Outcomes of Pediatric Hodgkin Lymphoma; A retrospective review of children and adolescents with Hodgkin lymphoma treated at King Fahad Medical City, Riyadh, 2006-2017

Amal Daghriri[1], FAHD AL MANJOMI[2], and Bilal AlBtoosh[1]

[1]King Fahad Medical City
[2]king fahad medical city

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Abstract

Background: Treatment outcomes for children and adolescents with Hodgkin lymphoma (HL) have improved over the past few decades. Most patients achieve long-term remission with a five-year survival of approximately 90%, as reported by different treatment groups in developed countries. However, there are limited data on the outcome of patients treated in developing countries. Here we report the outcomes of children and adolescents treated at a comprehensive cancer center in Riyadh, Saudi Arabia. Procedure: A retrospective review of the medical records of all pediatric patients younger than 16 years who were diagnosed with HL from July 2006 through December 2017 was performed. Results: Of the 54 patients with HL, 70.37% were boys with a median age of 9 years (mean ± SD, 9.11 ± 3.30). A total of 51.85% had B symptoms and 33.33% had bulky disease. The nodular sclerosis type was the most common histological subtype (48.15%). In total, 74.07% of the patients presented with advanced stage III and IV disease. The three-years relapse-free survival rate was approximately 82%, and the three overall survival (OS) rate was more than 95%. Conclusions: Survival outcomes in children and adolescents with HL in Saudi Arabia have improved with a five-year OS rate now exceeding 85%. However, further prospective larger collaborative studies are necessary.

Introduction

Hodgkin lymphoma (HL) is a curable malignancy of type B cells. This disease affects approximately 8000 new patients in the United States annually[1]. Worldwide, HL is more common in males, and it shows a bimodal pattern according to age. In developed countries, the peak incidence occurs between 15 and 35 years of age, whereas the incidence is higher in young children in developing countries[2]. The epidemiological, clinical, and pathological features vary according to geographic areas and the socioeconomic status of a given country[3-8]. HL is divided into two major types: classical and nodular lymphocyte-predominant, or non-classical. Nodular sclerosis, mixed cellularity, lymphocyte depletion, and lymphocyte-rich are subgroups of classical HL according to the 2008 WHO classification. The most common classical sub-type is nodular sclerosis, which has stable incidence rates[9-11]; conversely, studies have documented persistently decreasing rates of mixed cellularity[9,11,12]. The etiology of HL is unknown; however, Epstein–Barr virus infection is the most common risk factor and is associated with half of all cases[13]. Other risk factors include immunodeficiencies, a family history of lymphoma or immune deficiency, and socioeconomic status[14,15]. Approximately 25% of patients develop B symptoms, which include a fever higher than 38°C, night sweats, or weight loss of more than 10% of body weight within the last six months. The current standard for staging HL in children is the Ann Arbor staging system with Cotswolds' modification. This classification includes four stages, with stages I and II indicating localized disease and stages III and IV indicating advanced disease. Accurate assessments of the disease stage are essential for selecting the appropriate treatment. Risk stratification at diagnosis could al-

low earlier and more efficacious treatment modifications. The Childhood Hodgkin Lymphoma International Prognostic Score (CHIPS) system describes four clinical factors that are predictive of a worse event-free survival (EFS): advanced stage, large mediastinal adenopathy, low albumin, and fever[16]. Positron emission tomography scanning can identify the risk of recurrence and the response to therapy[17]. Bhethanabhotla et al identified that patients with advanced stage disease, a high total leukocyte count, and lymphopenia were associated with treatment failure compared with patients without these risk factors[18]. Adolescents and young adults shared similar clinical presentations, suggesting a rationale of harmonized treatment for these groups[19]. Treatment outcomes for children and adolescents with HL have improved over the past few decades, and most such patients have achieved long-term remission with a five-year survival rate of approximately 90% according to different treatment groups in developed countries. The goal of treatment is to reduce toxicity rather than cure the disease. The standard therapy for children and adolescents with Hodgkin's disease includes combination chemotherapy and low-dose involved-field radiation (LD-IFRT). Patients who received LD-IFRT had a significant EFS advantage compared with patients receiving only chemotherapy[20]. A recent report from the Dana-Farber/Boston Children's Cancer and Blood Disorder's Center by Ozuah NW et al demonstrated excellent survival with the omission of radiotherapy in more than 50% of pediatric patients with advanced HL who were treated with a dose-intensive chemotherapy regimen[21]. A greater challenge for clinical management is that 10%–25% of cases are relapse/refractory. There is currently no gold standard for second-line treatment, but the retrieval regimen for relapse and refractory patients includes salvage chemotherapy and high-dose chemotherapy, followed by autologous stem cell transplantation (ASCT). Similar to adult patients, pediatric patients show poor prognosis associated with a first relapse within one year from the time of diagnosis[22]. Most children and adolescents with relapsed HL who are treated with high-dose therapy and stem cell transplant achieve good remission[23].

The primary long-term complication of HL treatment is the development of secondary malignancy, which remains a cause for concern, particularly for pediatric HL patients.

We aimed to perform a baseline evaluation of the overall survival (OS) and EFS of our pediatric patients to review our guidelines for the diagnosis, treatment, and management of HL pediatric patients and to improve the outcomes of pediatric HL in Saudi Arabia.

Patients and Methods:

Study design:

The medical records of all pediatric HL patients less than 16 years old who were diagnosed and treated in the pediatric hematology/oncology service at PHO-KFMC, Riyadh, Saudi Arabia, from July 1, 2006 to December 31, 2017 were retrospectively reviewed. This study was approved by the research and ethical committees of our hospital Institutional Review Board (IRB). Patient data including age and gender, presenting symptoms, family history, routine laboratory results, disease diagnosis (histological subtypes), staging, treatment plan, follow-up, and outcome were collected from the hospital computer system (CORTTEX, CENTRICITY & HIM).

Patients:

HL was diagnosed based on histopathologic and immunophenotypic studies performed at our histopathology lab. Cases were histologically classified according to the WHO classification. At diagnosis, all patients underwent computed tomography (CT) scans of the neck, chest, and abdomen. Fluorodeoxyglucose-positron emission tomography (FDG-PET) scans were performed for all patients either inside or outside our hospital. Bone marrow aspiration and biopsy were performed for the patients with intermediate and high-risk factors. Clinical staging was performed following the Ann Arbor classification. Bulky disease was defined as a lymph node mass with a diameter greater than 6 cm or a mediastinal mass exceeding one-third of the maximum mediastinal width on an upright poster anterior chest radiograph. Patients classified as stage I and II without risk factors were considered low risk whereas patients classified as stages I and II with risk factors and stage IIIA irrespective of risk factors were considered intermediate risk. High risk included all cases of stages IIIB and IV irrespective of risk factors. Risk factors of HL include bulky mediastinal diseases, the presence of B

symptoms, extra nodal diseases, and a high ESR greater than 30 mm/h.

Treatment Protocol:

Most of our patients were treated with chemotherapy according to the Children Oncology Group (COG) protocol, and some patients were treated according to the EuroNet-PHL-C1 protocol. Low-risk patients were treated with four cycles of doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD). Intermediate-risk patients were treated with doxorubicin, vincristine, prednisone, and cyclophosphamide (AVPC) or doxorubicin, bleomycin, vincristine, etoposide, prednisone, and cyclophosphamide (ABVEPC). High-risk patients were treated with bleomycin, etoposide, Adriamycin, cyclophosphamide, vincristine, procarbazine, and prednisone (BEACOPP) or according to the EuroNet-PHL-C1 protocol (vincristine, etoposide, prednisone, doxorubicin, cyclophosphamide, vincristine, prednisone, and dacarbazine (OEPA-COPDAC)). Patients with an inadequate response to initial chemotherapy or bulky disease received involved field radiotherapy. PET/Gallium scans were performed for all patients at the time of initial diagnosis, during mid cycles of chemotherapy, and at the end of therapy in patients with partial response (PR) or stable disease (SD). Responses according to the PET scan results were categorized as follows: complete response (CR), which was defined as the complete disappearance of disease on radiography or more than 70% disappearance; PR, which was defined as a more than 50% decrease in the diameter of measurable lesions; progressive disease (PD), which was defined as a more than 50% increase in the diameter of measurable lesions or the detection of new lesions; and SD, which was defined as a failure to attain CR, PR, or PD. Following therapy completion, the patients continued to be followed-up in the Pediatric Oncology clinics. The patients were generally seen in the clinic four times a year during the first three years of follow-up, followed by every six months for the next three years and then annually.

Statistical analysis:

The dataset was prepared using SPPS for Windows Version 20. After performing quality control and assurance of the dataset, descriptive statistics were calculated. The outcome analysis was performed in light of the identified risk factors. Chi-square tests along with Fisher's exact test were used to identify the relationships between dependent variables. A bivariate analysis of the continuous data was performed using the Student's t-test for parametric distributions and the relevant non-parametric tests for non-normal datasets. OS and EFS were calculated using the Kaplan-Meier survival analysis and compared for independent variables identified in the Western literature.

Results:

From July 1, 2006 to December 31, 2017, 54 patients with HL were admitted to the Pediatric Oncology Unit of King Fahad Medical City Hospital. Two patients were excluded from the study, one of whom was immunodeficient and other who died at the time of treatment initiation.**Table 1** displays the clinical characteristics of the included patients. The median age was 9.22 years (mean +- SD, 9.11 +- 3.30). Sixteen patients were girls and 38 were boys (70.37%). B symptoms were present in 51.85% of patients and bulky disease in 33.33%. 27 patients had a high ESR of more than 30 mml/h. Data on EBV status were available for only 62.96% of patients (n = 34), and six patients were positive either by serology or PCR. The most commonly diagnosed histological subtype was nodular sclerosis (48.15%), followed by mixed cellularity. The lymphocyte-rich type was identified in 5.56% of patients, the nodular lymphocyte-predominant type was diagnosed in only five patients (9.26%), and no patients were diagnosed with the lymphocyte depleted type. We were unable to identify the histological subtype in six patients.

All patients were staged using the Ann Arbor staging system. Forty patients were classified as stages III and IV (74.07%), and 25.92% had localized disease.

Initial Therapy:

The median follow-up period was 43 months. Eight patients (14.81%) received ABVD (low-risk protocol) chemotherapy as the first-line therapy. Most of the patients received high-risk protocol chemotherapy (17

(31.48%) received the COG high-risk protocol whereas 11 (20.37%) received the Euro net high-risk protocol as in **Table 2** . Nineteen patients (35.19%) received radiotherapy.

Response and Disease Outcome:

The mean follow-up period for patients was 4.09 years (range, 0.47 to 11.30 years). Most of the patients with HL achieved CR (75.93%); 1.85% achieved PR, 3.70% achieved SD, and 3.70% had disease progression (**Table 3**).

Eight patients (14.81%) relapsed after the first-line therapy, of whom two achieved CR after chemotherapy and radiation and the others were referred for transplant after salvage therapy and no more follow-up. For most patients, relapse occurred with two years of their diagnosis. More than half of the relapsed patients were classified as stage IV at the time of initial diagnosis; this relationship was statistically significant **($P = 0.026$)** as in **Figure 1** . There was no statistically significant difference in the relapse rate between patients who received radiation and those who did not ($P = 0.392$) (**Table 4 and Figure 2**).

The EFS rate of classical HL was 82% as in **Figure 3** , and the OS for classical HL was 98% as in **Figure 4** . The EFS and OS for non-classical HL were 100%.

Treatment toxicity

Within our retrospective study, three patients developed invasive infections during treatment, one of whom died from an invasive streptococcus infection. One patient had pulmonary fibrosis secondary to bleomycin, two patients had cardiac toxicity, two patients had renal toxicity, and six patients had neurotoxicity. We did not document the secondary malignancy toxicities after the treatment in this study (**Table 5**)

Discussion

HL accounts for 3.6% of all cancers in Saudi Arabia, with 436 new cases among Saudi nationals in 2015 according to the Saudi Cancer Registry[24]. In the present study, we describe the clinical characteristics, diagnosis, management, and outcomes of 54 patients less than 16 years old with HL who were diagnosed and treated at the Pediatric Oncology unit of King Fahad Medical City, Saudi Arabia. The median patient age was 9.22 years, with a male predominance (70.37%), which is consistent with previous studies in developing countries[25-26]. Histologically, the nodular sclerosis subtype was observed in 48.15% of patients, followed by the mixed cellularity subtype (25.93%), which is similar to studies reported from developed countries[27]. These differences might be due to the improvement in socioeconomic status and infection environment. Our study results are comparable to a retrospective study performed in Saudi Arabia that showed no bimodal age pattern; in that study, HL was more common in younger patients with a male predominance, and the nodular sclerosis type was the most common subtype[28]. In the present study, 74.07% of patients had advanced stage (III and IV) disease, which might be attributed to the delay in diagnosis and referral to a cancer center. By contrast, in developed countries, 75% of newly diagnosed patients have early disease at presentation (stage I–II)[29]. We used different chemotherapy regimen protocols according to risk group classification to achieve good outcomes while minimizing the acute and long-term toxicities[21]. The EFS rate of our study was approximately 85%, which was comparable to those reported in developed countries[32] and to adult Saudi HL patients according to a recent study in 2017[33]. Belgaum et al reported that pediatric patients with advanced disease (stage IV) had worse outcomes than all other stages with an OS of 79.4% and an EFS of 63.9% at five years[31]. A recent report from the Dana-Farber/Boston Children's Cancer and Blood Disorder Center by Ozuah NW et al demonstrates excellent survival with the omission of radiotherapy in more than 50% of patients with pediatric advanced HL who were treated with a dose-intensive chemotherapy regimen[21]. In our study, there was no statistically significant difference in the relapse rate between patients who received radiation and those who did not receive radiotherapy ($P = 0.392$). The relapse rate in our patients was approximately 15%, which is similar to the relapse rate in pediatric HL patients in the USA[30]. Two of our relapsed patients achieved CR after chemotherapy and radiation and the other relapsed patients were referred for transplant after salvage therapy. This study did not evaluate the treatment and outcomes of relapsed patients. The three-year OS for our patients was 98%.

Conclusion

Survival outcomes in children and adolescents with HL in Saudi Arabia have improved with a five-year OS rate now exceeding 85%. However, further prospective larger collaborative studies are necessary.

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TABLE 2 Initial chemotherapy for patients.docx available at https://authorea.com/users/468974/articles/562161-outcomes-of-pediatric-hodgkin-lymphoma-a-retrospective-review-of-children-and-adolescents-with-hodgkin-lymphoma-treated-at-king-fahad-medical-city-riyadh-2006-2017

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TABLE 3 Treatment response.docx available at https://authorea.com/users/468974/articles/562161-outcomes-of-pediatric-hodgkin-lymphoma-a-retrospective-review-of-children-and-adolescents-with-hodgkin-lymphoma-treated-at-king-fahad-medical-city-riyadh-2006-2017

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TABLE 4 Radiation and relapse.docx available at https://authorea.com/users/468974/articles/562161-outcomes-of-pediatric-hodgkin-lymphoma-a-retrospective-review-of-children-and-adolescents-with-hodgkin-lymphoma-treated-at-king-fahad-medical-city-riyadh-2006-2017

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TABLE 5 Treatment.docx available at https://authorea.com/users/468974/articles/562161-outcomes-of-pediatric-hodgkin-lymphoma-a-retrospective-review-of-children-and-adolescents-with-hodgkin-lymphoma-treated-at-king-fahad-medical-city-riyadh-2006-2017