المرخص لهم في المملكة العربية السعودية. لذا كان الهدف دراسة أحوال ونتائج العلاج لهذه الفئة من الأطفال. تم إجراء مراجعة بيانية بأثر رجعي لجميع أطفال المهاجرين (أقل من ١٥ عامًا) الذين تم تشخيصهم وعلاجهم في مستشفى جامعة الملك عبد العزيز بجدة في الفترة من ديسمبر ٢٠١٥ إلى فبراير ٢٠٢٠. تم إجراء إحصائيات وصفية واحصاء نتائج العلاج ونسب الشفاء. تم دراسة ١٥ طفل في فترة البحث؛ وكانت الغالبية تمثل سرطان الغدد الليمفاوية - غير الهودجكين (٦٧٪). الصفة الظاهرة كانت التأخر الشديد في الوصول الى المستشفى. متوسط فترة المتابعة لجميع المرضى كانت ٣٦ شهر وكانت نسبة الشفاء خلال الثلاث سنوات تبلغ حولي ٩٠٪ لسرطان الغدد الليمفاوية - غير الهودجكين ونسبة١٠٠٪ لسرطان الغدد الليمفاوية –الهودجكين. أظهرت الدراسة ان علاج هذه الفئة المستضعفة من الأطفال المصابين بسرطان الغدد الليمفاوية ممكن ويتطلب عناية خاصة وتقنين للعلاج الكيماوي بما يتناسب مع وضعهم الصحي.

الكلمات الفتاحية: سرطان الغدد الليمفاوية - غير الهودجكين؛ سرطان الغدد الليمفاوية – الهودجكين؛ المهاجرون؛ الأطفال