Utility of bone marrow biopsy at diagnosis in pediatric Hodgkin's lymphoma

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ABSTRACT

Background
Bone marrow biopsy is considered essential for the staging and risk-adapted treatment of Hodgkin's lymphoma with unfavorable risk features. We reviewed the cases of pediatric Hodgkin's lymphoma in our institution to determine the impact of bone marrow involvement on treatment, relapse, and survival.

Design and Methods
We reviewed the clinical characteristics and outcome of 383 patients treated for Hodgkin's lymphoma at St. Jude Children's Research Hospital between August 1990 and August 2008. The 5-year survival estimates for patients with and without bone marrow involvement were compared.

Results
Of 228 patients who had a bone marrow biopsy at diagnosis, 21 had bone marrow involvement. Bone marrow findings changed the disease stage in only seven patients (3.1%): from IB to IVB (n=1), from IIA (with bulky disease) to IVA (n=1), from IIB to IVB (n=1), and from IIIB to IVB (n=4). One patient's risk assignment changed from intermediate to unfavorable risk without his chemotherapy being altered. No statistically significant difference was observed between patients with stage IV Hodgkin's lymphoma who did (n=21) and did not (n=61) have bone marrow involvement in 5-year relapse-free survival (89.6± 7% *versus* 73.9±6.1%; P=0.25) or 5-year overall survival (95.2±8.2% *versus* 87.3±4.9%; P=0.82).

Conclusions
Although bone marrow involvement changed the stage in 3.1% of pediatric Hodgkin's lymphoma patients, it did not change risk-adapted treatment or prognosis. We conclude that bone marrow biopsy need not be performed at diagnosis in patients who have unfavorable risk features, although this finding should be confirmed by larger prospective studies.

Key words: bone marrow, risk features, Hodgkin's lymphoma.

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Introduction

Bone marrow (BM) biopsy is part of the staging work-up for Hodgkin's lymphoma (HL) with unfavorable risk features. In low-income countries, many children undergo BM biopsy without anesthesia and at considerable cost to their families. Even in settings in which pain is controlled and out-of-pocket costs are limited, biopsy carries known risks.[1] In adult HL, BM involvement is associated with higher disease stage, certain histological subtypes, and the presence of B symptoms.[2-4] In pediatric patients, BM involvement is associated with higher disease stage, B symptoms,[5-7] and, in one study, anemia.[7] Because BM involvement is detected in less than 1% of adults[2,6] and less than 2% of children with stage IA and IIA disease,[7-9] staging practice reserves BM biopsy at diagnosis for patients who have unfavorable risk features. While clinical research has focused on predictive models for BM involvement in adult and pediatric HL,[9,10] it is still uncertain whether BM involvement alters the treatment or the prognosis of patients treated with combined-modality therapy. We, therefore, retrospectively assessed the impact of BM involvement at diagnosis on therapy assignment, relapse-free survival, and overall survival in pediatric patients with HL.

Design and Methods

Patients and therapy

We reviewed the medical records of all patients with newly diagnosed HL who received combined-modality therapy at St. Jude Children's Research Hospital from August 1990 to August 2008. The clinical, demographic, and disease characteristics assessed included sex, age at diagnosis, race, HL histology, risk group, mediastinal ratio, BM biopsy findings at diagnosis, sites of extranodal disease, information about relapse, and cause of death.

Patients were staged according to the Ann Arbor Staging classification[11] by using computed tomography and either positron emission tomography or gallium scans. A BM biopsy was obtained for patients with stage III or IV disease or if B symptoms were present, regardless of stage. Patients in the older studies with stage IA and IIA HL underwent BM biopsy if they had bulky disease (defined as peripheral nodal disease ≥ 6 cm or a mediastinum/thorax ratio ≥ 33%). All BM biopsies were analyzed in a core laboratory by a hematopathologist using standard immunohistochemistry as well as visual assessment. All patients were given risk-adapted, response-based chemotherapy, and most received involved-field radiation, unless they had favorable-risk disease after January of 2000 and were in complete remission after 8 weeks of chemotherapy, as previously described.[12-15]

The risk classification system differed somewhat between successive treatment protocols. The 1990 protocol (HOD90) classified stage I/II A or B, non-bulky disease as favorable and bulky stage I/II A or B disease and stage III/IV disease as unfavorable. The 1994 protocol (HOD94) classified any case involving B symptoms as unfavorable. The 1999 protocol (HOD99) introduced an intermediate-risk category. Stage IA and IIA disease involving fewer than three sites in the absence of mediastinal bulk or extranodal extension was considered favorable. Stage II and III disease with B symptoms and stage IV disease were unfavorable. All others were assigned to the intermediate risk group.

Analysis

All patients were included in the descriptive portion of the study. Only patients who underwent BM biopsy at diagnosis were included in analyses of the effect of BM involvement on staging, risk classification, and treatment. Patients with stage IV disease who had undergone BM biopsy at diagnosis were included in the analysis of the effect of BM involvement on therapy, relapse-free survival, and overall survival. We also analyzed the effect of BM involvement on therapy in patients who had stage IV disease with BM as the sole extranodal site at diagnosis. To assess the effect of BM biopsy results on therapy, we compared these patients' assigned stage and risk stratum with the stage and risk stratum that would have been assigned in the absence of BM involvement at diagnosis. The exact χ^2 test was used to compare presenting features including sex, stage, presence of B symptoms, and tumor histology between the study group and the whole cohort and between stage IV patients with and without BM involvement. The Wilcoxon-Mann-Whitney test was used for comparison of age and follow-up time between the cohorts. Relapse-free survival was defined as the time interval between diagnosis and treatment failure. Overall survival was defined as the time interval between diagnosis and death from any cause. Survival data were censored at the date of most recent follow-up and estimated by using the method of Kaplan and Meier.[16] All analyses were performed with SAS version 9.1 software (Cary, NC, USA).

Results

Patients' characteristics

Table I shows the clinical and demographic characteristics of the entire cohort (n=383) and the patients who underwent BM biopsy (n=228). The groups had comparable gender distribution and follow-up time but clearly differed in that only patients with unfavorable characteristics underwent routine BM biopsy. The median age of the entire cohort was 15.4 years (range, 3-22 years), and patients who underwent BM biopsy were older (median age, 15.8 years) than others (median age, 14.7 years; P=0.003). As expected patients who had a BM biopsy were significantly more likely to have B symptoms, advanced disease stage, and bulky mediastinal mass and were less likely to have lymphocyte-predominant HL, a histological classification associated with localized disease and favorable features. Ninety-four percent of patients had been seen within the past 2 years, and 74% within the past year as of June 1, 2009.

Sites of extranodal disease at diagnosis

Of the 228 patients who underwent bilateral BM biopsy at diagnosis (Figure 1), 21 (9%) had BM involvement. In 7 (33%) of these 21 patients, the BM was the only extranodal site of disease. Two of these seven patients experienced relapse; one died and the other one has remained in continued second remission for more than 7 years. The patient who died had a complicated course with treatment-refractory disease and persistent BM involvement. Of the 85 patients with stage IV HL (including 3 patients whose BM involvement was unknown) and a single extranodal site other than BM, 15 had extranodal bony disease, 40 had extranodal lung disease, and one had only extranodal liver disease. The remaining 22 patients had more than one site of extranodal disease including bone marrow, bone, lung, liver, and kidney.

Bone marrow involvement and risk-directed treatment

Table 2 shows the data for the seven patients who had stage IV disease with BM as the only extranodal site of involvement at diagnosis and the disease stage that would have been assigned in the absence of BM biopsy. One patient with involvement of a single node (stage I) and B symptoms would have been placed in the intermediate-risk category rather than in the unfavorable-risk category on our protocol. At our institution, where patients with intermediate and unfavorable risk were treated on the same chemotherapeutic regimen, this difference affected the radiation field (involved field *versus* targeted field) but not the dose (15 Gy or 25.5 Gy depending on early response to therapy). Two patients would have been assigned to stage II if BM disease had not been discovered. One of these would have been assigned to stage IIB and would, therefore, have been considered to have an unfavorable risk. The other patient (on the HOD94 protocol) would have been assigned to stage IIA but was considered to have an unfavorable risk because of bulky abdominal lymphadenopathy. Four patients would have been assigned to stage IIIB (unfavorable risk) on the basis of imaging findings. Therefore, of the seven patients who were restaged, only one had a change in risk category and none had a significant change in therapy. The other fourteen patients with BM involvement at diagnosis had evidence of disease in other extranodal sites and were, therefore, assigned to stage IV at the outset. BM biopsy results did not alter planned therapy in any of these patients.

Table 1. Characteristics of 383 children with Hodgkin's lymphoma.

Characteristic	All		BM biopsy		P*
	N. of patients	%	N. of patients	%	
N. of patients (%)	383	100	228	60	
Sex					
Male	214	56	122	57	0.26
Female	169	44	106	63	
Age at diagnosis, years					
Median	15.4		15.8		0.003†
Range	3.1 to 21.99		3.1 to 21.99		
Ann Arbor stage					
I-II	243	63	92	38	<0.0001
III-IV	140	37	136	97	
B symptoms					
No	263	69	110	42	<0.0001
Yes	120	31	118	98	
Mediastinal mass					
None	161	42	63	39	<0.0001
M/T ratio < 33%	109	28	69	63	
M/T ratio ≥ 33%	113	30	96	85	
Histology					
Nodular sclerosing	278	73	188	68	<0.0001
Mixed cellularity	50	13	25	50	
Lymphocyte predominant	40	10	5	13	
Classical NOS	15	4	10	67	
Follow-up period, years					
Median	9.1		8.5		0.70†
Range	0.2 to 18.4		0.5 to 18.4		

**P value obtained from the χ^2 test (unless otherwise indicated) comparing patients with and without BM biopsy. †P value obtained from the Wilcoxon-Mann Whitney test. M/T: mediastinum/thorax; NOS: not otherwise specified*

Bone marrow involvement and survival

There had been 21 deaths in our cohort at the time of this study. Two patients died of accidental causes, two of second malignancies (one of a paraspinal atypical teratoid/rhabdoid tumor of the spine and the other of acute myeloid leukemia), and two of cardiac complications related to therapy. The 14 remaining patients died of refractory or recurrent HL, but only one of these had BM involvement

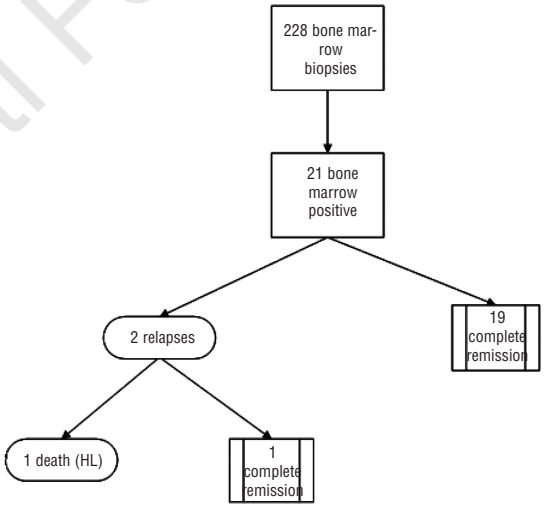

Figure 1. All bone marrow biopsies performed in pediatric patients with Hodgkin's lymphoma.

Table 2. Characteristics of patients with bone marrow as the sole extranodal site of disease involvement at diagnosis.

Age (years)	Stage had BM biopsy not been performed	Risk group had BM biopsy not been performed	Change in risk group	Change in treatment	Relapse	BM involvement at relapse	Died
19	IIIB	Unfavorable	No	No	Yes	Yes	Yes[1]
20	IIA	Unfavorable	No	No	No	NA	No
18	IIIB	Unfavorable	No	No	No	NA	No
19	IIIB	Unfavorable	No	No	No	NA	No
12	IIB	Unfavorable	No	No	Yes	No	No
11	IIIB	Unfavorable	No	No	No	NA	No
14	IB	Intermediate	Yes[2]	No	No	NA	No

[1]Patient died of Hodgkin's lymphoma. [2]Risk group with BM biopsy information was unfavorable. BM, bone marrow.

at diagnosis. None of the 21 patients with BM involvement at diagnosis had persistent involvement after 8 weeks of chemotherapy.

As shown in Figure 2, the 5-year relapse-free survival (89.6±7% *versus* 73.9±6.1%; *P*=0.25) and 5-year overall survival (95.2± 8.2% *versus* 87.3±4.9%; *P*=0.82) estimates did not differ significantly between patients with stage IV HL who did (n=21) and did not (n=61) have BM involvement. We also found no statistically significant difference between the 5-year relapse-free and overall survival estimates of patients with stage IV disease who did (n=7) and did not (n=75) have BM involvement as the only site of extranodal disease (relapse-free survival, 68.6±18.6% *versus* 77.3±5.1%, *P*=0.64; overall survival, 85.7±13.2% *versus* 90.3±3.8%, *P*=0.69). To explore whether other extranodal sites were prognostically significant, we compared the 5-year relapse-free and overall survival estimates of patients with isolated lung involvement with those of patients with isolated liver or bone involvement. No single site of involvement appeared to influence prognosis in this small sample of patients (*data not shown*). We also found no significant difference in 5-year relapse-free or overall survival rates between patients with stage IV HL who had only one site of extranodal disease compared with those who had two, three, or four sites.

Discussion

To our knowledge, this is the largest pediatric study to date that has evaluated the utility of BM biopsy and the prognostic significance of BM involvement at diagnosis of HL. Other studies of HL in childhood have addressed clinical predictors of BM involvement and the subsets of patients who should undergo BM biopsy,[7-9] but not the value and prognostic significance of BM involvement at diagnosis. This question has been investigated in several studies of adults with HL, but the results have been inconsistent.[2-4,6,17-20] In the 1970s and 1980s, BM involvement in adults with HL was found to confer a poor prognosis and to indicate disseminated disease;[17,19,20] more recent studies controlling for stage and B symptoms suggest that BM involvement is no longer prognostically significant.[2-4,21,22] Recent studies of prognostic scoring systems for adult HL have not identified BM involvement as a significant predictor of outcome[18,23] and have not included it in the prognostic scoring system.[18,23,24]

In previous pediatric studies, the incidence of BM involvement at diagnosis ranged from 1.8% to 6.5%.[7-9] In our study, the incidence was 5.5% in the whole cohort. Importantly, although this incidence appears comparable to the incidences found in the previous studies, all patients included in those studies had undergone BM biopsy,[7-9] as compared to approximately 60% of our study group. At our institution, BM biopsy at diagnosis was dictated by the current protocol; therefore, some patients with stage I and II HL, assumed to have a negligible risk of BM involvement,[2,6] did not undergo the procedure.

Mahoney *et al.* reported BM involvement in two of 110 pediatric patients with HL.[8] Both patients experienced relapse, and one eventually died of HL; however, the small size of the cohort did not allow analysis of the prognostic impact of BM involvement.[8] In our cohort, 21 of 228 (9%) BM biopsies performed at diagnosis were positive, but only two of these patients experienced relapse and only one died of HL. We also found that, as in adults,[2,3,18] BM involvement did not significantly affect the relapse-free survival or overall survival of patients with stage IV HL, nor did it carry any prognostic disadvantage in stage IV HL.[25,26] This finding is extremely important because in some low-income countries, patients with BM involvement at diagnosis may be incorrectly deemed incurable, and curative frontline therapy or radiotherapy may be withheld. Furthermore, neither the site of extranodal disease (bone, lung, or liver) nor the number of extranodal sites (1, 2, 3, or 4) significantly affected the relapse-free or overall survival of patients with stage IV HL. Previous reports of the prognostic significance of involvement of non-bone marrow extranodal sites have been mixed, and we found no studies about the prognostic value of liver involvement in adult or pediatric HL. A pediatric study found that the prognosis of patients with lung involvement was actually more favorable than that of patients with metastases at other sites.[27]

After analyzing the prognostic significance of BM involvement, we investigated whether BM biopsy information influenced therapy. In the absence of BM biopsy information, only one of the seven cases of stage IV disease with BM as the only extranodal site would have been classified differently. Given the risk stratification criteria in our protocols, we do not believe that any prognostic information was lost when these cases were staged without the BM biopsy information. Most importantly, none of the seven patients would have received different therapy in the absence of BM biopsy, including the one patient whose risk category did change. Similarly, Simpson *et al.* and Mahoney *et al.* reported that the

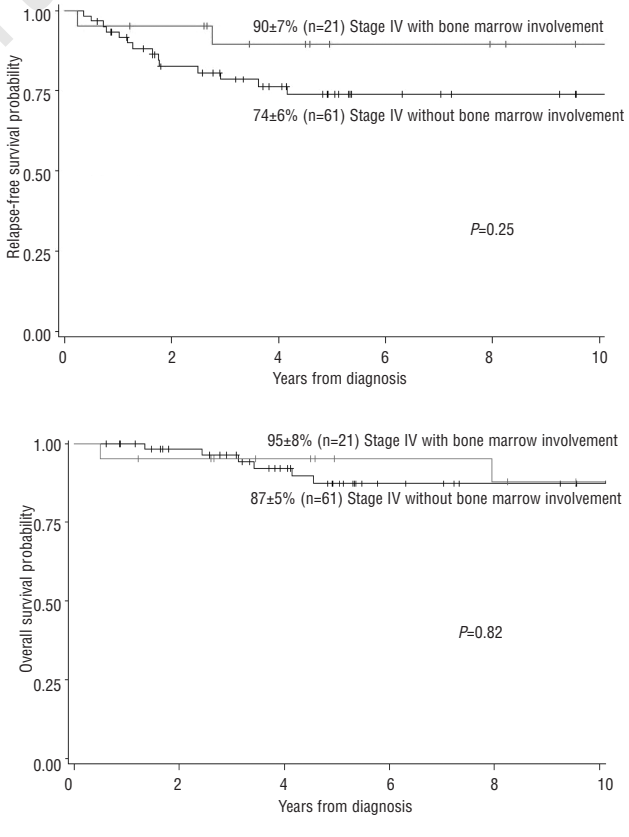

Figure 2. Five-year survival estimates of pediatric patients with stage IV Hodgkin's lymphoma who did and did not have bone marrow involvement. (A) Relapse-free survival. (B) Overall survival.

Table 3. Risk criteria in contemporary Hodgkin's lymphoma protocols.

Protocol /Stages	IA	IB	IIA	IIB	IIIA	IIIB	IVA	IVB
HOD 90	No mediastinal or peripheral bulk (6 cm)				*	*	*	*
	* Mediastinal or peripheral bulk (6 cm)							
HOD 94	No mediastinal or peripheral bulk (6 cm)	*	No mediastinal or peripheral bulk (6cm)	*	*	*	*	*
	* Mediastinal or peripheral bulk (6 cm)		* Mediastinal or peripheral bulk (6cm)					
HOD 99	No "E" No mediastinal bulk	*	< 3 sites No "E" No mediastinal bulk	*	*	*	*	*
	* "E" or mediastinal bulk		* >2 sites "E" or mediastinal bulk					
POG 8265(30) POG 8426(31) POG 8725(32) POG 9226(33)	* No mediastinal bulk			*	* No mediastinal bulk No lower abdomen or pelvis	*	*	*
	* Mediastinal bulk				* Mediastinal bulk or Involvement of lower abdomen and pelvis			
CCG 521-P (34, 35)					* With either bulky mediastinal mass, multiple splenic lesions or lower abdomen and pelvis *	*	*	*
CCG 5942(36)	< 4 sites No hilar adenopathy, no mediastinal or peripheral bulk (10 cm)			*	*	*	*	*
	> 3 sites Hilar adenopathy, or mediastinal or peripheral bulk (10 cm)							
CCG 59704				* With mediastinal or peripheral bulk (> 10 cm)		* With mediastinal or peripheral bulk (> 10 cm)	*	*
AHOD0431 AHOD0031	No mediastinal or peripheral bulk (6 cm) or "E"	*	No mediastinal or peripheral bulk (6 cm) or "E"	*	*		*	
	* Mediastinal or peripheral bulk (6 cm) or "E"		* Mediastinal or peripheral bulk (6 cm) or "E"					
GPOH-HD (37, 38)		*	No "E"	* No "E"	* No "E"	*	*	*
			"E"	* "E"	* "E"			

*Mediastinal bulk, mediastinal to thoracic ratio > 33%; "E", extranodal extension; * bone marrow biopsy mandated per protocol; HOD, St. Jude, Stanford, Dana-Farber Hodgkin Consortium; POG, Pediatric Oncology Group; CCG, Children's Oncology Group; AHOD, Frontline Studies by the Children's Oncology Group; GPOH-HD, German Pediatric Hematology-Oncology Hodgkin's Disease. White, favorable risk; light gray, intermediate risk; dark gray, unfavorable risk; black, no information available – not included in the trial.*

therapy of patients with BM involvement in their cohorts did not change on the basis of BM biopsy findings.[7,8] BM biopsy findings also did not change the initial management of adults with HL.[4,22] With the increasing sensitivity of imaging modalities, more extranodal sites of disease are being detected, leading to upstaging of patients at diagnosis and possibly leading to a decreased number of patients being upstaged because of BM biopsy findings.

All pediatric patients at our institution currently undergo ^{18}F-fluoro-deoxyglucose positron emission tomography (FDG-PET) scanning during initial staging, response evaluation, and post-treatment follow-up. The use of FDG-PET to detect BM involvement in patients who otherwise do not have high risk features should be re-evaluated in the light of the absence of prognostic value of BM involvement at diagnosis and the risk of over-treating some patients. Studies in mixed cohorts of adults with HL and non-Hodgkin's lymphoma showed that FDG-PET could be more sensitive than BM biopsy in detecting BM involvement, causing the upstaging of several patients in two studies.[28,29] No studies have been undertaken to evaluate the specificity and sensitivity of FDG-PET in detecting BM involvement in pediatric HL. Our cohort did not include a sufficient number of FDG-PET scans to address this question; however, it should be resolved before FDG-PET is routinely used to detect BM involvement.

Several limitations of this study may affect the interpretation of our results. Despite the relatively large number of patients in our cohort, the number of patients with stage IV disease and the number with BM involvement remained relatively small, limiting statistical power. Most importantly, there was no consistency among protocols or consensus among study groups regarding risk stratification of pediatric HL, as seen in Table 3. Since there was heterogeneity between protocols, the results from this study cannot be generalized.

We found that BM involvement did not alter the prognosis of our pediatric patients with HL. Not only did BM biopsy not provide useful prognostic information, it also did not change any of our patients' therapy. Modern intensive combination chemotherapy for unfavorable-risk disease is likely to eradicate both gross and minimal BM involvement. These results suggest that BM biopsy need not be routinely performed at diagnosis of pediatric patients with HL. After confirmation in other pediatric cohorts, the routine practice of BM biopsy at diagnosis in pediatric patients with HL should be reassessed.

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