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Clinical characteristics and outcome of pediatric patients with stage IV Hodgkin lymphoma

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BACKGROUND AND OBJECTIVES: While treatment outcomes for patients with Hodgkin lymphoma (HL) have improved remarkably, patients with disseminated disease still have a poorer outcome. Stage IV HL is often reported with other 'advanced stage' categories, confusing the specific contribution of disease dissemination to the outcome. This single-institution report looks at characteristics and outcomes of this specific category.

PATIENTS AND METHODS: The medical records of pediatric HL patients (<14 years) from 1975 through 2003 were retrospectively reviewed and the data analyzed.

RESULTS: Stage IV patients (n=67) had more poor-risk characteristics than patients in stages I-III (n=300) (B symptoms 86.6% vs. 19.3%, bulky disease 57.6% vs. 45.5% and mediastinal mass 77.6% vs. 29.7%; *P*<.001 for all characteristics). The liver was the most common extralymphatic site (in 51.5% of patients with stage IV disease. Stage IV patients received chemotherapy (CT) alone (n=55) or combined modality therapy (CMT) (n=12). Fifty-four patients (80.6%) achieved complete remission, 2 (3%) partial remission, 10 (14.9%) had progressive disease and 1 was lost to follow up. Overall survival was 79.4% and event-free survival (EFS) was 63.9% at 5 years. There was a non-significant benefit for CMT (OS=91.7% v. 77.1%, *P*=.3; EFS=70.7% v. 62.7%, *P*=.3). Ten of 12 relapsed and only 1 of 10 progressive disease patients were salvaged. On multivariate analysis, failure to achieve complete remission with CT was associated with a poorer outcome.

CONCLUSION: Stage IV disease is associated with poor risk features and confers a worse outcome than stage I-III disease. Achievement of complete remission with CT is an important prognostic feature. Slow responders may require novel and/or aggressive therapy to achieve complete remission.

Treatment outcomes for patients with Hodgkin lymphoma (HL) have improved significantly over the past three decades to the extent that current treatment strategies for most HL subcategories focus on toxicity reduction rather than further improvement in disease cure.[1] This has led to the development of risk-stratified treatment assignment with more aggressive therapy limited to patients with 'advanced' disease. Unfortunately, the definition of 'advanced' disease varies.[2-6] While differences exist in the inclusion of all patients with stage III disease or only those with B symptoms or bulky disease in the 'advanced' disease category, all clinicians agree that stage IV is definitely high risk.

Toxicity reduction strategies have employed multimodality therapy, with the use of lower doses of both chemotherapy and radiation therapy. While this has been definitely successful in lower stage disease, the use of radiation therapy as consolidation in patients with stage IV disease remains controversial. Studies in adult patients seem to indicate a lack of benefit for using radiation therapy in patients who have achieved a complete response (CR) to chemotherapy.[7] However, while pediatric studies continue to show a statistical benefit in event-free survival for involved-field radiation therapy (IFRT) as consolidation following CR to chemotherapy,[8] debate regarding the degree of benefit in terms of survival is ongoing.[9] The utility of such radiotherapy may actually differ in different risk groups of patients.

Certainly, in patients with stage IV disease, due to the extent of disease involvement, the field of radiation that should be used, if all sites of initial involvement were irradiated, would be quite extensive. This has led many to attempt to treat the majority of such patients with only chemotherapy, while strategies to determine specific sites of involvement that should receive irradiation continue to evolve.[6,10]

While the number of nodal sites has been shown to be of prognostic value, little information is available regarding the prognostic significance of either the number of extranodal sites involved or the specific organs that are involved with metastatic disease. There may certainly be patients with stage IV HL that are at a higher risk of treatment failure than others, and if these are identifiable they may benefit from novel or aggressive therapeutic strategies.

With these questions in mind we have studied the data regarding pediatric patients with stage IV HL treated at our institution, and have attempted to determine clinical characteristics that may further define risk stratification in this group of high-risk patients. Although this is a retrospective evaluation we have also explored the outcome of single- versus multi-modality therapy.

PATIENTS AND METHODS

Medical records of HL patients diagnosed and treated in the pediatric hematology/oncology service at our institution from 1975 through 2003 were retrospectively reviewed. Data regarding the pathological diagnosis, staging, treatment, and outcome were collected and analyzed. The collection, analysis and reporting of this data was conducted under the review and approval of the Institutional Research Advisory Council which acts as the Institutional Review Board for the Department of Pediatric Hematology/Oncology, King Faisal Specialist Hospital and Research Center, Riyadh, Saudi Arabia.

The diagnosis of HL was based on the cytomorphology, and on the immunohistochemical and cytochemical stains. The REAL (Revised European-American Classification of Lymphoid Neoplasms) classification, and subsequently the WHO classification, were used for sub-categorization.[11] All patients were staged according to the Ann Arbor HL staging criteria prior to treatment initiation.[12] Staging workup was non-surgical, and included a CT scan of the chest, and either a CT scan and/or an ultrasound of the abdomen. A CT scan was also done for all other sites with suspected involvement on clinical evaluation. Other radiological studies including plain x-rays and a gallium scan were conducted for several patients. In addition, a bone marrow aspirate and trephine biopsy were conducted on the majority of patients.

Due to the extent of the disease, the treatment strategy for these patients relied on systemic delivery of therapy using chemotherapy. The decision on use of radiation therapy was left to the individual treating physician, and was therefore used in only a very few patients. Only 4 of 38 patients diagnosed prior to 1997 received radiation. Two of these patients had documented residual disease at completion of scheduled chemotherapy. One had bulky mediastinal disease at diagnosis and received 3600 cGy radiation to the mediastinum. The fourth patient received 3500 cGy to the mantle field following completion of chemotherapy; unfortunately, his response to chemotherapy could not be determined. After 1997, our strategy for radiation therapy changed, and based on the experience from the Hospital for Sick Children, Toronto,[13] we started using significantly lower doses (1500 cGy) of radiation for consolidation therapy. For patients with stage IV disease radiation therapy was only used if patients had bulky disease at presentation (administered only to those sites with bulky disease) and to those who exhibited a slow response to chemotherapy. Eight patients diagnosed since 1997 received radiation therapy, and all were given the 1500 cGy dose.

Statistical Package for Social Sciences (SPSS) version 13.0 was used for statistical analysis. Relative incidences for the clinical characteristics of patients with stage IV disease and those with stages I-III were compared using the chi square test for categorical variables and the t test for continuous variables. Treatment outcome was evaluated using Kaplan-Meier analysis and the differences between outcomes were tested using the log-rank test.

RESULTS

Between January 1975 and December 2003, 494 patients younger than 14 years of age were treated for HL at our institution. Data for 35 patients was unavailable; 92 were diagnosed elsewhere and had initiated therapy there. These patients were referred to our institution either for radiation therapy alone, for continuation of first-line chemotherapy, or at the time of relapse for second-line therapy. These patients were not included in the analysis. The remaining 367 patients were diagnosed and received all their treatment at our institution. Sixty-seven (18.3%) diagnosed with stage IV disease at the time of their initial presentation form the basis of this evaluation.

While there was no difference in the demographic characteristics of the patients with stage IV as compared to those with stages I-III, there were significant

Table 1. Clinical characteristics of patients with stage IV Hodgkin lymphoma compared with patients in all other stages.

	Stage IV (n=67)	Stages I-III (n=300)	*P*
Mean age (years)	8.95	8.13	.055
M:F ratio	2.53	2.95	.64
Duration of symptoms (mo)			
Mean	9.5	8.5	
Median	6	5.5	.48
Range	0.2-48	0.3-72	
B symptoms	58 (86.6%)	58 (19.3%)	<.001
Bulky disease	34 (n=59; 57.6%)	133 (n=292; 45.5%)	.001
Mediastinal mass	52 (77.6%)	89 (29.7%)	<.001
Hemoglobin level (g/L)			
Mean	91.6 (n=62)	116.2 (n=288)	
Median	92	118	<.001
Range	36-152	60-161	
Lactate dehydrogenase (U/L)			
Mean	592.3 (n=42)	563.1 (n=183)	
Median	526	522	.50
Range	229-1634	183-2051	
Erythrocyte sedimentation rate (mm/H)			
Mean	82.2 (n=28)	39.8 (n=149)	
Median	91.5	24	<.001
Range	2-150	1-150	
No. of lymph node sites involved			
Mean	4.03	2.14	
Median	4.0	2.0	<.001

associations between stage IV disease and other known poor prognostic markers, such as bulky disease, mediastinal involvement, systemic symptoms and a lower hemoglobin level (Table 1). Patients with stage IV disease also had more sites of lymph node involvement than those patients with lower stage disease. The liver was the most frequent site of extranodal involvement, with 34 of 66 (51.5%) patients having liver metastases. Five patients had nodular lesions in the kidneys. Three patients had pleural seeding with an effusion, while one patient had a soft tissue mass in the chest wall that was not contiguous with any lymph node sites. Most patients had only one site of extranodal involvement (n=41; 62.1%). The liver was most often involved as the solitary metastatic site (n=18; 52.9% of all patients with liver involvement), constituting 43.9% of all patients with a single metastatic site. The lungs were most often associated with other sites of involvement; 10 (83.3%) of the 12 patients with lung metastases had involvement of other extranodal sites as well. Similarly, all five patients with kidney involvement also had metastatic disease in the liver or the lungs.

Fifty-five patients were treated with chemotherapy alone (Table 2). Twelve patients received combined modality therapy (CMT) with chemotherapy and radiation therapy (Table 3). Overall, patients received a median of six cycles of chemotherapy (range 1-16 cycles). The 30 patients who were treated with an ABVD-containing protocol (ABVD or ABVD/COPP) received a median of six cycles (range 4-10 cycles) of chemotherapy, while patients treated with other therapies (n=36; mainly MOPP) received a median of 6.5 cycles (range 1-16 cycles) of therapy. Five of the patients who were treated with CMT received the ABVD regimen, while six were treated with alternating cycles of ABVD and COPP. One patient received MOPP chemotherapy. Nine of these patients achieved a compete response with chemotherapy and then received consolidation radiation therapy. Eight received a 1500 cGy dose of radiation therapy (5 extended field and 3 involved field) while the ninth patient received 3600 cGy to the mediastinum. Two patients had residual disease at the end of chemotherapy and received 3000 cGy and 4140 cGy to areas of residual disease. The chemotherapy response status for one patient was unknown and he received 3500 cGy to a mantle field following four cycles of ABVD.

Fifty-four (80.6%) patients achieved complete response to first-line therapy, 2 (3%) had a partial response, 10 (14.9%) had progressive disease (PD) and 1 had early loss to follow-up. At a median follow-up of 5.6 years (mean 8.4 years; range 0.04-27.4 years) estimated 5-year overall survival (OS) and event-free survival (EFS) was 79.4% and 63.9%, respectively. The median follow-up for surviving patients was 7 years (mean 10.2 years, range 0.2-27.4 years). The outcome of patients with stage IV disease was significantly worse than that for patients with all other stages (Figure 2). Although statistical significance was not achieved,

there was a trend towards better survival for patients who received radiation therapy in addition to chemotherapy (Figure 3). However, when we studied only those patients who had achieved a complete response to chemotherapy, the addition of radiation therapy as consolidation to these good responders showed only a marginal benefit without any statistical significance. For this group of patients the OS at 5 years was 100% for those who received radiation as compared to 91.5% for those who did not (P=.4; log rank test) and EFS was correspondingly 87.5% and 73.7% (P=.4; log rank test). This trend towards a better outcome with CMT could also have been impacted by the era of therapy. The EFS for patients treated after 1997 was 72.3% compared to 56.5% for those treated before 1997 (P=.4; log rank test). Eight of the 12 patients who received CMT were treated after 1997, and almost all were treated using an ABVD-containing regimen.

Factors in these high-risk patients that may contribute to outcome and help in prognostication include age, gender, number of lymph nodal sites involved, sites of extranodal involvement and response to therapy. Predictably, by both univariate and multivariate analysis, achievement of complete response at the end of scheduled chemotherapy had a significant impact on survival (Table 4). The only extranodal site that predicted survival by univariate analysis was the lung. However, when this was included in the multivariate model, lung involvement lost its importance achieving only marginal significance.

Table 2. Chemotherapy in patients with stage IV disease.

Regimen	n
ABVD	12
MOPP	25
COPP	1
Combination	17
MOPP/ABVD	3
COPP/ABVD	9
Other	5
Total	**55**

ABVD: Adriamycin, bleomycin, vinblastine, dacarbazine, MOPP: mechlorethamine, vincristine, procarbazine, prednisone, COPP: cyclophosphamide, vincristine, procarbazine, prednisone.

Table 3. Combined modality therapy in patients with Stage IV disease.

Chemotherapy	n	Radiotherapy	n
ABVD	5	1500 cGy IF	1
		1500 cGy EF	2
		3500 cGy IF	1
		3600 cGy IF	1
ABVD/COPP	6	1500 cGy IF	2
		1500 cGy EF	3
		4140 cGy IF	1
		3000 cGy IF	1
MOPP	1	3000 cGy IF	1

IF= involved field; EF= extended field. ABVD: Adriamycin, bleomycin, vinblastine, dacarbazine, MOPP: mechlorethamine, vincristine, procarbazine, prednisone, COPP: cyclophosphamide, vincristine, procarbazine, prednisone.

DISCUSSION

Modern treatment strategies have resulted in significant improvements in outcome for patients with HL. Most patients nowadays can expect a greater than 90% chance of treatment success. However, this high survival rate is primarily restricted to patients without disseminated disease; patients with dissemination (stage IV) in most pediatric and adult studies continue to suffer a worse outcome than all other stages, with disease-free survival rates ranging between 50% and 85%.[2, 5,14,15] Our results confirm this difference in outcome.

Treatment strategies for these patients have focused primarily on chemoreduction. However, use of radiation therapy remains controversial. While some study groups have elected to restrict radiation therapy to only those patients with initial bulky disease or with residual disease following chemotherapy, others are continuing to use this modality for all patients, albeit with response-directed restrictions on field and dose.[2,4-5,14,16] The majority of our patients were treated with chemotherapy alone. Some patients received radiation therapy at the discretion of the treating physician; these were patients with either suboptimal responses to chemotherapy or with initial bulky sites of disease. Our results suggest that there does seem to be some benefit of additional therapy for patients who suffered a suboptimal response to chemotherapy. On the other hand, radiation as consolidation for patients who had achieved a complete response to chemotherapy did not result in an additional positive impact on the outcome. This result is consistent with Loeffler et al, who questioned the benefit of adding radiation therapy after a meta-analysis of studies that randomized patients to receive chemotherapy alone or CMT.[17] Other investigators have concurred, suggesting no benefit of additional radiation therapy.[18] However, considerable confusion remains regarding the

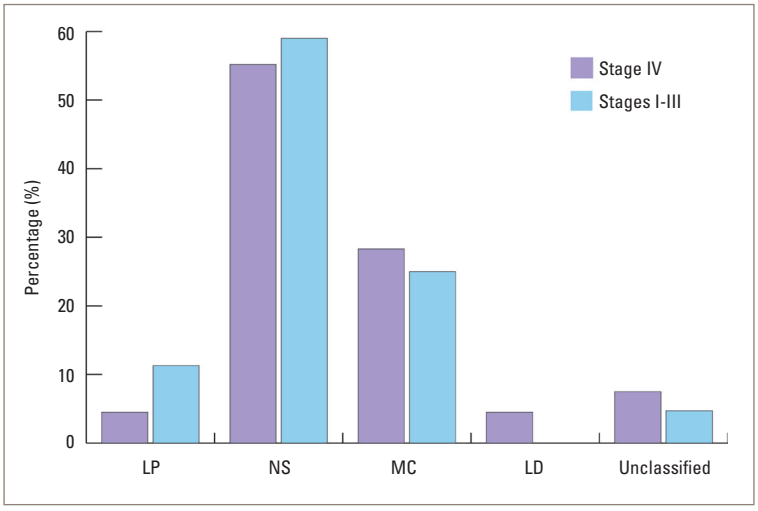

Figure 1. Percentage distribution of histological subtypes comparing stage IV with all other stages. LP=lymphocyte predominance; NS=nodular sclerosis; MC=mixed cellularity; LD=lymphocyte depletion.

Table 4. Effect of predictor variables on survival (logistic regression analysis).

Risk factors	Exp (B)	95% confidence interval of Exp (B)	*P*
Unadjusted analysis			
Age at diagnosis	1.002	0.822-1.222	.983 .908[a]
Gender (male)	2.308	0.675-7.892	.183
No. of lymph node sites (1 vs. >1 lymph nodes)	0.255	0.015-4.354	.345
No. of lymph node sites (≤median vs. >median)[b]	0.953	0.278-3.272	.939
Lung involvement	5.750	1.479-22.358	.012
Liver involvement	0.293	0.081-1.059	.061
Bone and/or bone marrow involvement	1.543	0.455-5.234	.487
Failure to achieve complete response at end-of-chemotherapy	37.5	7.228-94.544	<.001
Adjusted analysis[c]			
Failure to achieve complete response at end-of-chemotherapy	73.595	7.336-738.309	<.001
Lung involvement	9.378	0.866-101.612	.066

[a]Mann-Whitney U-Test; [b]Median number of lymph node sites = 4; [c]Adjusted for age at diagnosis, gender, lymph nodes sites (≤ median vs. > median), lung, liver, bone and/or bone marrow involvement and failure to achieve CR-1. Relapse/PD was not included in the model due to its highly significant dependence on failure to achieve CR-1 (*P*<.0001, Fisher exact test).

utility of radiation therapy. Nachman et al showed a statistically significant benefit for radiation therapy in a clinical trial that randomized patients who achieved complete response to chemotherapy to receive radiation therapy or not.[8] More recently, in an update of the same protocol, it was suggested that the benefit for radiation therapy may be restricted only to subsets of patients definable by histology and clinical risk features.[19] This would suggest that attempts at improvement in the outcome for these patients should rely on identification of these higher risk patients, either by pre-treatment risk stratification or by response evaluation. Addition of radiation therapy to existing chemotherapy protocols or increasing the efficacy of chemotherapy could then be utilized for those patients who are likely not to achieve an optimal response.

Prognostication and risk scoring has been used for several malignancies to determine appropriate therapeutic intensity. The International Prognostic Score for HL has significant utility in this regard, but is definitely more relevant in adult patients.[20] Several other prognostic scores that have been developed, in particular for advanced stage HL, have not included children (≤14 years) either in their initial evaluation or during subsequent validation.[21,22] Smith et al reported the results of a multi-institutional clinical trial in pediatric patients with HL and proposed a prognostic scoring system.[14] This included five criteria (male gender, high stage, bulky mediastinal disease, WBC >13.5×10^9/L and hemoglobin <11 g/L) that were found to independently predict inferior outcome. Application of this scoring system on our cohort of stage IV patients did not further categorize patients according to outcome (patients with scores of 1-3 v. 4-5; OS 79.7% v. 78.8%; EFS 60.6% v. 64.2%; *P*>.5 [log rank test] for both comparisons). One other study of prognostic factors in pediatric HL patients found only stage IV as an independent risk factor on multivariate analysis.[23] Our own efforts to identify prognostic variables that might predict outcome and guide treating physicians in clinical decision making failed to reveal any pre-treatment variables of significance.

As expected, response to treatment in these very high-risk patients did predict eventual outcome. Although the methodology used to determine response to therapy in our study was fairly crude when compared to current available techniques, clearly a complete response to chemotherapy does predict a superior outcome. The availability of functional imaging such as FDG-positron emission tomography (FDG-PET) has resulted in more sensitive assessments of therapeutic response. FDG-PET has a significant predictive value in patients with advanced stage disease and can potentially

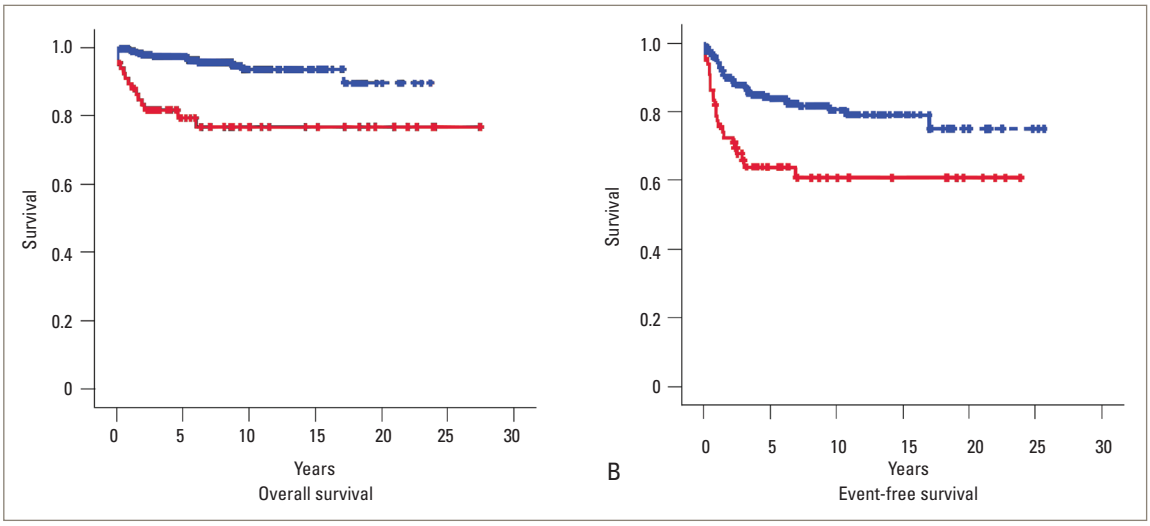

Figure 2. Overall and event-free survival for patients with stage IV (blue line) and stages I-III (red line). 5-year overall survival for stage IV is 79.4% and for stages I-III is 97.5% (*P*<.001; Log-rank test). 5-year EFS for stage IV is 63.9% and for stages I-III is 83.8% (*P*<.001; Log-rank test).

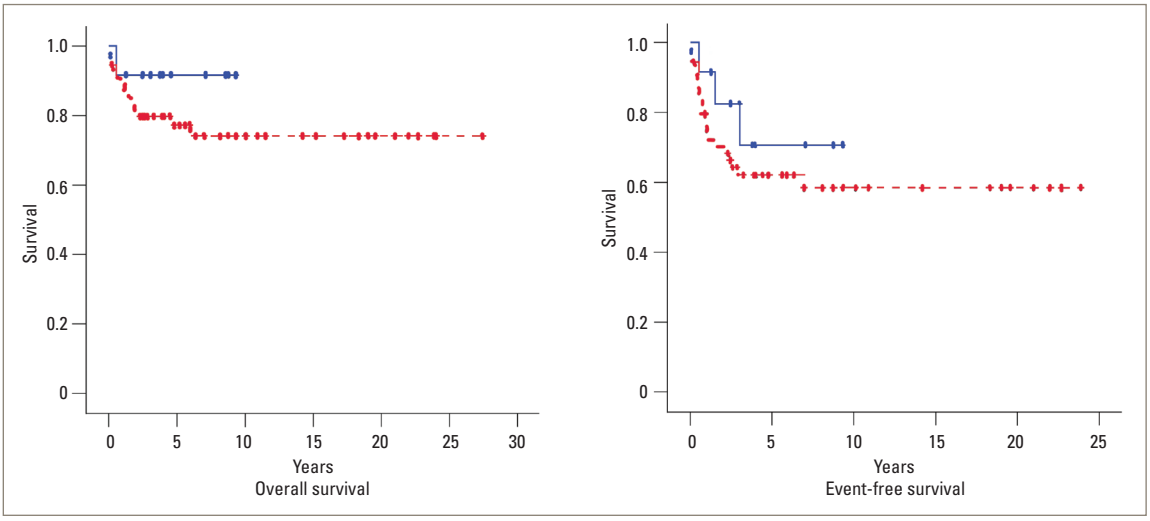

Figure 3. Overall and event-free survival for patients treated with chemotherapy (CTX) alone (red line) and combined-modality therapy (CMT) (blue line). 5-year overall survival for CTX is 77.1% and for CMT is 91.7% (*P*=.3; log-rank test). 5-year EFS for CTX is 62.7% and for CMT is 70.7% (*P*=.4; Log-rank test).

be used to tailor therapeutic strategies.[24-26] For stage IV patients, where risk of treatment failure is significantly higher than for other stages, a suboptimal response to two or three cycles of standard therapy could be an indication for using more intensive or novel therapy, which may include autologous stem cell transplantation or targeted immunotherapy. However, more study is required before this suggestion could be implemented as a recommendation.

Intensification of first-line therapy to improve initial responses may also be a feasible strategy. While ABVD has remained effective therapy for most patients, clinical trial results using BEACOPP (bleomycin, etoposide, Adriamycin, cyclophosphamide, vincristine, procarbazine, prednisone and escalated BEACOPP have shown significant advantages, particularly in the advanced stage patients.[4,10,16] Such intensive protocols may result in a lower incidence of poor early response to chemotherapy, more complete responses at the end of scheduled chemotherapy and possibly a better disease outcome. However, there is the potential for significant toxicity in pediatric patients,[27] maybe at the cost of

overtreatment for a subset of patients who may have responded well to less intensive regimens. This is certainly demonstrated in our cohort of patients who achieved a complete tumor response with less intensive protocols and had excellent outcomes.

In conclusion, HL patients with disease dissemination at diagnosis continue to pose a significant therapeutic dilemma. Attempts at risk stratification have as yet failed to yield any notable pre-treatment criteria. While treatment intensification has improved outcomes for these patients, this may result in overtreatment in a subset with the consequent risk of treatment-related toxicity. Better criteria for measurement of treatment response as a mechanism for risk stratification, and the identification of intensive or novel strategies for those patients with poor responses may be the best way to proceed with treatment in traditionally poor-risk HL patients.

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