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RESEARCH ARTICLE
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Impact of using combined chemotherapy regimen in children with Hodgkin lymphoma in countries with limited resources: a single center experience in Iraq

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ABSTRACT

Objective/Background: Data about Hodgkin lymphoma (HL) in developing countries are scattered. The aim of this study is to present clinical features and outcome of children with HL using combined different chemotherapy regimens. Response-based approach was applied irrespective of risk stratification.

Methods: Patients aged 18 years and younger who were diagnosed with HL between January 2014 and December 2021 in a cancer center in Iraq, were recruited. Patients were stratified into three risk groups. Initial treatment with induction chemotherapy (i.e., 2 cycles of ABVD) was applied to all patients. Patients who achieved complete radiological response to induction chemotherapy continued with 4-6 cycles of ABVD; radiotherapy was omitted. Patients with slow early response received 3 cycles of COPDac after 3rd cycle of ABVD, followed by radiotherapy.

Results: fifty-nine patients were enrolled in this study. The median age was 7 years. Twenty (33.9%) patients were stage III, followed by stage II (32.2%). Twenty-five patients had B symptoms. Initial splenic involvement was found in 11 patients. Approximately one third of patients had bulky disease (n = 19; 32.2%). The most common histology was mixed cellularity (n = 44). The median follow-up was 2.7 year (range from 0.1 to 7.5 years). The 5-year estimates of survival and EFS were 92% and 78% ±10%, respectively. Only bulky disease had a significant negative influence on the outcome.

Conclusion: Good outcomes for pediatric HL patients can be achieved in low and middle income countries. Response-based therapy approach is feasible to reduce long term treatment-related sequel.

Keywords: *Hodgkin lymphoma, developing countries, combined chemotherapy*

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INTRODUCTION

Pediatric Hodgkin lymphoma (HL) is a curable malignancy, However, cure rate remains variable in developing countries [1][2][3][4][5].

Data about HL in low- and middle-income countries (LMIC) countries are scattered and infrequent; the prognostic factors are different from the high-income countries (HIC) because of the significant disparities in healthcare in the context of treatment provision, radiological facilities, and patients' adherence to treatment [1][6][7][8][9][10].

Chemotherapy alone in rapid early responders (i.e., complete remission CR after 2 courses) has been proved to be as good as combined modality treatment (i.e., chemotherapy and radiotherapy). Elimination of radiotherapy in those patients is probably safe [8][11][12]. Direction towards minimizing treatment-related sequelae has become considerably of paramount importance. Combined chemotherapy regimen has been used in HL with variable results [8][13][14][15].

The aim of this study is to present the clinical features and outcome of children who diagnosed with HL, aged 0-18 year, using combined different chemotherapy regimens: ABVD (doxorubicin, bleomycin, vinblastine, and dacarbazine), and COPDac (cyclophosphamide, vincristine, prednisolone, and dacarbazine). In this study, response-based therapy was implemented irrespective of risk stratification.

The study also focused on the means that were performed for avoidance of abandonment, tracking patients, adherence to treatment, and follow up especially during the curfew with pandemic of COVID-19 infection.

MATERIALS AND METHODS

Patients aged 18 years and younger with histologically confirmed HL (all histologies) that presented between January 2014 and December 2021 to the main cancer center in Kerbalaa, Iraq, were recruited to this study.

Baseline evaluations were performed within 3 weeks from the diagnosis. Pre-treatment evaluation included: history and physical examination; complete blood count (CBC) with differential, erythrocyte sedimentation rate, renal and hepatic chemistries; cervical, thoracic, abdominal, and pelvic computed tomography (CT) scan with contrast. Bone marrow biopsy was only performed for high risk group. Positron emission tomography (PET) scan was optionally used to monitor response; it was done upon family preference because of the high cost.

Patients were clinically stratified into three risk groups (low, intermediate, and high) based on Ann Arbor staging for lymphoma [16], presence of B symptoms (unexplained documented fevers > 38o, drenching night sweats or > 10% weight loss in the preceding 6 months), presence of bulky disease (defined as the mediastinal mass to intrathoracic cavity ratio of one third or greater on upright chest radiograph or a peripheral lymph node mass greater than 6 cm in longest diameter), and presence of extranodal disease extension.

Patients with high risk disease included all those with Ann Arbor stage IIB or IIIB with bulky disease or extranodal disease extension, or any stage IV.

Patients with intermediate risk disease included all those with Ann Arbor stage IA or IIA with bulky disease and/or extranodal disease extension, stage IB or IIB without bulky disease and/or extranodal disease extension, stage IIIA, and stage IIIB without bulky disease.

Patients with low risk disease included all those with Ann Arbor stage IA or IIA.

Upon confirmation of HL diagnosis, a meeting session with patient`s guardians and the primary physician was organized, to explain the disease nature, staging, prognosis, treatment options and pertinent family obstacles to avoid abandonment. Incipient inquiry about residency (whether the patient inhabits rural or urban area) was also required at the 1st meeting. Rural regions include areas with large agricultural lands and underdeveloped infrastructure comprising houses, roads, and commercial buildings. Urban areas include cities and towns with well-developed human structures and facilities (like houses, roads, and bridges) and no agriculture base.

Treatment plan

The standard chemotherapy regimen ABVD was used as the initial treatment for all patients. Subsequent therapies with COPDac and radiotherapy were applied upon the initial response to induction treatment (i.e., 1st two cycles of ABVD).

ABVD chemotherapy was administered as follows: doxorubicin 25 mg/m2 intravenously (IV) on days 1 and 15; bleomycin 10 units/m2 IV on days 1 and 15; vinblastine 6 mg/m2 IV on days 1 and 15; and procarbazine 375 mg/m2 on days 1 and 15. COPDac chemotherapy was administered as follows: vincristine 1.4 mg/m2 on days 1 and 8 (maximum of 2 mg); cyclophosphamide 600 mg/m2 IV on days 1 and 8: prednisolone 40 mg/m2/d orally on days 1 through 14; procarbazine 250 mg/m2/d on days 1 through 3.

ABVD cycle was repeated every 4 weeks while COPDac cycle was repeated every 21 days, as permitted by blood count recovery. Radiotherapy was applied if complete remission was not achieved after the second cycle of chemotherapy. All sites of initial disease were irradiated. The radiation therapy dose was 25.5 Gy in 1.5 Gy fractions for all initially involved sites at presentation.

Early response evaluation

After completion of the second ABVD cycle, all patients were evaluated for chemotherapy response by clinical examination and CT scan, or PET-CT scan if cost was afforded. Any node at supraclavicular, infraclavicular, epitrochlear, brachial, preauricular, and popliteal areas with longest transverse diameter of more than 1.5 cm at the time of diagnosis was considered compatible with disease involvement in the absence of a compelling alternative etiology. Cervical, axillary, inguinal and mesenteric lymph nodes were considered involved with HL if reached a diameter of 2 cm. Any distinctive focal mass lesion of a visceral organ (such as liver, spleen, kidney) was considered involved in the absence of reasonable alternative explanation (e.g. cyst, hemangioma, abscess).

Complete response was defined as disappearance of constitutional symptoms if initially present and complete resolution of all measurable disease, or reduction in the size of each of the nodal masses by 80% or more of the primary nodes, or 75% or more of the sum of diameters of the previously confluent nodes, resolution of any focal visceral lesions, no new lesion(s), and/or PET-negative scan as interpreted by nuclear medicine specialist using Deauville score according to fluorodeoxyglucose (FDG) uptake status in comparison with physiological uptake of liver and mediastinum.

Partial response was defined as at least 50% reduction in the sum of the diameters of all measurable lesions and disappearance of constitutional symptoms if initially present.

Patients who achieved complete response to induction chemotherapy continued with the ABVD regimen for a maximum of 4 cycles for low-risk group and 6 cycles for intermediate- and high-risk group. Radiotherapy was not applied to those patients.

Patients with slow early response (i.e. those who did not achieve CR after 2 courses of ABVD), received 3 cycles of COPDac after the 3rd cycle of ABVD, followed by radiation therapy at the end of chemotherapy treatment.

After-therapy monitoring

After completion of therapy, patients were followed up regularly on monthly basis for 6 months, every 2 months for the 1st year, every 3 months for the 2nd year, every 4 months for the 3rd year, every 6 months for the 4th year, and annually for the 5th year. Follow-up examinations included physical examination, chest x-ray, ultrasonography, and routine laboratory studies (complete blood count CBC with differential, erythrocyte sedimentation rate). CT scans of neck, chest, abdomen, and pelvis was performed at 3 months, 6 months, and 1 year off therapy. Further examinations were determined accordingly if clinical situation was suggestive of disease recurrence.

At the end of treatment, patients who did not reveal any abnormalities indicative of disease progression, or with stable or improved residual abnormalities at previous sites of disease, were considered to be in complete remission. Biopsy was required to confirm disease progression or relapse.

Statistical analysis

The collected data were collected retrospectively and statistically analysed using the Statistical package for the Social Sciences (SPSS). Data were described as mean, range, frequencies, and percentages when appropriate. Survival analysis was estimated by the Kaplan-Meier method. Potential prognostic factors (B symptoms, bulky disease, splenic involvement, clinical stages and risk stratification) for overall survival (OS) and event-free survival (EFS) were analysed by applying the two-sided log-rank test. OS was measured from the date of diagnosis to the date of last follow up or death from any cause. EFS was measured from the date of diagnosis to the date of relapse, disease progression, abandonment, or death due to any cause. P values <0.05 were considered statistically significant.

RESULTS

Patient characteristics

Demographic characteristics of the patient cohort are shown in Table 1. The median age at the time of study enrollment was 7 years (range, 2.5 to 16 years). More than half (61%) were male (n = 36). Fourteen (23.7%) patients were residing in rural areas. The most common histology was mixed cellularity in 74.57% of patients (n = 44), followed by nodular sclerosis (n =12; 20.3%). The most common nodal involvement was cervical (n = 55), followed by mediastinal (n = 26), and then supraclavicular (n = 25). The median follow-up was 2.7 years and ranged from 0.1 to 7.5 years. Stage distribution was I in 18 patients (30.5%), II in 19 patients (32.2%), III in 20 patients (33.9%), and IV in 2 patients (3.4%). Twenty-seven patients were stratified as low risk, followed by intermediate and high risk (n=16 for each group). B symptoms were present in 25 patients (42.4%; stage I = 1, stage II = 8, stage III = 14, stage IV = 2). Initial splenic involvement was found in 11 patients. Approximately one third (n = 19; 32.2%) of patients had bulky disease (Table 2).

Response to treatment

Twenty-one (35.6%) patients accomplished complete response after two cycles of ABVD chemotherapy, 15 of them were classified as low risk, 4 as intermediate risk, and 2 as high risk. Partial response was achieved in 38 patients (64.4%), 12 with low risk, 12 with intermediate risk, and 14 with high risk disease; one patient did not respond to treatment and subsequently died of progressive disease despite further intensive therapy. Noteworthy, 2 patients (one in the low risk group, and the other in the high risk group) continued to receive ABVD chemotherapy regimen upon the family preference in spite of partial response to induction chemotherapy; both received radiotherapy after completion of chemotherapy.

Combined chemotherapy regimen (i.e., ABVD and COPDac) was applied to 36 patients because of partial response to induction chemotherapy (Table 2), but only 19 went on to receive radiotherapy at the end of chemotherapy. In the other 17 patients, radiotherapy was not performed either because of family refusal (n=6) or because of radiotherapy obstacles (prolonged duration of more than 2 months after the end of chemotherapy, disapproval by radiation oncologist because of extensive field of radiation, or technical problems). Thirteen of those 17 patients were in CR after completion of chemotherapy.

Outcome

Estimates of OS and event free survival EFS at 5 years were 92% (Figure 1) and 78% (Figure 2), respectively. Regarding splenic involvement, presence of B symptoms, presence of bulky disease, staging, and risk stratification, only bulky disease has had a significant statistical difference (Table 3). In this current study, EFS was significantly higher in children without bulky disease (Figure 3).

DISCUSSION

Excellent survival rates for pediatric HL have been achieved in HIC [14][17][11]. However, results from LMIC are variable [1][4][5][18]. Non-cross resistant combined modality therapy has been used in pediatric HL [8][13][15].

In this study, in an attempt to improve the outcome of pediatric patients with HL, a non-cross resistant combined modality approach was implemented according to the initial response to induction treatment (i.e., response-based therapy). The purpose of applying this approach was to limit radiotherapy as it is one of the major barriers in LMIC in the context of unintentional postponement due to considerable number of patients waiting for RT. Moreover, combined modality approach exposes cancer cells to different chemotherapeutic agents; subsequently, drug resistance is minimized and optimal results are obtained.

Although abandonment to treatment (missing to return for chemotherapy appointments for 4 or more weeks) is more common in LMIC (which may be related to educational, social, and financial factors) [6][7][9][10], efforts were made to lessen this substantial impediment during the course of treatment; this was attained by a properly-structured and well-orchestrated 1st session meeting with the patient`s caregivers to disclose promising prognosis once adherence to treatment is accomplished, as well as pertinent obstacles that may be encountered. Internet services including Viber, WhatsApp, and telegram were very helpful to mitigate abandonment and contributed to successful follow-up, especially during COVID pandemic curfew. During the period of curfew due to the COVID 19 pandemic, patients who resided in distant areas were followed by online communications (Viber, WhatsApp, or Telegram) with the primary physician; the aforementioned investigations were requested to be performed locally and then sent to the primary physician. Further examinations were requested at the discretion of the primary physician.

In this study, there is a slightly male gender predilection. Many other studies have shown a male gender preponderance [3][7][19][20]. Majority of patients were residing in urban areas; this may reflect lack of medical awareness in rural regions, although environmental exposure may play a role. Urban-rural status has been investigated in some malignancies including leukemia and lymphomas suggesting that environmental factors may have an influence on the incidence of malignancy [21][22][23]. Mixed cellularity histology was predominant in this study (74.5%) which is comparable with some studies in limited resource settings [5][19][20][24]; however, in other studies, particularly in HIC, nodular sclerosis histology was prevailing[8]. Peripheral lymph node involvement was noticed in all patients; cervical (93.2/%), followed by mediastinal (44%) regions were the most common sites. Cervical lymph nodes are the most common peripheral nodal sites involved in most of the studies [2][3][24][25]. B-symptoms were present in 25 (42.4%) patients. Although presence of B-symptoms have been found to be bad prognostic factor [26][27], some studies have not shown such significant prognostic effect [28]. Our results did not show significant worse outcome for children with B-symptoms, which may be related to the risk stratified treatment approach that may have diminished the influence of this prognostic factor. Although splenic involvement was considered a risk factor that affects outcome [29], results in this study showed no significant prognostic value.

We also observed that bulky disease significantly affects outcome; this result was also shown in other published studies [28][30]; this may be related by the relatively prolonged period interval between the onset of symptoms, diagnosis, and treatment outset.

In this study, there is no statistically significant difference in outcome related to staging ($p=0.5$) or risk ($p=0.3$). Although some other studies showed comparable results [24][28], response-based strategy may contribute to this satisfactory result. However, small cohort of patients may be an additional factor.

The estimated 5-year EFS and OS of the entire cohort of patients was 78% and 92%, respectively. Although there was a significant number of low risk patients in this study, appropriate clinical approach, persistent communication between the primary physician and patient`s guardians, compliance to treatment, and application of combined chemotherapy approach may contribute to this successful results. Our results were relatively superior to other published results from countries with limited resources [1][2][3][4][8][19][24][26][28].

In this study, although the total cumulative doses of alkylating agents are comparable with other studies, there was a limited cumulative dose of bleomycin and anthracyclines; subsequently, the long term cardiac and lung toxicities encountered by using those chemotherapeutic agents are expected to be reduced. In addition, the rational of a chemotherapy response-directed RT approach was explicit; the response-adapted treatment strategy with omission of RT in patients with chemotherapy-induced CR can be safe. Noteworthy, protocol violation was demonstrated in a significant number of patients (n=17) who did not receive radiotherapy after completion of chemotherapy course (i.e., against medical decision) because of radiotherapy technical problems. In this study, 38 (64.4%) patients did not receive radiotherapy, either because of complete response to induction chemotherapy (21 patients), or because of protocol violation (17 patients). This may furthermore reassure us that omission of RT in children with CR after chemotherapy is safe.

In summary, we implemented this trial of response-adapted combined modality therapy in an endeavor to maintain high cure rates and reduce treatment-related morbidity and mortality in children and adolescents with Hodgkin lymphoma.

Remarkably, this study has some limitations because of the relatively small cohort of patients. Further collaborations are foreseen to continue to build upon our success.

CONCLUSIONS

In conclusion, good outcomes for pediatric HL patients can be achieved in LMIC. Combined chemotherapy regimen and adherence to treatment contribute to this successful outcome. Response-based therapy approach is feasible to potentially reduce long term treatment-related sequelae. Elimination of radiotherapy is probably safe in patients treated with chemotherapy that achieve an early CR.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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TABLE 1: Characteristic features of enrolled children with HL

Age	
Median (years)	7
Range (years)	2.5 to 16
Gender	
Female	23
Male	36
Origin	
Rural	14
Urban	45
Histopathology	
Lymphocyte rich	3
Mixed cellularity	44
Nodular sclerosis	12
LN groups	
Cervical	55
Axillary	7
Supraclavicular	25
Infraclavicular	1
Mediastinal	26
Para aortic	19
Inguinal	2

Note. LN = lymph nodes

TABLE 2: Characteristic risk factors and treatment modalities for patients with HL

Stage	
I	12
II	13
III	14
IV	2
Stratification	
Low	27
Intermediate	16
High	16
B symptoms	
No	34
Yes	25
Splenic Involvement	
Yes	11
No	48
Bulky disease [a]	
No	40
Yes	19
Type of chemotherapy	
ABVD	23
ABVD, COPDac	36
Radiotherapy	
Yes	19
No	40

[a] Bulky disease definition: mediastinal mass to intrathoracic cavity ratio $\geq$ 1/3 on upright chest radiograph or a peripheral lymph node mass > 6 cm in longest diameter

TABLE 3: Estimated 5-years EFS according to risk factors

Splenic involvement No Yes	 96% 80%	0.4
B Symptoms No Yes	 95% 90%	0.9
Bulky disease No Yes	 100% 77%	0.03
Stage I II III IV	 100% 90% 80% 100%	0.5
Risk Low Intermediate High	 100% 90% 85%	0.3

Legends

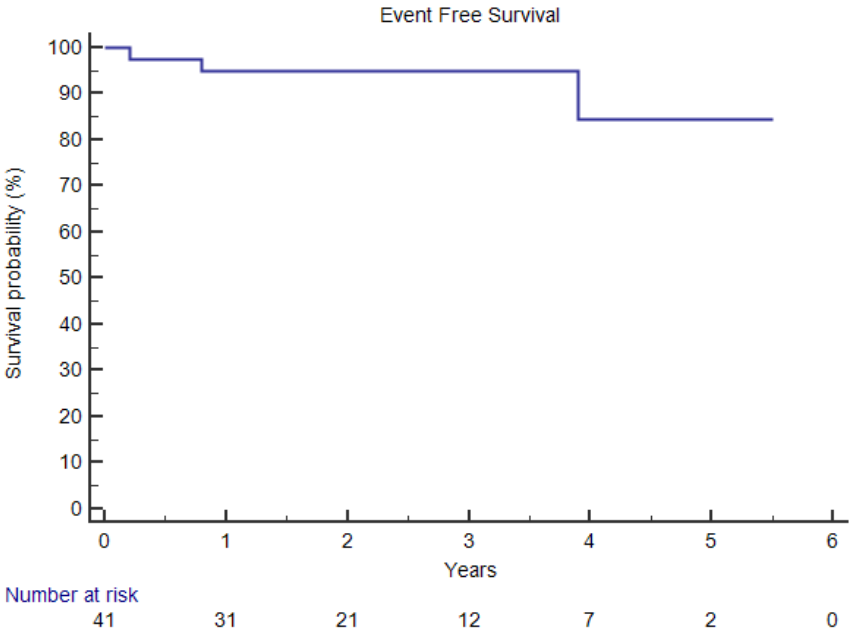

FIGURE 1 Estimated EFS of enrolled children with HL

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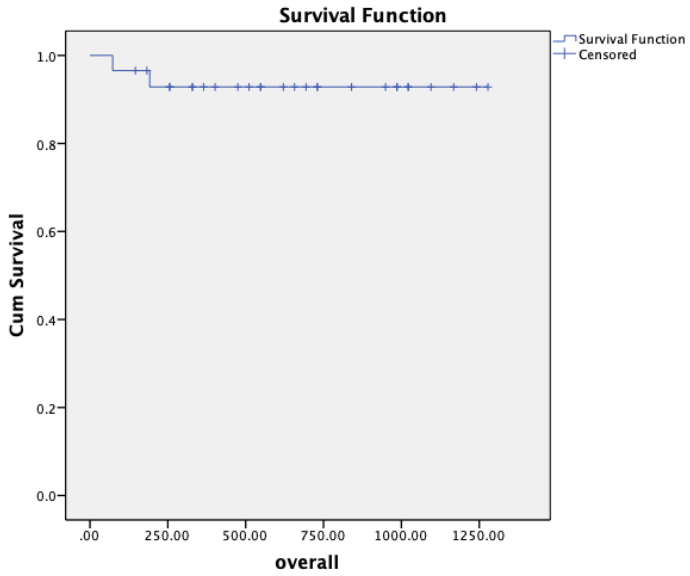

FIGURE 2 Estimated OS of enrolled children with HL

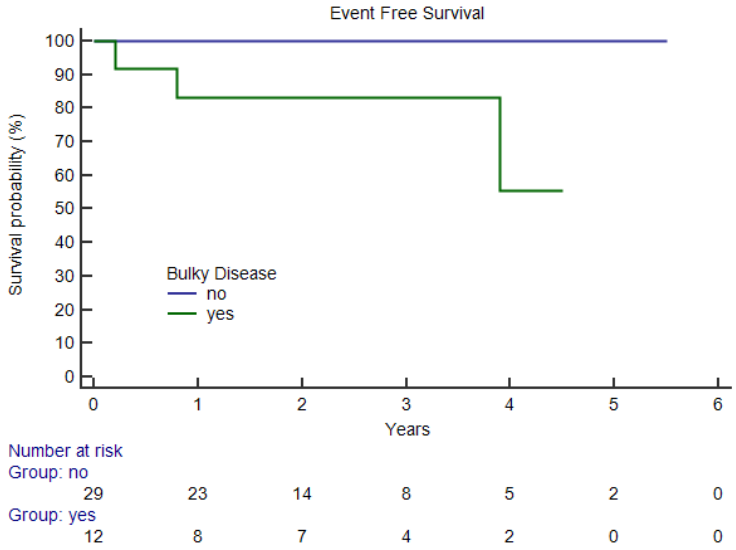

FIGURE 3 Estimated EFS according to bulky disease