Article published online: 2021-06-03

Original Article

Response and Relapses in Pediatric Hodgkin's Lymphoma Treated with Chemotherapy Alone

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Abstract

Aims: The aims of this study were to analyze the sociodemographic profile, disease characteristics, event-free survival (EFS), overall survival (OS), and risk factors for relapse in patients with Hodgkin's lymphoma (HL) treated with only chemotherapy as per unit protocol. **Subject and Methods:** Case records of children with HL diagnosed and treated at our center between January 2005 and December 2014 were retrospectively analyzed. **Results:** A total of 90 patients with mean age of 8.13 ± 2.65 years (median age 8 years; range 4.5–15 years) were diagnosed and treated for HL during the study period. Male-to-female ratio was 7.2:1. Almost 12.2% and 87.8% of patients had early and advanced stage disease, respectively. B symptoms were present in 87.8% of patients. Mean duration of symptoms was 9.66 ± 6.30 months (median 8 months; range 2–36 months). Mixed cellularity was the most common histologic type. Multiagent chemotherapy was mainstay of treatment. OS and EFS were 88.8% and 84.5%, respectively. OS in patients with or without bulky disease was 53.3% and 92.2%, respectively. Older age (≥10 years), presence of bulky disease, low hemoglobin (≤7.0 g/dl), and high leukocyte count (≥12000/mm^3) at the time of diagnosis, and protocol used (cyclophosphamide, vincristine, procarbazine, and prednisone) were the risk factors for relapse. **Conclusions:** Our patient population had younger age, advanced disease, more B symptoms, and bulky disease. Still, we achieved good OS and EFS with chemotherapy-alone protocols. Patients with bulky disease had poor OS and EFS. If radiotherapy is included in the protocol for bulky disease, the survival rates can be improved further.

Keywords: *Chemotherapy, Hodgkin's disease, lymphadenopathy, lymphoma, survival*

Introduction

Hodgkin's lymphoma (HL) accounts for 5%–6% of all childhood cancers. It displays characteristic epidemiological, clinical, and pathological features in different geographical areas depending on their socioeconomic level.[1-3] It manifests at a younger age in developing countries with the incidence decreasing with age. Moreover, advanced stage disease is also more common in developing countries. In contrast, HL is very uncommon at young age in developed countries and the incidence increases with age, with more adolescents and young adults being affected. Early-stage disease is also more common with less patients presenting with advanced disease.[2,4] Although HL has different manifestations, its treatment has achieved high-cure rates in both developed and developing countries.[5,6] Treatment modalities using only nodal radiotherapy (RT), combined chemo-RT, and chemotherapy alone have all been tried.[7,8] Chemotherapy-alone protocols are considered more suitable for younger children as they avoid long-term sequelae of RT, especially premature epiphyseal fusion and secondary malignancies. However, the optimal strategy to treat HL still remains a question of research. There is a need to risk stratify the treatment to minimize late effects while maintaining high-cure rates.

Ours is a pediatric oncology center in North India using chemotherapy only protocol for the last one decade. Lack of published data on HL from our region prompted us to carry out this study. We have analyzed the sociodemographic profile, disease characteristics, event-free survival (EFS), overall survival (OS), and risk factors for relapse in patients treated with only chemotherapy as per unit protocol.

Subjects and Methods

This was a retrospective, observational study carried out in the Division of

How to cite this article: Gupta V, Singh TB, Gupta SK. Response and relapses in pediatric Hodgkin's lymphoma treated with chemotherapy alone. Indian J Med Paediatr Oncol 2019;40:341-6.

Submitted: 13-Jan-2018
Revised: 29-Mar-2018
Accepted: 27-Apr-2018
Published: 04-Dec-2019

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Access this article online

Website: www.ijmpo.org

DOI: 10.4103/ijmpo.ijmpo_13_18

Quick Response Code:

Hematology Oncology of Department of Pediatrics in a university teaching hospital. Children below the age of 15 years diagnosed with HL between January 2005 and December 2014 were included in the study. Data were retrieved from clinic files maintained for each patient. Patients presenting with relapse or with inadequate treatment at another hospital were not included in the study.

Demographic characteristics including age, sex, place of residence, duration of illness, clinical symptoms, and examination findings were noted for each child. Clinical findings included size and group of lymph nodes involved, enlargement of liver and spleen, presence of anemia, and nutritional status. Laboratory investigations included complete blood count, liver and renal function tests, and tests for HIV infection. Lymph node biopsy was done in all patients, and everyone had histologically proven HL. Histological categorization was done according to Rye classification. Immunohistochemistry (IHC) was carried out using four CD markers such as CD 3, CD 20, CD 15, and CD 30. For staging, computed tomography of the neck, chest, and abdomen and bone marrow biopsy were carried out. None of the patients had a staging laparotomy or splenectomy.

Patients were treated with multiagent chemotherapy as per the unit protocol. From year 2005 to 2010, patients received either cyclophosphamide, vincristine, procarbazine, and prednisolone (COPP) or alternating cycles of COPP and adriamycin, bleomycin, vinblastine, and dacarbazine (ABVD) protocol. From 2011 onward, patients received only ABVD protocol. Patients received 6–8 cycles of chemotherapy according to disease stage. Stages IA, IB, and IIA were taken as early-stage disease, and Stages IIB, III, and IV were taken as advanced-stage disease. Patients with early-stage disease received 4–6 cycles, whereas those with advanced-stage disease received 6–8 cycles of chemotherapy. Remission was defined as complete regression of clinical and radiological lesions. Patients with partial/no remission after 8 cycles were given high-dose chemotherapy with bleomycin, etoposide, doxorubicin, COPP (BEACOPP). RT was not part of the protocol routinely. However, two patients received RT as they had bony involvement. None of the patients underwent stem cell transplantation during the study period. Children were followed up regularly after completion of chemotherapy. They were followed up every 3 months for 2 years and then every 6 months for next 3 years. After 5 years, they were followed up once a year.

Statistical analysis

Data have been presented as mean ± standard deviation, median, and range or frequencies and percentages when appropriate. Survival analysis was done for different outcomes using Kaplan–Meier statistics calculating the mean and median survival time for each group with 95% confidence interval (CI) and their survival graphs. $P < 0.05$ was considered statistically significant. All statistical calculations were done using computer program Statistical Package for the Social Science (SPSS; SPSS Inc., Chicago, IL, USA) version 15 for Microsoft Windows.

Results

Patient characteristics

A total of 90 patients were diagnosed with HL during the study period. Clinical and hematological characteristics of the disease have been presented in Table 1. One-third of patients (30%) belonged to urban area, whereas remaining patients (70%) were from rural area. The male-to-female ratio was 7.2:1. The mean age of the patients was 8.13 ± 2.65 years (median age 8 years, range 4.5–15 years).

Table 1: Clinicohematological characteristics of patient population

Parameter	*n* (%)
Age (years)	
<5	6 (6.7)
5-10	68 (75.6)
>10	16 (17.8)
Gender	
Male	79 (87.8)
Female	11 (12.2)
Area of residence	
Rural	63 (70.0)
Urban	27 (30.0)
Clinical stage	
I	4 (4.4)
II	17 (18.9)
III	63 (70.0)
IV	6 (6.7)
B symptoms	79 (87.8)
Early stage	11 (12.2)
Advanced stage	79 (87.8)
Bulky disease	14 (15.6)
Hb (g/dl)	
≤7.0	28 (31.1)
>7.0	62 (68.9)
LDH level (U/l)	
<1000	54 (60)
≥1000	36 (40)
Histopathology	
Mixed cellularity	40 (44.4)
Nodular sclerosis	24 (26.7)
Lymphocyte predominant	6 (6.7)
Lymphocyte depletion	4 (4.4)
Not specified	16 (17.8)
Chemotherapy protocol	
COPP	24 (26.7)
COPP/ABVD	30 (33.3)
ABVD	36 (40.0)

LDH – Lactate dehydrogenase; Hb – Hemoglobin;
COPP – Cyclophosphamide, vincristine, procarbazine, prednisone;
ABVD – Adriamycin, bleomycin, vinblastine, dacarbazine

Seventeen patients (18.9%) were below the age of 5 years. Majority of the patients (63.3%) were between 6 and 10 years of age. Only 11 (12.2%) patients had early stage disease, while the remaining 79 (87.8%) had advanced stage disease. B symptoms were present in 87.8% patients whereas fever was the most common presenting symptom followed by weight loss. Night sweats were present in only two patients. One patient had intense pruritus which proved to be very difficult to control. This patient also had progressive disease. The mean duration of symptoms was 9.66 ± 6.30 months (median 8 months; range 2–36 months). Approximately one-third of the patients (31.1%) had hemoglobin level ≤7 g/dl. Low counts (<5000/cumm) were present in eight patients. Lactate dehydrogenase (LDH) level was high (≥1000 U/l) in 36 patients (40%), and majority of the patients had a raised erythrocyte sedimentation rate. Cervical lymphadenopathy was the most common site of involvement followed by mediastinal, axillary, and inguinal lymph nodes. Fourteen patients had bulky disease. Splenic enlargement (>2 cm) was seen in three-fourth (75.6%) of patients, whereas splenic infiltrates were present in 16 (17.8%). Two patients presented with features of superior mediastinal syndrome. Two patients had bony involvement in the form of vertebral infiltrates. Both presented with paraparesis and one had bladder and bowel involvement also. Two patients each had lymphomatous deposits in the liver and kidney, whereas one had deposits in the lungs. Four patients had ascites at the time of presentation and two had pleural effusion. One patient presented with unilateral proptosis and was found to have lymphomatous deposit in the superior rectus muscle of the right eye.

Histologic subtype

Mixed cellularity was the most common subtype (44.4%), followed by nodular sclerosis (26.7%), lymphocyte-predominant (6.7%), and lymphocyte-depleted subtype (4.4%). In 16 patients (17.8%), the subtype was not specified.

Therapy

Patients received COPP (24), alternating cycles of COPP and ABVD (30), or ABVD (36) protocols. Number of chemotherapy cycles was decided according to stage of disease and response to chemotherapy. Median number of cycles received was 6.0 (range 4–8). Two patients with bony involvement received RT in addition to chemotherapy and made complete recovery. One patient with progressive disease received BEACOPP protocol. He did not achieve remission and succumbed to progressive disease. One patient expired due to unrelated illness during the study period. Five patients did not complete chemotherapy and defaulted during treatment.

Table 2: Risk factors for relapse in patients with Hodgkin's lymphoma

Variables	Relapse (*n*=11)	No relapse (*n*=72)	RR	95% CI	*P*
Gender					
Male	10	63	1.37	0.29-8.18	NS
Female	1	9			
Age (years)					
≥10	5	9	4.11	1.46-10.77	0.017*
<10	6	63			
Stage					
Advanced	10	63	1.37	0.29-8.18	NS
Early	1	9			
Bulky disease					
Present	6	8	5.91	2.14-15.60	0.002*
Absent	5	64			
B symptoms					
Present	10	62	1.53	0.31-9.13	NS
Absent	1	10			
Hb (g/dl)					
≤7	5	12	3.24	1.3-8.83	0.04*
>7	6	60			
TLC (/mm^3)					
>12,000	7	10	6.79	2.37-19.66	0.001*
≤12,000	4	62			
Protocol used					
COPP	6	16	2.46	0.75-8.45	0.047*
COPP/ABVD	3	24	4.64	1.18-19.44	
ABVD	2	32	1.30	0.31-5.38	

*Statistically significant. Hb – Hemoglobin; CI – Confidence interval; COPP – Cyclophosphamide, vincristine, procarbazine, prednisone; ABVD – Adriamycin, bleomycin, vinblastine, dacarbazine; RR – Relative risk, TLC – Total leukocyte count; NS – Not significant

Relapses

Eleven patients had relapse during the study period. All patients with relapse except the patient with intracranial relapse had repeat biopsy with IHC to confirm the diagnosis. Nine patients had Stage III disease, whereas one each had Stage I and Stage II disease. All the patients except one had B symptoms. Majority of the patients[9] had relapse after 2 years of completing chemotherapy. Two patients had relapse within 1 year of therapy. The mean duration of relapse was 33.3 ± 21.8 months (range 6–84 months; median 30 months). Nine patients had lymph node relapse, whereas two patients had unusual sites of relapse. One patient had intracranial relapse, 6 months after completing frontline chemotherapy. He was treated with alternative protocol and achieved complete remission. The second patient had spinal cord relapse. Of the 11 relapses, six could be salvaged with alternative chemotherapy protocol, whereas five succumbed to progressive disease.

We also looked at the risk factors for relapse which included age, gender, stage of the disease, presence or absence of bulky disease and B symptoms, hemoglobin level, total leukocyte count, and protocol used. Of the various factors, older age at presentation (≥10 years), presence of bulky disease, low hemoglobin (≤7 g/dl), and high leukocyte count (≥12000/mm^3) were found to be associated with high risk of relapse [Table 2].

Survival

There were total seven deaths during the study period; five due to relapsed disease, one due to progressive disease, and one due to unrelated cause. The 5-year OS was 88.8% [Figure 1]. The OS in early-stage and advanced-stage disease was 90.0% and 89.0%, respectively [Figure 2]. OS in patients with bulky disease was 53.3% and without bulky disease was 92.2% [Figure 3]. The EFS for all patients was 84.5%. The EFS in early-stage disease and advanced-stage disease was 90.0% and 83.8%, respectively. We looked at the EFS in relation to bulky disease; it was 59.3% for patients with bulky disease and 86.5% for those without bulky disease.

Discussion

The Division of Hematology Oncology started as a unit in the Department of Pediatrics in the middle of 2004 as there was no dedicated pediatric cancer unit in this region. This region of Northern India is densely populated and generally more resource constrained as compared to other parts of the country with low-income and education level. After the initial hiccups, organized care and data keeping could be started from January 2005. In the initial years, little financial and medical support was available for the patients, and almost all or a large part of the treatment was self-financed. This resulted in different chemotherapy protocols for patients as the cost of drugs for ABVD was much higher than that of COPP. Use of COPP as the

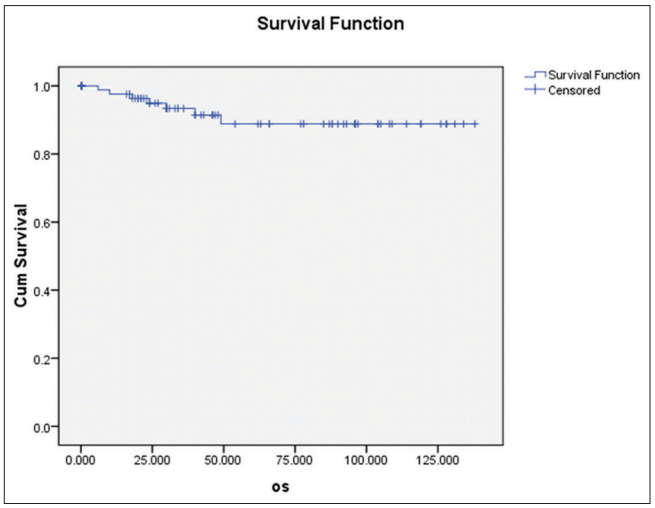

Figure 1: Overall survival of all patients with Hodgkin's lymphoma

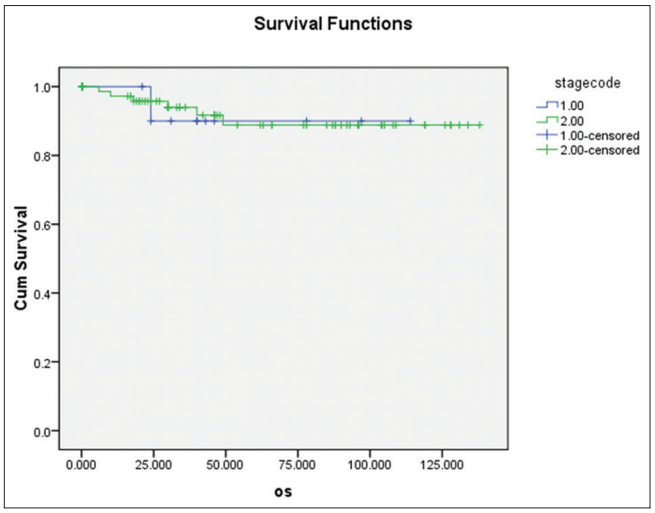

Figure 2: Overall survival of patients according to stage of disease. Blue line represents early disease; green line represents advanced disease

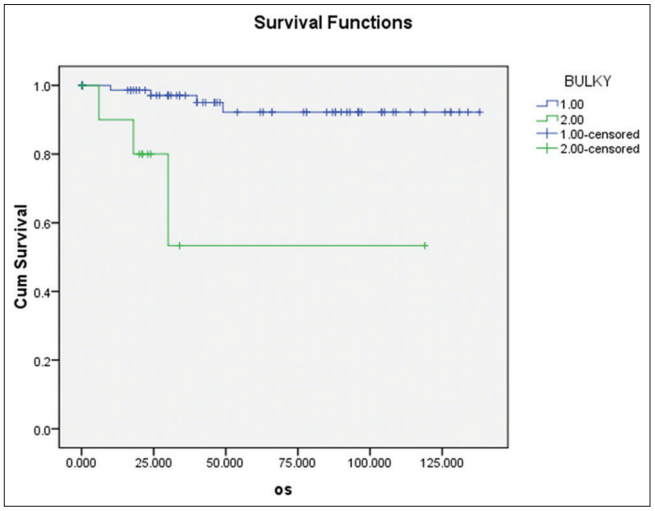

Figure 3: Overall survival of patients in relation to the presence or absence of bulky disease. Green line represents bulky disease; blue line represents nonbulky disease

first-line chemotherapeutic protocol was not an appropriate choice but was chosen because of resource constraints in initial years. Later on, resources improved with very good support from government and nongovernment sources, and all patients could receive ABVD protocol. Another problem was availability of RT services. Due to heavy load of adult patients, pediatric patients did not get priority for RT dates which resulted in delay. Shortage of RT services in government hospitals has been highlighted in another study from India.[9] Due to these constraints, we decided on chemotherapy alone protocols for our patients. A published report on HL in Indian children, which appeared after a couple of years, also showed that chemotherapy protocols resulted in good survival outcome which further gave credence to our efforts.[10] After a decade of starting treating children with lymphoma, we have analyzed our data to see how they compare with published literature from our country and other countries.

The mean age of our patients was 8 years which was younger than reported age from developed countries.[11] However, it was similar to that reported in other Indian studies.[6,9,12] 18.9% of the patient population was below the age of 5 years. Another study from India reported 37% patients younger than 5 years which was lower than our study.[9] A study from Egypt reported median age of 6 years with 22% patients below the age of 5 years which was very similar to our study. However, the male-to-female ratio in this study was 1.7:1, which was very different from ours.[13] There was a male preponderance in our patients (M:F: 7.2:1) which was similar to other Indian studies where the ratio has ranged from 6:1 to 10.5:1.[5,6,9,12] The proposed explanation has been that females have less access to health care and treatment at tertiary centers is denied to them by family. We believe that this may not be entirely true and there is a genuine male preponderance in India as reported in several other Indian studies also. The gender bias for treatment has narrowed to a large extent in recent years with more awareness among general population. Mean duration of symptoms was 9 months, which was similar to other studies where mean duration was 8 and 12 months, respectively.[9,12] However, in many patients (9.7%), the diagnosis was delayed for more than 2 years. Many of these patients had received antitubercular treatment before a definite diagnosis of lymphoma was made. This is not an uncommon situation as the prevalence of tuberculosis is high in India. Fourteen patients had bulky disease. The prevalence of B symptoms and advanced disease was very high (87.8%) in our patient population which is close to two other studies which reported advanced disease in 81.7% and 83% patients, respectively.[9,12] However, two other studies reported advanced disease in 52% and 63.5% patients which is lower than our study.[6,11] The difference could be because of the area from which patients come. As ours is a relatively financially constrained patient population, there is a tendency to seek treatment at a tertiary center at a late stage. Splenic infiltrates were seen in 17.8% patients which were similar to another study reporting splenic infiltrates in 14.4% cases.[14] None of the patients in our cohort had bone marrow involvement which was reported in 2.7% patients in a large series.[11] Interestingly, two patients had bony involvement at the time of presentation which was a very rare manifestation and has been reported by us earlier.[15] Both patients made complete recovery and are enjoying EFS for more than 7 years. Another study reported osseous involvement in 4.5% patients.[16] However, two of these had osseous lesions at the time of relapse. One more patient had rare presentation with ptosis of the right eye. This patient also achieved complete remission with only chemotherapy.[17] In this study, mixed cellularity was the most common histologic subtype.[6,9,11]

In spite of the advanced disease in majority of the cases, we achieved high 5-year OS and EFS with chemotherapy alone. Other Indian studies have also reported OS ranging from 79% to 92.7% and EFS ranging from 53% to 87.9%. When we looked at the risk factors for relapse, older age at presentation (≥10 years), bulky disease, low hemoglobin (≤7.0 g/dl), and high leukocyte count (≥12000/cumm) at presentation, and protocol used (COPP) were important risk factors for relapse. In one Indian study, the OS of patients with or without bulky disease was similar, although patients with bulky disease had not received RT,[12] whereas another study reported bulky disease as a risk factor.[18] Yet, another study reported anemia, B symptoms, advanced disease, and splenic involvement as adverse prognostic factors.[11] Two other studies found infradiaphragmatic disease, involvement of more than four lymph node regions, and serum LDH level ≥500 IU/l to be additional risk factors.[5,19] Older age (>10 years), low hemoglobin, and high total leukocyte count were reported as independent predictors of poor survival by Smith *et al.* and Weiner *et al*.[20,21] Most of the studies have reported B symptoms and advanced disease as risk factors for relapse which we did not find in our study. The reason could be that overwhelming majority of our patients had B symptoms and advanced disease (87.8%), and therefore, it was not a risk factor for relapse.

Conclusions

Our patient population had younger age, advanced disease, more B symptoms, and bulky disease. Still, we could achieve high OS and EFS with chemotherapy-alone protocols. Bulky disease was found to be a major risk factor for relapse. If RT is included in the protocol for bulky disease, the survival rates are likely to improve further.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

References

1. Chang ET, Zheng T, Weir EG, Borowitz M, Mann RB, Spiegelman D, *et al.* Childhood social environment and Hodgkin's lymphoma: New findings from a population-based case-control study. Cancer Epidemiol Biomarkers Prev 2004;13:1361-70.
2. Dinand V, Arya LS. Epidemiology of childhood Hodgkins disease: Is it different in developing countries? Indian Pediatr 2006;43:141-7.
3. Thomas RK, Re D, Zander T, Wolf J, Diehl V. Epidemiology and etiology of Hodgkin's lymphoma. Ann Oncol 2002;13 Suppl 4:147-52.
4. Barros MH, Hassan R, Niedobitek G. Disease patterns in pediatric classical Hodgkin lymphoma: A report from a developing area in Brazil. Hematol Oncol 2011;29:190-5.
5. Jain S, Kapoor G, Bajpai R. ABVD-based therapy for Hodgkin lymphoma in children and adolescents: Lessons learnt in a tertiary care oncology center in a developing country. Pediatr Blood Cancer 2016;63:1024-30.
6. Trehan A, Singla S, Marwaha RK, Bansal D, Srinivasan R. Hodgkin lymphoma in children: Experience in a tertiary care centre in India. J Pediatr Hematol Oncol 2013;35:174-9.
7. Nachman JB, Sposto R, Herzog P, Gilchrist GS, Wolden SL, Thomson J, *et al.* Randomized comparison of low-dose involved-field radiotherapy and no radiotherapy for children with Hodgkin's disease who achieve a complete response to chemotherapy. J Clin Oncol 2002;20:3765-71.
8. Castellanos EM, Barrantes JC, Báez LF, Gamboa Y, Peña A, Alabi S, *et al.* A chemotherapy only therapeutic approach to pediatric Hodgkin lymphoma: AHOPCA LH 1999. Pediatr Blood Cancer 2014;61:997-1002.
9. Chandra J, Naithani R, Singh V, Saxena YK, Sharma M, Pemde H, *et al.* Developing anticancer chemotherapy services in a developing country: Hodgkin lymphoma experience. Pediatr Blood Cancer 2008;51:485-8.
10. Metzger M, Krosin MJ, Hudson MM, Pizzo PA, Poplack DG. Hodgkin Lymphoma. Priciples and Practice of Pediatric Oncology. 16th ed. Philadelphia: Wolters Kluwer/Lippincott, Williams and Wilkins; 2011. p. 639-62.
11. Arya LS, Dinand V, Thavaraj V, Bakhshi S, Dawar R, Rath GK, *et al.* Hodgkin's disease in Indian children: Outcome with chemotherapy alone. Pediatr Blood Cancer 2006;46:26-34.
12. Verma N, Kumar A. Treating Hodgkin's lymphoma in a resource poor setting: Challenges and outcome. Cancer Oncol Res 2015;3:11-6.
13. Sherief LM, Elsafy UR, Abdelkhalek ER, Kamal NM, Elbehedy R, Hassan TH, *et al.* Hodgkin lymphoma in childhood: Clinicopathological features and therapy outcome at 2 centers from a developing country. Medicine (Baltimore) 2015;94:e670.
14. Arya LS, Dinand V, Bakhshi S, Thavaraj V, Singh R, Dawar R, *et al.* Significance of splenomegaly in childhood Hodgkin disease. J Pediatr Hematol Oncol 2004;26:807-12.
15. Gupta V, Srivastava A, Bhatia B. Hodgkin disease with spinal cord compression. J Pediatr Hematol Oncol 2009;31:771-3.
16. Singh P, Bakhshi S. Osseous involvement in pediatric Hodgkin's lymphoma. Indian J Pediatr 2010;77:565-6.
17. Gupta V, Kumar M, Gupta SK. Ptosis: A rare presentation of Hodgkin lymphoma. J Pediatr Hematol Oncol 2014;36:163-5.
18. Seth R, Das RR, Puri K, Singh P. Clinical profile and chemotherapy response in children with Hodgkin lymphoma at a tertiary care centre. J Clin Diagn Res 2015;9:SC25-30.
19. Ganesan P, Kumar L, Raina V, Sharma A, Bakhshi S, Sreenivas V, *et al.* Hodgkin's lymphoma – Long-term outcome: An experience from a tertiary care cancer center in North India. Ann Hematol 2011;90:1153-60.
20. Smith RS, Chen Q, Hudson MM, Link MP, Kun L, Weinstein H, *et al.* Prognostic factors for children with Hodgkin's disease treated with combined-modality therapy. J Clin Oncol 2003;21:2026-33.
21. Weiner MA, Leventhal B, Brecher ML, Marcus RB, Cantor A, Gieser PW, *et al.* Randomized study of intensive MOPP-ABVD with or without low-dose total-nodal radiation therapy in the treatment of stages IIB, IIIA2, IIIB, and IV Hodgkin's disease in pediatric patients: A Pediatric oncology group study. J Clin Oncol 1997;15:2769-79.