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Original Article

Hodgkin Lymphoma in Children: A 16-year Experience at the Children's Welfare Teaching Hospital of Baghdad, Iraq

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Abstract. ***Background*: Childhood Hodgkin lymphoma (HL) is an eminently curable disease. Good outcomes can be achieved even in resource-limited settings, and the focus is increasingly on limiting long-term toxicity. Contemporary treatment incorporates a risk-stratified, response-adapted approach using multiagent chemotherapy with/without low-dose radiotherapy. Many developing countries continue to use ABVD-based regimens due to limited acute toxicity, cost, and ease of delivery.**

***Objective*: We herein report the outcomes of childhood HL diagnosed and treated in an Iraqi single centre over 16 years.**

***Methods*: Children ≤14 years old with biopsy-proven HL were enrolled. Most patients received ABVD chemotherapy or COPP/ABV when Dacarbazine was unavailable. Radiotherapy was not available.**

***Results*: Three hundred-three children were consecutively newly diagnosed with HL; 284 were considered eligible for the retrospective analysis (treatment refusals 9; deaths before therapy 5; initially diagnosed of non-Hodgkin lymphoma 5). ABVD scheme was administered to 184 children (65%), COPP/ABV to 83 (29%), and other schemes to the remaining 17 patients. Complete response (CR) was achieved in 277 (98%); 4 (1.4%) showed disease progression, and 1 had stable disease. Four patients in CR abandoned therapy and were in CR at the time of analysis, 2 died from infection. Relapse occurred in 42 patients (15%). The 15-year OS and EFS are 89.7% and 70.3%, respectively.**

***Conclusion*: In this single Centre, over 16 years, almost 90% of children suffering from HL survive, despite the numerous limitations in diagnostic procedures, shortage of chemotherapy, no radiotherapy facilities, absence of effective second-line treatments, and finally, therapy abandonment for social and financial reasons.**

Keywords: Hodgkin Lymphoma; Children; chemotherapy; Developing Countries.

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Introduction. Hodgkin lymphoma (HL) accounts for 5%-6% of all childhood cancers.[1] This disease is highly responsive to treatment and represents one of the success stories of paediatric oncology.[2] Current treatment protocols for childhood HL have undergone considerable modifications in order to reduce both acute toxicity and long-term therapy-related complications without compromising the excellent clinical results.[3] In the Western World, the 5-year survival of paediatric HL exceeds 95%.[4] However, survival in low-income countries is lower. Many factors, including delayed diagnosis, withdrawal from therapy, and insufficient intensive and supportive care, have resulted in decreased survival rates for HL children living in these countries.[5-7] In Iraq, numerous limitations in diagnostic procedures, shortage of chemotherapy agents, no radiotherapy (RT) facilities, absence of effective second-line therapies, and finally, therapy abandonment for social and financial reasons have made it difficult to treat children with HL. Since 2003, in the context of a Telemedicine Project between Sapienza, University of Rome, Italy, and The College of Medicine in Baghdad, Iraq, it has been possible to review the children's histological materials, to set up a prospective clinical registry and, subsequently, to adopt guidelines for paediatric patients with HL in Iraq.

The purpose of this study was to retrospectively analyse the outcome of HL children treated with ABVD-based therapy, diagnosed and managed at the Children's Welfare Teaching Hospital (CWTH) in Baghdad over 16 years.

Patients and Methods.

Diagnostic Evaluation. This study includes children up to 14 years of age with a diagnosis of HL treated at the CWTH in Baghdad between January 2004 and December 2019. Histological diagnosis was based on a biopsy of a lymph node or of an involved organ. From January 2007, the patients' pathology specimens were reviewed in the Pathology Department of Sapienza University of Rome. Immunohistochemistry was available in 61% of patients. Upon admission, medical history, including the presence of B symptoms, physical examination, blood chemistry, chest X-ray, superficial node and abdominal sonography, and, when available, neck and chest computed tomography (CT), bone marrow biopsy (BM) for stage III, IV, or presence of B symptoms and cardiac function were obtained. Bulky disease was defined as the presence of a lymph node mass of at least 10 cm in diameter or a mediastinal mass with a diameter exceeding one-third of the maximum mediastinal width on an upright posteroanterior chest radiograph. Staging of the disease followed the Ann Arbor/Cotswold's classification.[8] For this analysis, children with stages IA, IB, and IIA were classified as early diseases, and those with stages IIB, III, and IV as advanced diseases.

Treatment. Most children received ABVD courses or COPP/ABV when Dacarbazine was unavailable. The number of cycles ranged from 4 to 8, based on the initial stage and treatment response. Response was evaluated using the same diagnostic techniques employed at diagnosis, during, and at the end of chemotherapy. Complete response (CR) was defined as a >80% regression of the clinical and radiological lesions. Partial response (PR) was defined as the reduction in all disease sites by at least 70% compared to the initial involvement. Stable disease (SD) was defined as less than a 70% reduction in total tumour size. Disease progression (DP, ≤ 3 months) or relapse (>3 months from therapy completion) was defined as an increase of at least one measurable lesion or the appearance of new lesions. In January 2014, Treatment Guidelines were designed and adapted to the local resources and modulated according to patients' risk and response. The "interim response" evaluation after the first 2 cycles was introduced. The good interim response was defined when a 2-dimensional reduction in size greater than 50% was achieved. Patients were divided into 3 risk groups: standard, stage IA or IIA with < 3 nodal sites and no bulky disease; intermediate: stage IA, IIA or IIIA with ≥ 3 nodal sites or bulky disease; high: stage IIB, IIIB or IV. The ABVD scheme was chosen as effective and safe for all risk groups. The number of cycles was 4 for standard-risk, 6 for intermediate-risk, and 8 for high-risk patients (**Table 1**).

RT was not available for the whole period, and patients with interim response < 50% received treatment

Table 1. Iraqi paediatric Hodgkin lymphoma treatment guidelines (2014).

Treatment Group	Disease Stage	Chemotherapy Details
Standard	IA or IIA with < 3 nodal sites and no bulky disease	ABVD x 2 CR*, PR°>50%--> 2 more ABVD cycles (total 4 ABVD) PR< 50% or NR^→ BEACOPP 2 + 2 cycles (total 4 cycles)
Intermediate	IA, IIA or IIIA with bulky disease or ≥ 3 nodal sites M/T>0.33	ABVD x 2 CR, PR> 50%--> 4 more ABVD cycles (total 6 ABVD) PR<50% or NR→ BEACOPP 2 + 4 cycles (total 6 cycles)
High	IIB, IIIB or IV	ABVD x 2 CR, PR> 50%--> 6 more ABVD cycles (total 8 ABVD) PR< 50% or NR→ BEACOPP 2 + 4 cycles (total 6 cycles)

*CR: complete response; °PR: partial response; ^NR: no response.

Table 2. Patients' demographic and diagnostic characteristics.

Characteristics	Number (n)	Percentage (%)
Total number of patients	303	100
Age (years): median – (range)	7.8 - (<3 – 14.5)	
Gender: male/female	215/88	71/29
PS* (WHO): 0 - ≤2 3 - 4	 292 11	 96 4
Nutrition status < 3°perc: yes/no	45/258	15
Living in: Baghdad/outside	161/142	53/47
Duration of symptoms (months): median – (range)	5 – (0.75 – 60)	
Bulky disease: Mediastinum >1/3 Lymph node >10 cm	 105 59	 35 19
Spleen involvement: yes	131	43
Extranodal involvement:	18	6
Histological subtype: MC** NS° LR°° LD^ NA^^	181 86 25 1 10	60 28 8 1 3
Symptoms: A/B	150/153	49/51

*PS: performance status; **MC: mixed cellularity; °NS: nodular sclerosis; °°LR: lymphocyte-rich; ^LD: lymphocyte-depleted; ^^NA: not available.

intensification with standard BEACOPP (bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, prednisone) (**Table 1**).

ABVD chemotherapy was administered in daycare on an outpatient basis; BEACOPP cycles required the patient's hospitalization.

The study received approval from the official local institutional review board.

Follow Up. After completion of therapy, the follow-up plan included clinical evaluation every 3 months in the first year, every 4 months in the second year, every six months from the third to the fifth year, and yearly after that. At each visit, in addition to obtaining any relevant history and a physical examination pertinent to HL, no imaging studies or blood investigations to detect relapse were routinely recommended for asymptomatic patients with normal physical examinations. Pulmonary and/or cardiac assessments were only carried out for symptomatic patients. In patients with a suspicion of relapse, imaging studies and a new biopsy were performed. For patients who did not turn up for the follow-up, clinical status was confirmed by phone.

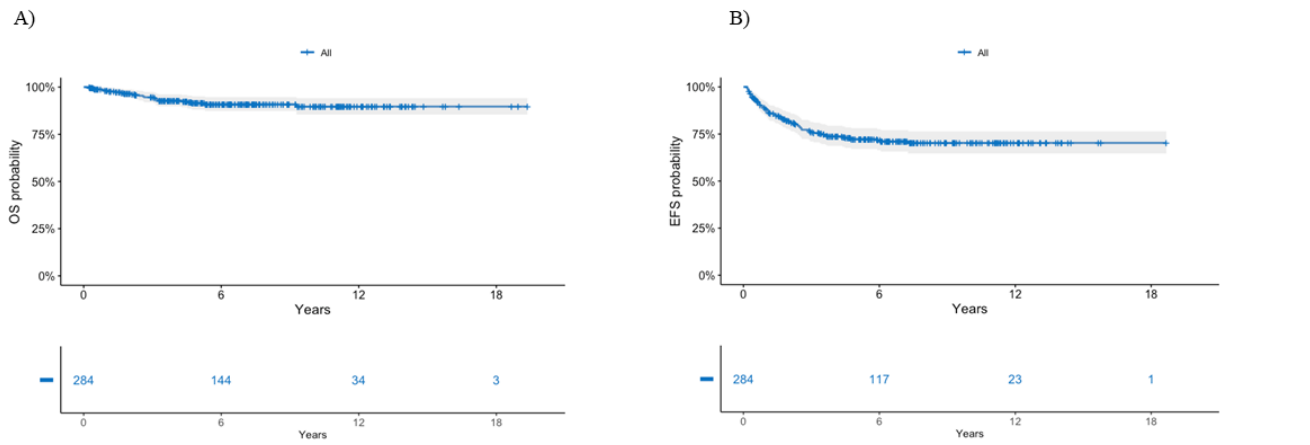
Statistical Analysis. Patient's characteristics were summarised by frequencies and percentage values for categorical variables, while continuous variables were described with median values and their relative ranges. Overall survival (OS) was defined as the time from diagnosis to death or the date of the last follow-up. Event-free survival (EFS) was defined as the time from diagnosis to the date of failure (no response, treatment abandonment, relapse, or death) or the date of the last follow-up. The probabilities of OS and EFS were estimated following the Kaplan–Meier product limit method, while the results of univariate comparisons were performed according to the Log-Rank test. All tests were two-sided with a significance level of 0.05, and confidence intervals were calculated at a 95% level. All analyses were performed using the R version 4.2.2.

Results. At the CWTH of Baghdad, from January 2004 to December 2019, 303 children with a median age of 7.8 years (range 3–14) were newly diagnosed with HL. Patients' demographic profiles and diagnostic characteristics are reported in **Table 2**. A male predominance was observed (215 vs 88), 47% of patients lived outside Baghdad and nutrition status was <3rd percentile in 45 children (15%). The median duration of HL symptoms before diagnosis was 5 months (range 1-60). Twenty-six children (9%) presented co-morbidities. The most severe included: cerebral atrophy (1), absence of the left kidney, nephrectomy or renal impairment (5), ataxia telangiectasia (1), Castleman disease (1), Wilson disease (1), congenital heart disease (1), immune thrombocytopenia (2), immune deficiency (1), bone marrow fibrosis (1), anaemia (4). One hundred and fifty-three children (51%) presented B symptoms and 105 (35%) had bulky disease. Forty-seven children had stage I (IA 38; IB 9), 106 stage II (66 IIA, 40 IIB), 122 stage III (IIIA 43, IIIB 79) and 28 stage IV (IVA 3, IVB 25). The most frequent histological subtype was mixed cellularity (MC: 181 patients, 60%) followed by nodular sclerosis (NS: 86 patients, 28%). An immunohistochemical analysis was performed in 186 samples; EBV, as assessed by in situ hybridization for EBER-(Epstein-Barr encoded)-RNA, was positive in 82/100 (82%) cases studied at the Pathology Department in Rome.

Two hundred and eighty-four children were considered eligible for the study evaluation. Nine were excluded because of treatment refusal, 5 (1 with a previous renal impairment; 1 with Wilson disease) died before treatment and 5 were initially diagnosed as non-Hodgkin lymphoma (NHL) and received a different treatment. Of the 284 eligible patients, 84 (16%) aged less than 5 years and 239 (84%) were older; 47 (17%) were classified as stage I (37 IA, 10 IB), 96 (34%) stage II (59 IIA, 37 IIB), 114 (40%) stage III (43 IIIA, 71 IIIB), 27 (10%) stage IV (3 IVA, 24 IVB). According to our analysis criteria, 107 children (38%) were considered with early and 177 (62%) with advanced disease. ABVD scheme was administered to 184 children (65%), COPP/ABV to 83 (29%), and the remaining 17 patients received different HL chemotherapy schemes. One hundred and forty-three children (78%) treated with ABVD received 6-8 cycles (median 6), and 41 (22%) received 2-5 cycles (median 4). Response evaluation at the end of therapy documented a CR in 174 children (95%); 3 of them abandoned the treatment after the first 3-4 cycles and are still alive and in CR. One child died from DP, and another 9 patients with early PR underwent treatment intensification and achieved a CR. Forty-six of the 83 children treated with COPP/ABV schema (55%) received 6-8 cycles (median 6), and 37 (45%) received 2-5 cycles (median 4). Eighty-two children achieved a CR; one patient died of DP. Twelve of the 17 patients (71%) who received different HL treatments achieved a CR; 2 died of DP; 1 child with a good response abandoned therapy and is still alive, and 2 patients showed an NR. A total of 268/284 treated patients (94%) achieved a CR with the first-line therapy; another 9 further patients with a poor response to first-line therapy intensified treatment and achieved a CR. The total response rate for all the evaluable patients was 98% (277/284).

A relapse was recorded in 42/277 patients (15%) (10 stage I, II; 32 stage III, IV) at a median time from diagnosis of 20 months (range 9-84). Twenty-nine had received an ABVD scheme, 9 COPP/ABV, and 4 different front-line treatments. All relapsed children received salvage schemes, and 28 (67%) achieved a second CR; 13 died during treatment, and 1 is still alive with persistent disease.

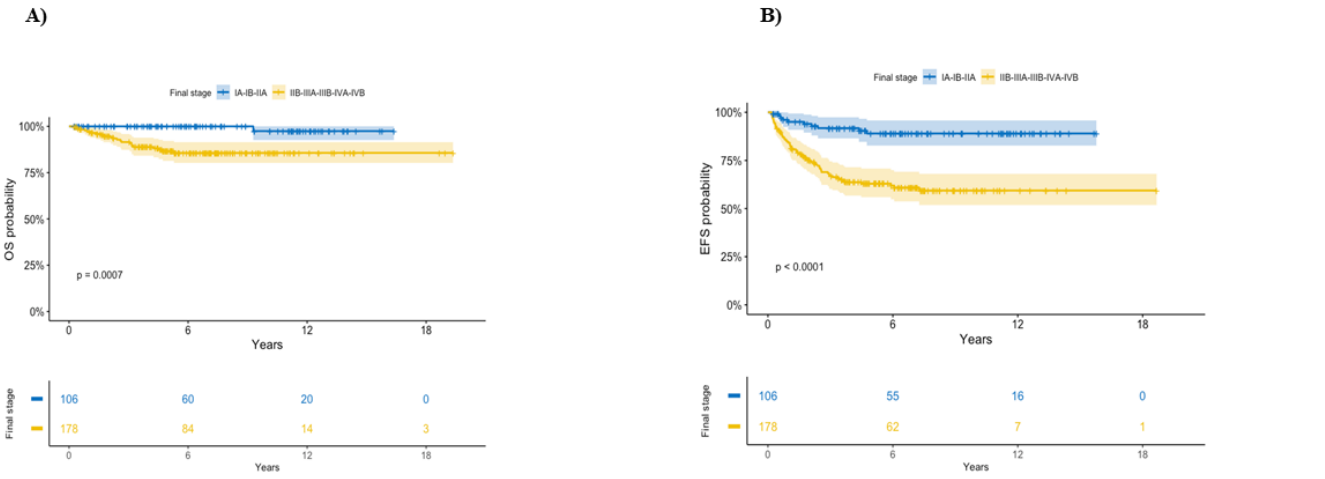
At a median follow-up of 6.42 years (4.11-10.12), the 15-year OS and EFS for the entire cohort of children are 89.7% and 70.3%, respectively (**Figure 1**). There is no difference in outcome in children under or over 5 years (15-year OS and EFS: 82.9% and 65.8% vs 91.1% and 71.2%, respectively; p=0.43 and 0.46), histological subtype MC and NS (10-year OS and EFS: 89.8% and 71.7% vs 90.3% and 66.9%, respectively; p=0.85 and p=0.19,) and living in Baghdad or outside (15-year OS and EFS: 91.4% and 75% vs 87.5% and 64.3%; p=0.095; p=0.076). Based on the type of treatment (ABVD vs COPP/ABV), we did not observe a difference in the OS (10-year OS 93.3% vs. 87.8%; p=0.2), even if the EFS at 10 years resulted in inferior in the group of children that had received ABVD scheme (66.5%) compared to those treated with COPP/ABV (82.9%). A significantly better outcome has been observed in stage I-II patients compared to stage III-IV children (15-year OS and EFS: 96.9% and 82.6% vs 82.8% and 57.7%, respectively; p<0.0001), and in patients classified as early compared to advanced stages; the 15-year OS is 97.4% vs 85.7% (p=0.0007) and EFS 89% vs 59.4% (p<0.0001),



Characteristic	5 Years (OS)	10 Years (OS)	15 Years (OS)
Overall	91.5% (88.0%, 95.1%)	89.7% (85.4%, 94.1%)	89.7% (85.4%, 94.1%)

Characteristic	5 Years (EFS)	10 Years (EFS)	15 Years (EFS)
Overall	72.4% (67.1%, 78.1%)	70.3% (64.7%, 76.4%)	70.3% (64.7%, 76.4%)

Figure 1. A) Overall survival and **B**) event-free Survival.



Characteristic	5 Years (OS)	10 Years (OS)	15 Years (OS)
Stage class			
IA-IB-IIA	100.0% (100.0%, 100.0%)	97.4% (92.6%, 100.0%)	97.4% (92.6%, 100.0%)
IIB-IIIA-IIIB-IVA-IVB	86.6% (81.4%, 92.1%)	85.7% (80.3%, 91.5%)	85.7% (80.3%, 91.5%)

Characteristic	5 Years (EFS)	10 Years (EFS)	15 Years (EFS)
Stage class			
IA-IB-IIA	89.0% (82.7%, 95.8%)	89.0% (82.7%, 95.8%)	89.0% (82.7%, 95.8%)
IIB-IIIA-IIIB-IVA-IVB	62.9% (55.9%, 70.8%)	59.4% (51.8%, 68.0%)	59.4% (51.8%, 68.0%)

Figure 2. A) Overall survival and **B**) event-free survival by risk group: early and advanced.

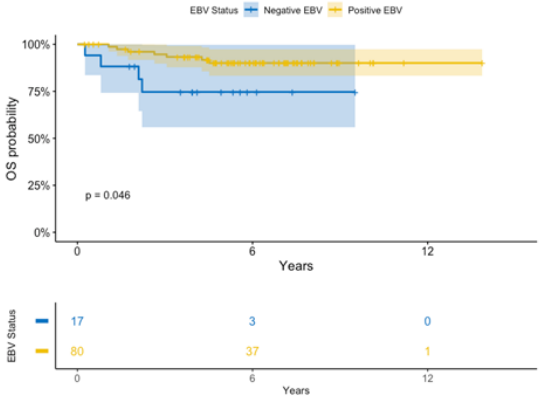
respectively (**Figure 2**). Multivariate analysis confirmed the statistically better OS and EFS for children classified as early compared with advanced stage (HR 16.0, [95%CI 2.13-12.1]; p=0.007 and 4.32, [95%CI 2.20-8.49]; p<0.001) (**Supplemental Table 1** and **Table 2**).

The 5-year OS of the 82 EBV-positive children was 90.1% compared to 74.7% for the EBV-negative cases (p=0.046). The 5-year EFS was also statistically better in EBV-positive vs EBV-negative patients (75.4% vs 36.8%; p=0.00017) (**Figure 3**).

Results After Guideline Implementation. Since January 2014, 130 newly diagnosed HL children entered the new protocol guidelines. One hundred and twenty-four were evaluated, and 6 children were moved to another treatment centre. Sixteen patients had stage I (11 IA, 5 IB), 41 stage II (23 IIA, 18 IIB), 52 stage III (17 IIIA, 35 IIIB), and 15 stage IV (2 IVA, 13 IVB) disease. One patient with stage IIA abandoned therapy, and 123 continued the treatment as planned. These children were evaluated for disease response after the second ABVD course; 109 (89%) showed a good response, while 14 (11%) had a poor response. Intensification of treatment (7 BEACOPP, 4 IGEV-ifosfamide, gemcitabine, vinorelbine, prednisone) was administered to 11 patients; 9 achieved a CR, and 2 showed a DP and died. Of the remaining 3 poor responders, 1 abandoned treatment, 1 died before starting intensification therapy, and 1 continued the ABVD cycles but relapsed and is still alive after salvage treatment. The good responders continued ABVD treatment. Seventeen (17/118; 14%) patients relapsed at a median of 20 months (range 9-78) from diagnosis; 11 are still alive and 6 have died of DP. A total of 113/123 (92%) patients treated with the new HL guidelines were still alive at the last follow-up (**Table 3**).

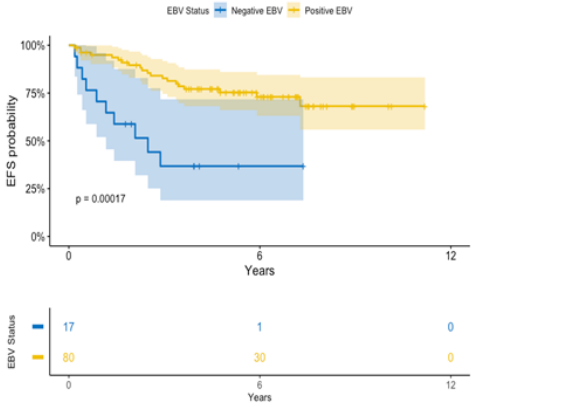
An improved outcome was observed in children

A)



Characteristic	5 Years (OS)	10 Years (OS)	15 Years (OS)
EBV Status			
Negative EBV	74.7% (55.9%, 99.7%)	— (—, —)	— (—, —)
Positive EBV	90.1% (83.3%, 97.4%)	90.1% (83.3%, 97.4%)	— (—, —)

B)



Characteristic	5 Years (EFS)	10 Years (EFS)	15 Years (EFS)
EBV Status			
Negative EBV	36.8% (18.8%, 71.7%)	— (—, —)	— (—, —)
Positive EBV	75.4% (66.1%, 86.0%)	68.2% (55.9%, 83.2%)	— (—, —)

Figure 3. A) Overall survival and **B**) event-free survival by EBV: positive and negative.

Table 3. Characteristics and outcome of paediatric patients treated according to 2014 Hodgkin lymphoma therapy-guidelines.

	Number	Percentage (%)
Number of patients	130	100
Number of patients treated at CWTH* Number of patients referred to other hospitals	124 6	95 5
Diagnostic Ann Arbor stage I A+ IB IIA + IIB IIIA + IIIB IVA + IVB	 11 + 5 23 + 18 17 + 35 2 + 13	 13 33 42 12
Number of evaluable patients Number of abandonments before therapy	123 1	99 1
Response after 2 ABVD cycles: Good response Poor response	 109 14	 89 11
Response at the end of treatment CR** CR after intensification Number total CR Abandonment Death DP°	 110 9 119 1 1 2	 89 7 97
Relapses	17	14
Alive in CR	113	92

*CWTH: Children Welfare Teaching Hospital, Baghdad; **CR: complete response; °DP: disease progression.

treated with the 2014 guidelines compared to the others, but the difference is so far not statistically significant (5-year OS and EFS 93.1% and 75.7% vs 90.4% and 70.3%, respectively; p=0.67, p=0.37).

Acute and Late Toxicities. Acute toxicity observed during first-line treatment included fatal pneumonia in 1 child after the second chemotherapy course. Acute varicella complicated by a fatal pneumonia occurred in a child 6 months after treatment completion.

Symptomatic bleomycin pulmonary toxicity and cardiomyopathy were not observed. A second malignant neoplasm in the form of osteosarcomas and acute lymphoblastic leukaemia occurred in 2 children, after 8 and 10 years, respectively, from chemotherapy completion. Both patients had received treatment with 6 COPP/ABV courses.

Discussion. Paediatric HL is a highly curable malignant tumour with overall survival rates exceeding 95%.[2,3] These excellent outcomes, however, come at the cost of an increased risk of long-term toxicities due to

chemotherapy and/or radiation.[9-11] The current risk- and response-adapted treatment for children with HL, which aims at maximizing survival while minimizing toxicity, should be the standard of care for the disease in this patient population.

In adults with HL, the ABVD scheme has been considered the de facto standard of care for several decades due to its effectiveness and excellent toxicity profile.[12,13] ABVD continues to be widely used in resource-limited settings owing to low costs, ease of delivery, and limited acute toxicity, allowing for safe delivery, even at centres with suboptimal supportive care. In a survey of paediatric oncology providers in India, ABVD was the first-line chemotherapy in 73% of paediatric oncologic centers.[5] Satisfactory results have been reported in these children treated with ABVD[5,6,14] but at the cost of 6 or more cycles of chemotherapy with RT delivered to a varying proportion of patients. ABVD was the treatment of choice for paediatric patients with HL in 2 Egyptian centres. Good results were reported in 59 children treated over 8 years; with a median follow-up of 39 months, the 5-year OS and EFS were 96.6% and 84.7%, respectively. Patients with advanced stages received 8 ABVD courses.[7]

In this present retrospective analysis, we have reported the real-life experience in Iraq in treating children with HL over 16 years with an ABVD-based therapy. RT was not feasible in the country with a long waiting list. The pretreatment disease characteristics such as low median age at presentation (7.8 years), male preponderance (71%), proportion of patients with B symptoms (51%), and high-stage disease (63%) are similar to those reported in previous studies from India and Latin-America.[5-7,15-17] The treatment outcome in terms of 15-year OS and EFS was 89.7% and 70.3%, respectively, comparing favourably with the published literature from India and limited resource centers.[5-7]

However, most children (141/184, 77%) received 6-8 chemotherapeutic ABVD cycles, accounting for doxorubicin and bleomycin exposures of ≥ 400 and ≥ 160 mg/m^2, respectively. The feasibility of reducing the chemo-radiotherapeutic burden for early and intermediate-risk patients has been demonstrated by the German Society of Paediatric Oncology, the Children Oncology Group (COG), and the European EuroNet-PHL-C1 (EudraCT number: 2006-000995-33).[18-21] The Stanford, Dana Farber, and St. Jude Consortium and German trials have demonstrated that for patients who achieved a CR after 2 cycles with [F-18]2-fluoro-2-deoxyglucose (FDG)-positron emission tomography (PET)-based response assessment, treatment can be reduced to 4 cycles without adjuvant RT. In a recent study (POG-HL-15-01) conducted in low- and middle-income countries, the impact of using CT and PET after 2 ABVD courses on treatment decisions and outcomes was compared. In a cohort of 382 HL children, the use of PET as the modality for early response evaluation clearly indicated a satisfactory response compared to CT.[22] In Baghdad, during the study period, no patients could be staged and reassessed with an FDG-PET due to the impossibility of carrying out the procedure. In Iraqi children who entered the 2014 new guidelines, the early response evaluation was not based on PET, and this could have produced inconsistent results. Furthermore, greater uncertainty relating to less accurate staging and response assessments, as well as the unavailability of RT, has led to an increase in the number of chemotherapy cycles, even in more limited stages of disease.

In Western countries, in order to decrease late chemotherapy-related side effects and restrict exposure to alkylating agents and anthracyclines, new treatment schemas have been employed in paediatric HL. In the EuroNet-PHL-C1,[21] OEPA (prednisone, vincristine, doxorubicin, etoposide) for the first 2 courses, followed by COPDAC (prednisone, vincristine, doxorubicin, etoposide, cyclophosphamide), was administered to children with newly diagnosed HL. However, it is well recognized that OEPA chemotherapy is associated with significantly more acute toxicity, especially in the first cycles. In a study from India,[23] 69 febrile episodes during neutropenia were reported in 54 patients with a treatment-related mortality of 5.3% (7/132) and a treatment abandonment of 10%.[23] Parambil et al. also reported a no-relapse mortality of 4.3% in advanced-stage HL with the same strategy.[24] The reported incidence of febrile neutropenia and toxic mortality following ABVD is much lower.[5] In the present experience, only 1 child died during treatment due to a pulmonary infection; no other acute toxicities were observed. Abandonment during first-line therapy was also limited (<2% of patients) despite limitations in the country's social and financial resources. However, 2 patients presented a second neoplasm after 8 and 10 years, respectively, even without RT. Hence, in resource-limited settings, there is a need to discern how best to balance the risk of early treatment-related toxicity versus late sequelae.

In developing countries, HL patients are likely to be younger and more likely to have EBV-driven disease.[25-27] Whether EBV-driven disease is more responsive to treatment is actively debated, and treatment strategies for these young patients need to be more focused.[28] In our cohort of patients up to 14 years of age, EBV could only be assessed in one-third of cases; 82 out of 100 patients tested resulted in EBV-positive. The outcome of these children, regardless of the stage and type of treatment received, was significantly better than that of those who resulted negative (5-year OS and EFS 90.1% and 75.4% vs 74.7% and 36.8%, respectively). The high frequency of childhood EBV-associated HL is also described in other developing countries,[28] and some studies report a favourable effect of EBV-positive HL on survival, as we

have observed in our cohort of Iraqi children. This finding supports further investigation of EBV as a prognostic marker for children with HL living in these countries.

There are, however, some limitations to this study. Many patients could be under staged (extra nodal involvement only 6% of cases) because the diagnostic tools, such as PET and CT, were not always available in the centre, and the initial staging was assessed only with chest X-ray, superficial node, and abdominal sonography. Moreover, before January 2014, this was not a clinical trial and chemotherapy regimens were chosen based on the availability of drugs. The number of chemotherapy courses was often based on each child's clinical outcome. Finally, the number of late side effects may be underestimated because the status of the patients who did not turn up for follow-up was confirmed by phone.

Conclusions. In this large paediatric HL series managed in Baghdad with long-term follow-up, good results in terms of OS and EFS have been achieved despite the numerous limitations in diagnostic procedures, shortage of chemotherapy, and no RT facilities. This analysis has provided a platform for planning future prospective studies. Furthermore, PET is now available in the centre, and in the near future, it will be used for diagnostic staging and assessing the early response to therapy. RT is currently organized in the country also for paediatric patients. There is clearly a need to adapt the intensity of treatment to the initial disease's stage and the early response to treatment in order to improve the long-term results further and avoid acute and late therapy-related side effects.

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