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Short Communication

Primary bone lymphoma: a clinicopathological retrospective study of 28 patients in a single institution

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Abstract

BACKGROUND: Primary bone lymphoma (PBL) is a rare disease and distinct clinicopathological entity. The optimal treatment strategy is still unclear. Because of rarity of PBL, we report our institute experience in PBL clinicopathological feature and treatment results.

METHODS: 28 patients diagnosed with PBL were referred to Omid Hospital, cancer research center (CRC), between March 2001 and February 2009. Immunophenotype studies on 16 out of 28 pathological blocks were performed. We analyzed disease free survival (DFS) and overall survival (OS) rates.

RESULTS: 14 patients with PBL were analyzed retrospectively. 17 patients (60.7%) were male and 11 (39.3%) were female with a median age of 41 years (range: 11-79). Long bones were the most primarily site of involvement (71%). 26 (93%) patients had diffuse large B cell lymphoma and 2 (7%) had small lymphoblastic lymphoma. One (3%) patient received radiation alone, 18 (66%) cases received combined modality (chemotherapy + radiotherapy) and 8 (30%) received only chemotherapy during their treatment period. The median follow up was 18 months (range: 1-82). Mean DFS was 51 months (range: 37-66). Overall survival (OS) was 54 months (range: 40-68). OS was significantly better in the chemoradiotherapy group compared with other two groups (64 versus 27 months, respectively, p=0.014). DFS was also significantly better in combined modality arm compared with other two groups (64 versus 21 months, respectively, p=0.003).

CONCLUSIONS: In spite of small number of patients reported in this study, combined modality treatment (chemotherapy and radiotherapy) was shown to be useful as an effective treatment strategy in PBL.

KEYWORDS: Primary Bone Lymphoma, Diffuse Large B Cell Lymphoma, Chemotherapy, Radiotherapy.

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Primary bone lymphoma (PBL) is a rare disease, accounting for approximately 3% of all primary bone malignancies.[1,2] PBL constitutes <5% of extra nodal lymphoma [1,2,3] and less than 1-2% of all malignant lymphomas in adults.[4-6] PBL has been reported in association with some specific conditions including human immunodeficiency virus (HIV), sarcoidosis, Gaucher disease, hereditary exostosis, Paget's disease, and osteomyelitis.[7] Patients with PBL trend to be younger, with median age of 45-60 years old.[3,7]

The long bones are primarily affected and femur is the most commonly involved location as a single site.[3-5] The common sign and symptoms are local bone pain (80-95%), with or without soft tissue swelling (30-40%) and pathological fracture (15-20%).[3,8] Spinal cord compression is reported in 14% of patients with vertebral involvement but presence of B

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symptom is relatively uncommon (5-15%).[8] B symptoms are defined as fever ≥38°C, night sweating or weight loss greater than 10% of body weight during 6 months. Diffuse large B cell lymphoma (DLBCL) is the most common histopathological diagnosis of PBL (70-90%). [3-5] Because of rarity of PBL, we report our institute experience in PBL clinicopathological features and treatment results.

Methods

Patients

We retrospectively analyzed all patients (28 ones) who were diagnosed with PBL and referred to our center, (Omid hospital), between March 2001 and February 2009. All pathological paraffin blocks were reviewed by an experienced pathologist in our center and the PBL diagnosis was confirmed.

Immunophenotype studies on 16 out of 28 pathological blocks were performed. We also classified patients based on age, sex, performance status (according to the Eastern Cooperative Oncology Group), international prognostic index (IPI) score, presence of B symptoms, clinical stage, serum lactate dehydrogenase (LDH) level, primary site and treatment protocol.

Clinical staging and IPI score

Clinical staging was determined according to the revised American Joint Committee on Cancer (AJCC) for lymphoid neoplasm.[9] The patients had the following laboratory work ups: complete blood count (CBC), serum lactate dehydrogenase (LDH) level, alkaline phosphatase (ALP) , liver function tests, renal function tests, and X-ray or computed tomography (CT) of the bone lesion, chest X-ray (CXR), abdominopelvic ultrasonography (US) or CT, and bone marrow biopsies (BMB) in 9 patients.

All patients were evaluated for presence of B symptoms (fever≥38°C, night sweating, and weight loss≥10 kg in 6 months).

Statistical analysis

Overall survival (OS) was calculated from the date of pathological diagnosis to the date of the last follow up or death from any cause. Disease free survival (DFS) was calculated from the date of diagnosis to the date of the first relapse. Survival curves were constructed according to the method of Kaplan-Meier [10] and compared using the log rank test. Differences were considered significant if the P value was ≤ 0.05 (two tailed). All survival analyses were performed using the SPSS (IBM company, United States), version 14.

Results

Patients' characteristics

28 patients were diagnosed between March 2001 and February 2009. Demographic and clinical characteristics of all cases are summarized in Tables 1 and 2.

Table 1. Patients' demographic characteristics

Parameter	Number %
Patients	28
Median age (year)	41
< 60 year	23 (82)
> 60 year	5 (18)
Sex	
Male	17 (60)
Female	11 (40)
Male: female ratio	1.5:1

Table 2. Patients' clinical characteristics

Parameter	Number %
Stage	
I	17 (60)
II	4 (15)
IV	7 (25)
B Symptoms	15 (54)
LDH	
Normal	6 (30)
Elevated	14 (70)
IPI Score	
Low	6 (30)
Low intermediate	7 (35)
High	7 (35)
Treatment	
Chemotherapy	8 (30)
Chemotherapy + radiotherapy	18 (66)

LDH, lactate dehydrogenase; IPI, international prognostic index;
B symptoms (fever≥38°C, night sweating, weight loss≥10 kg in six months)

Long bones were the most primarily site of involvement (71%) including humerus 7 (25%), femur 7 (25%), and tibia 4 (14.3%). The pelvis was the second most common site of involvement in 7 (25%) cases. Mandible was involved in 1 (3.5%), radius in 1 (3.5%) and clavicle in 1 (3.5%) patient. The primary involved sites of the bone are shown in Figure1.

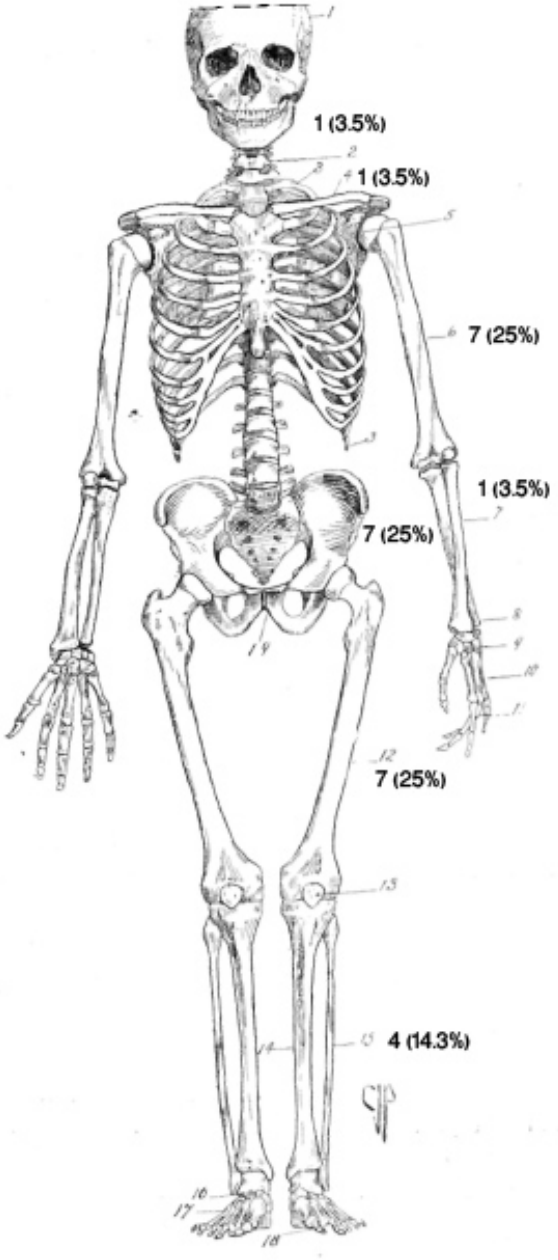

Figure 1. The primary involved sites of PBL.

26 (93%) patients had DLBCL and 2 (7%) patients had small lymphoblastic lymphoma. In 15 (53.6%), patients B symptoms were reported. Serum LDH level was recorded in 20 patients; in 6 (30%) patients was ≤500 and in 14 (70%) >500. According to Eastern cooperative oncology group (ECOG) performance status scoring, 5 patients (17.9%) had PS of -1, 9 (32.1%) had PS of -2, 12 (42.9%) had PS of -3 and 2 (7.1%) ones had PS of -4.

Clinical staging

Clinical stages of the patients are shown in Table 1. We didn't have any patient with stage 3 (based on AJCC staging system). A stage 4 was defined as multiple bone sites lesions (2 cases), diffuses involvement of single bone (3 cases) or BM involvement (1 case).

Because it was impossible to distinguish PBL from bone involvement due to nodal lymphoma, we excluded all patients with bone lymphoma and non-regional lymph node involvement.

Treatment modalities

Chemotherapy with cyclophosphamide (CTX), vincristin (VCR), doxorubicin (ADR) and prednisolone (CHOP regimen) used for 26 patients with standard doses.[3] The mean chemotherapy cycles were 5 (range: 1-8). One patient did not receive any adjuvant treatment and one patient received radiotherapy only with a total dose of 5000 cgy, on cobalt 60 conventional protocol. 18 (66%) cases received combined modality (chemotherapy + radiotherapy). Mean radiation dose was 4700 cgy (range: 4000-5500). 8 (30%) received only chemotherapy during their treatment period.

Survival and statistical analysis

The median follow up was 18 months (range: 1-82). We excluded two patients from survival analysis because one did not take any treatment and another did not finish his treatment program. At the end of follow up, 16 (61.5%) patients were still alive without any recurrence. DFS didn't reach the median because of small number of events (death or recurrence) but the mean DFS was 51 months (range: 37-66). Overall survival was 54 months (range: 40-68, Figure 2).

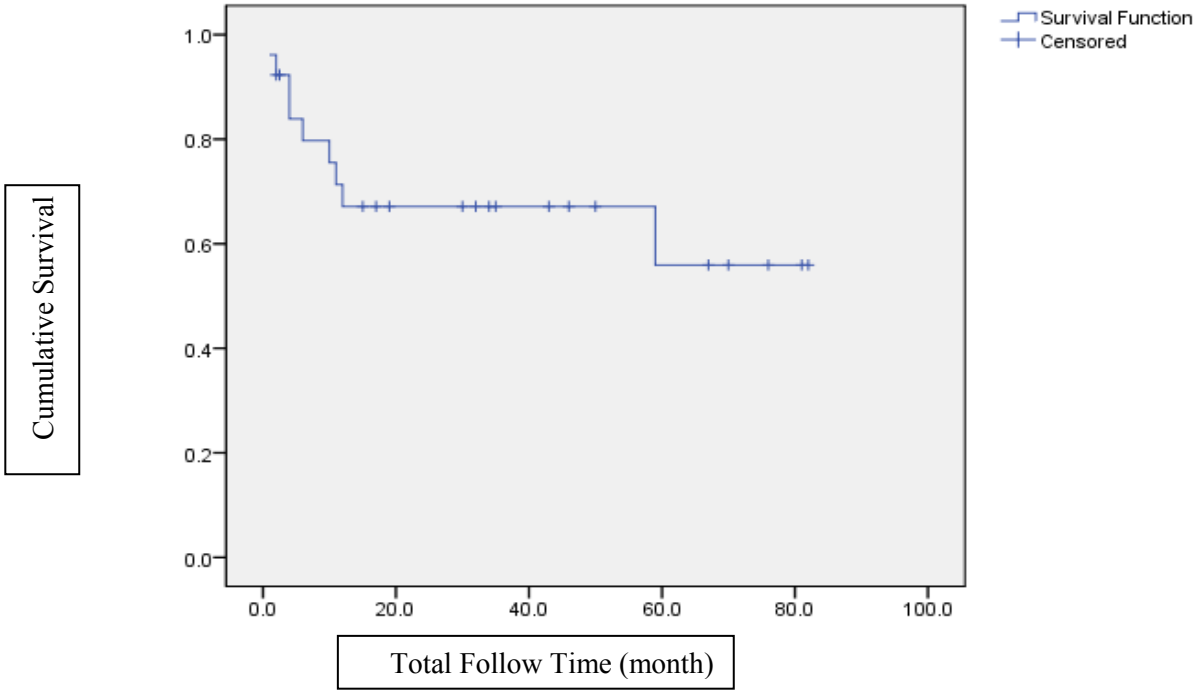

Figure 2. Overall survival curve

4 (15%) cases recurred. The mean time to progression was 16 months. 2 cases recurred with non regional lymphadenopathies, 1 patient had brain recurrence and in 1 case recurrence was in humerus. 9 patients (29%) died because of disease progression in 5 cases, recurrence in 3 cases and treatment complication in one. We also compared chemotherapy alone with chemoradiotherapy based on DFS and OS (Figures 3 and 4).

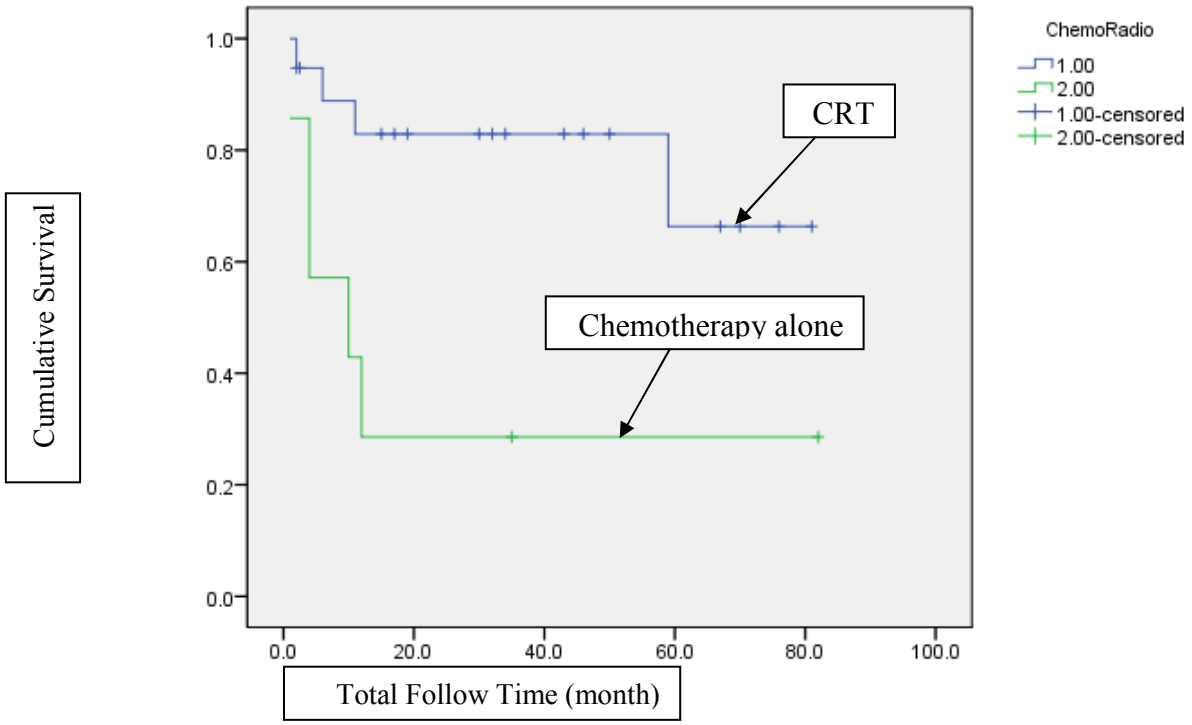

Figure 3. DFS curves comparing chemoradiotherapy (CRT) (1) versus chemotherapy alone (2)

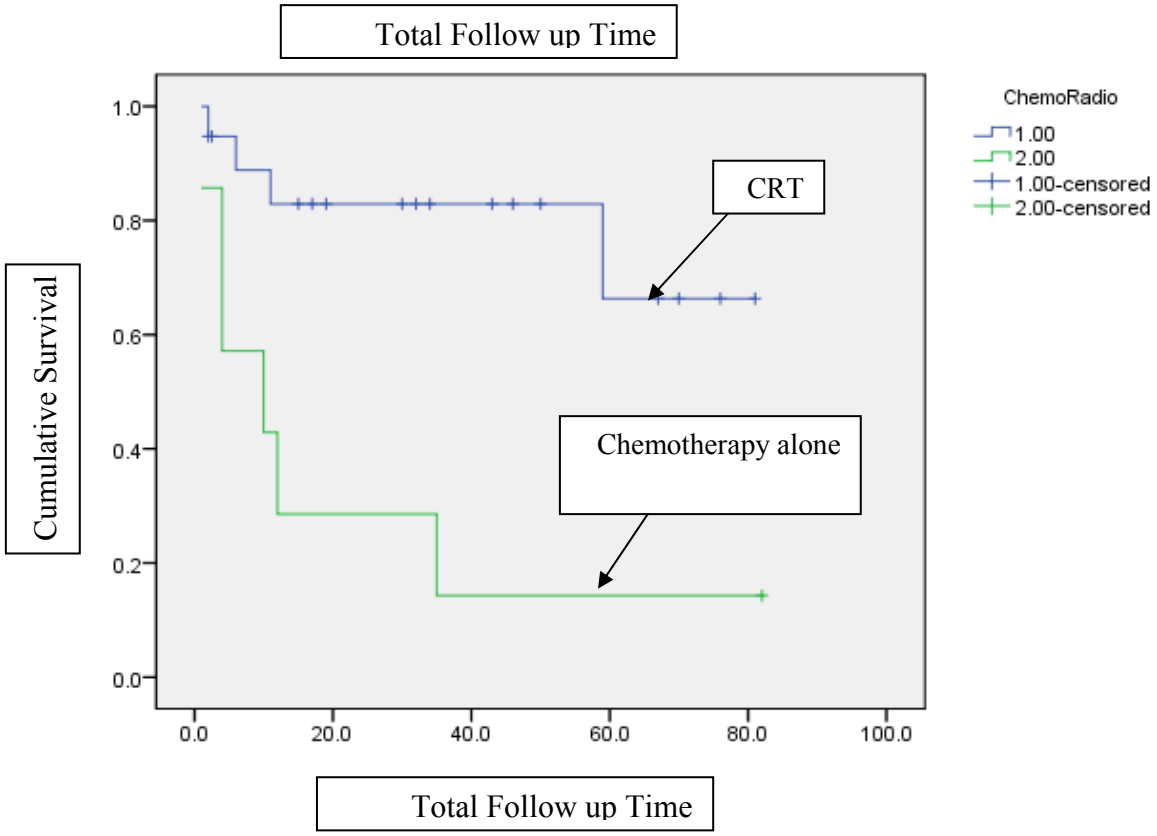

Figure 4. OS curves comparing chemoradiotherapy (CRT) (1) versus chemotherapy alone (2)

19 (73%) patients received chemoradiotherapy and 7(27%) patients received chemotherapy alone. OS was significantly better in the chemoradiotherapy group compared with other two groups (64 vs. 27 months, respectively, p=0.014). DFS was also significantly better in combined modality arm compared with other two groups (64 versus 21 months, respectively, p=0.003).

Discussion

PBL is a rare presentation of non Hodgkin's lymphoma. It was first described as a distinct clinicopathological entity in 1939 by Parker and Jackson.[11] The real prevalence of PBL is unclear because of the considerable difficulty distinguishing primary from secondary bone lymphoma. In our study PBL did constitute 5.3% of all DLBCLs like many previous study results.[3,12] Long bone was the primarily affected site in our case series, the same as Western country reports in which femur was the most affected site.[3,6,7,13] But in Ramadan et al. results, spine involvement had the same prevalence as the long bones (33%).[4] In Dai Maruyama et al. report, the pelvis was the common involved site (54%).[5] Horsman et al. reported that the most commonly presented site was the pelvis, although they described that the femur was the most frequently involved bone.[13] Most of our patients were younger than 60 years which was similar to other reports.[3]

According to the WHO classification, lymphoma involving the bone can be classified in four groups: group 1, lymphoma in a single bone site with or without regional lymph node involvement; group 2, lymphoma in multiple bones, but no visceral or lymph node involvement; group 3, bone tumor with involvement of other visceral sites or lymph nodes at multiple sites; and group 4, lymphoma involving any other site and found by bone biopsy which was done to rule out possible involvement. We defined PBL in our study according to WHO classification groups 1 and 2. WHO classification and some previous reports have indicated

that groups 1 and 2 should be considered as PBL, but Group 3 should be excluded from PBL and be considered as systemic lymphoma regardless of the bone lesion. Histopathologically, the previous studies reported that the majority of patients with PBL had DLBCL.[3,6,15] In our study, 26 (93%) patients had DLBCL and 2 (7%) patients had small lymphoblastic lymphoma. Several studies have suggested that the combined modality (chemotherapy and radiotherapy) was the best treatment for patients with PBL.[3,6] Beal et al. concluded that PBL patients treated with combination chemotherapy and irradiation had significantly better survival than the patients treated with single modality (chemotherapy or radiotherapy alone), but the 5-year OS rate between the two groups was not significantly different.[16] In our study, OS and DFS was significantly better in combined modality group (OS was 64 vs. 27 months, respectively, p=0.014, and DFS was 64 vs. 21 months, p=0.003). Ramadan et al. reported patients with advanced-stage disease who received chemotherapy plus irradiation with a poor outcome when compared with those who received chemotherapy alone (10-years OS were 25% and 56%, respectively).[4] However, this difference must be very cautiously interpreted because the decision to use radiotherapy was individualized. Because of small number of patients in our study, further studies are necessary to clarify the characteristics of PBL and its optimal treatment strategy. We will continue our study on PBL and report our results with more patients and longer follow ups.

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Conflict of Interests
Authors have no conflict of interests.

Authors' Contributions
All the authors have carried out the study, participated in the design of the study and acquisition of data performed the statistical analysis and wrote the manuscript. All authors read and approved the final manuscript.

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