Non-Hodgkin's lymphoma with bone involvement: a single center experience with 18 patients

Kemik tutulumlu Hodgkin dışı lenfoma: Onsekiz hasta ile tek merkez deneyimi

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Abstract

Objective: Non-Hodgkin's lymphoma (NHL) of bone is a rare entity. The most common histological subtype is diffuse large B cell lymphoma (DLBCL). The major presenting symptoms are soft tissue swelling, bone pain and pathological fracture. Treatment options are chemotherapy, radiotherapy, surgery, or a combination of these modalities.
Materials and Methods: We retrospectively analyzed the 18 patients (11 females, 7 males) with NHL of bone who were diagnosed and treated between 1995-2005. The median age was 56.5 years. The median duration of symptoms was 4.5 months. The bone pain was the first symptom in all patients. Tru-cut biopsy was performed for diagnosis in most of the cases. Diagnosis in five patients (27.8%) required open biopsy.
Results: DLBCL (77.8%) was the most common histological type among all patients. Other histological subtypes were anaplastic large cell lymphoma (11.1%), Burkitt-like lymphoma (5.6%) and marginal zone lymphoma (5.6%). According to Ann Arbor staging system, 44.4% of patients were Stage I, 11.1% were Stage II and 44.4% were Stage IV. Bone marrow involvement was determined in four patients (22.2%). All patients except one were treated with anthracycline-containing regimens and eight patients (44.4%) received rituximab combination with chemotherapy. Radiation therapy was performed as the first-line therapy in 9 (50%) patients. The median follow-up was 37 months (range, 2-124 months). Among the 17 patients who achieved complete remission, five (27.8%) relapsed. All patients were still alive. The five-year relapse-free survival was 73.5%.
Conclusion: The treatment of bone lymphoma can be planned according to the stage and location of the disease. Although we had a relatively low number of patients, it could be concluded that whether or not radiation therapy is performed, rituximab in combination with systemic chemotherapy has been proven beneficial on survival.
(Turk J Hematol 2010; 27: 29-33)
Key words: Non-Hodgkin's lymphoma, bone, lymphoma

Received: November 13,2006 *Accepted: October 10, 2009*

Özet

Amaç: Kemik lenfomaları oldukça nadirdir ve en sık görülen histolojik alt tip diffüz büyük B-hücreli (DBBHL) non-Hodgkin lenfomadır (NHL). Hastalar çoğunlukla kemik ya da yumuşak dokuda şişlik, kemik ağrısı ve patolojik kırık yakınmaları ile başvururlar. Tedavi genellikle cerrahi, radyoterapi, kemoterapi veya bunların kombinasyonu şeklindedir.
Yöntem ve Gereçler: Bu çalışmada, merkezimizde 1995 ve 2005 yılları arasında tanı alan 18 primer kemik NHL'lı (11 kadın, 7 erkek) hasta retrospektif olarak analiz edilmiştir. Hastaların tanı anındaki medyan yaşı 56.5 (27-78) yıl olup, medyan 4.5 (1-36) aylık semptom süresinden sonra kliniğe başvurmuşlardır. Tüm hastalarda ağrı semptomu birinci sırada yer almakla birlikte 3 hastada (%16.7) B-semptomları da saptanmıştır. Tanı yöntemi olarak çoğunlukla "tru-cut" biyopsi (%66.7) uygulanırken, hastaların %27.8'inde açık operasyonla tanı konulmuştur.

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Bulgular: DBBHL % 77.8 (14 hasta) oranında en sık görülen histolojik alt tip olup, %11.1'i anaplastik büyük hücreli lenfoma, %5.6'ı Burkitt-benzeri, %5.6'ı marjinal zon lenfoma olarak belirlenmiştir. Ann Arbor klinik evreleme sistemine göre hastaların %44.4'ü Evre-I, %11,1'i Evre-II, %44.4'ü Evre-IV olarak değerlendirilmiş, kemik iliği tutulumu %22.2 hastada saptanmıştır. Bir hasta dışında tümüne CHOP veya benzeri antrasiklin içeren kemoterapi protokolleri uygulanmış, 8 hastada (%44.4) Rituximab tedaviye eklenmiştir ve bu hastaların hiçbirinde relaps izlenmemiştir. %50 hastada radyoterapi birinci sıra tedavisi olarak uygulanmıştır. Medyan 37 (2-124) aylık izlemde, tedavilerini tamamlayan ve tam remisyon sağlanan 17 hastanın 5'inde (%27.8) relaps gelişmiş olup halen tüm hastalar sağdır. 5 yıllık hastalıksız sağ kalım oranı %73.5 olarak belirlenmiştir.
Sonuç: Kemik lenfomaların tedavisi hastalığın evresi ve lokalizasyonuna göre planlanmalıdır. Radyoterapi uygulansın veya uygulanmasın, özellikle rituximab ile birlikte sistemik kemoterapi yaşam süresini olumlu yönde etkiler görünmektedir.
(Turk J Hematol 2010; 27: 29-33)
Anahtar kelimeler: Hematolojik hastalıklar, çocuk, invazif mantar infeksiyonu

Geliş tarihi: 13 Kasım 2006 *Kabul tarihi: 10 Aralık 2009*

Introduction

Non-Hodgkin's lymphoma (NHL) of bone is a rare disease, accounting for approximately 5% of all NHLs and 3% of all primary bone malignancies [1,2]. There is a slight male predominance and most patients are diagnosed in their fourth or fifth decade [3]. Although very rare, bone involvement of NHLs has been determined in some cases, and primary bone lymphoma has also been seen. The most common symptoms in bone involvement are classified as bone pain, soft tissue swelling and pathologic fracture. Long bones are the most commonly affected sites [3]. Histologically, diffuse large B cell lymphomas (DLBCL) are the most prominent subtype [4-6]. Tru-cut or open biopsy of affected sites is generally required for the diagnosis of bone lymphoma. On full staging evaluation, most of the patients have early stage disease (stage IE-IIE) and the remaining few have advanced stage [3]. Treatment options have been defined as chemotherapy, radiotherapy, surgery, or a combination of these modalities. Traditionally, stage I or II diseases have been treated with radiotherapy [3]. Combinational therapy modalities including CHOP, CHOP-like regimen and rituximab added to these modalities have been found to be the most effective regimens in the last decade [3,7,8].

Herein, we report a retrospective analysis of 18 patients who were diagnosed as NHL with bone involvement; all patients were diagnosed and followed up between 1995 and 2005.

Materials and Methods

Between 1995-2005, the records of 18 patients with NHL of bone who were diagnosed and treated in our center were analyzed retrospectively. All patients had a biopsy-proven diagnosis of lymphoma established by experienced hematopathologists. Patients were evaluated according to current World Health Organization classification [9]. Information including patient age, sex, presenting symptoms, sites of involvement, presence of B symptoms, type of diagnostic procedure, histological subtype, presence of bone marrow involvement, stage of the disease, treatment strategies, response rate, relapse pattern, and survival time were ascertained from the hospital records. Pretreatment staging evaluations included medical history, physical examination, laboratory investigation of complete blood count and lactate dehydrogenase (LDH) level, computed tomography (CT) scan of the neck, thorax and abdomen, and staging bone marrow (BM) biopsy. The clinical stage of the disease was designated by using the Ann Arbor classification system. Patients with lymph node involvement outside the affected site and all patients with other extranodal involvement such as lung, liver, etc. were excluded from the study. B-symptoms were defined as recurrent fever of more than 38°C, night sweats and an unexplained weight loss of more than 10% of actual body weight within 6 months prior to diagnosis.

Complete remission (CR) was defined as absence of disease signs and symptoms one month after the completion of treatment. Relapse was defined as the appearance of a new lesion in a patient in CR. Overall survival (OS) was calculated from the time of diagnosis to the time of death or last follow-up. Relapse-free survival (RFS) was measured from the time of diagnosis to the time of treatment failure, relapse/progression or death from lymphoma. Informed consent was obtained from all patients.

Statistical Analysis

All descriptive and survival analyses were performed using the SPSS software for Windows. Survival curves (OS and RFS) were calculated using Kaplan-Meier method.

Results

The median age of the 18 patients was 56.5 years (range, 27-78 years). Male/female ratio was 7/11. The median duration of symptoms was 4.5 months (range, 1-36 months). The median follow-up was 37 months (range, 2-124 months). Bone pain was the first symptom in all patients. Long bones were involved in 6 patients (34%). Three patients (16.7%) had B symptoms at initial presentation. Elevation in serum LDH was detected in 5 (27%) patients. The most common diagnostic procedure applied during the first application was tru-cut biopsy (12 patients, 66.7%). Open biopsy had to be performed in 5 patients (27.8%) and 1 patient was diagnosed with lymph node biopsy. DLBCL (14 patients, 77.8%) was the most common histological type of lymphoma among all patients. Others were diagnosed as anaplastic large cell lymphoma (2 patients, 11.1%), Burkitt-like lymphoma (1 patient, 5.6%) and marginal

Table 1. Patients characteristics, treatment modalities and outcomes

Patient	Age	Gender	Involved sites	B symptoms	Diagnostic procedure	Histology	Stages	Radiotherapy	Chemotherapy	Response	Relapse	Current status
1	37	M	Tibia	No	Tru-cut	DLBCL	I	Yes	R-CT	CR	No	CR
2	40	F	Clavicula	No	Open biopsy	DLBCL	IV	No	R-CT	CR	No	CR
3	63	F	Temporal	No	Tru-cut	DLBCL	IV	Yes	CT	CR	No	CR
4	56	F	Femur	Yes	Tru-cut	DLBCL, ANAPLASTIC	IV	Yes	CT	CR	No	CR
5	49	F	Humerus	No	Tru-cut	DLBCL	IV	No	R-CT	CR	No	CR
6	58	F	Ulna	No	Tru-cut	BURKİTT-LIKE	IV	No	CT	CR	No	CR
7	58	M	Rib	No	Tru-cut	DLBCL	I	No	R-CT	CR	No	CR
8	67	M	Spine	Yes	LN biopsy	DLBCL	II	No	R-CT	CR	No	CR
9	52	F	Mandibula	No	Open biopsy	DLBCL	II	No	R-CT	CR	No	CR
10	78	F	Palatinum	No	Tru-cut	MARGINAL ZONE	I	Yes	No	CR	Yes	Alive with disease
11	55	F	Iliac	Yes	Tru-cut	DLBCL	IV	No	CT	CR	Yes	Alive with sites
12	37	M	Spine	No	Open biopsy	DLBCL	IV	Yes	CT	CR	Yes	Alive with disease
13	69	M	Femur	No	Tru-cut	DLBCL	I	Yes	CT	LFU	-	LFU
14	58	M	Ethmoid	No	Tru-cut	DLBCL	I	No	CT	CR	No	CR
15	63	F	Pelvis	No	Open biopsy	DLBCL	IV	No	CT	CR	Yes	CR
16	33	F	Sternum	No	Tru-cut	ALCL	I	Yes	CT	CR	Yes	CR
17	27	M	Acromion	No	Open biopsy	DLCBL	I	Yes	R-CT	CR	No	CR
18	57	F	Femur	No	Tru-cut	DLCBL	I	Yes	R-CT	CR	No	CR

M: Male, F: Female, DLBCL: Diffuse large B cell lymphoma, R: Rituximab, CT: Chemotherapy, ALCL: Anaplastic large cell lymphoma, CR: Complete response, LFU: Lost to follow-up

zone lymphoma (1 patient, 5.6%). According to the Ann Arbor staging system, 8 patients (44.4 %) were Stage I, 2 patients (11.1%) were Stage II and 8 patients (44.4%) were Stage IV. Bone marrow involvement was determined in 4 patients (22.2%).

Since we did not have an established and documented clinical protocol, and since there was an extended period between the first and last patient, each patient was treated with different approaches, such as only radiotherapy, chemotherapy, or a combination of both. All patients except one were eventually treated with CHOP or CHOP-like anthracycline-containing regimens. Eight patients (44.4%) also received rituximab with chemotherapy in combination. Radiation therapy was the first-line therapy in 9 patients (50%). Only 1 patient was treated with radiotherapy alone.

At the time of the latest follow-up, no patient had died and 1 patient was lost to follow-up. The OS was 100% and the RFS was 73.5% at five years (Figure 1). Five (27.8%) of the 17 patients who achieved CR at the end of the treatment relapsed; 3 of these relapsed patients showed resistance to salvage treatments and were alive with disease. The remaining 2 patients were treated with high-dose chemotherapy with autologous stem cell transplantation and achieved a second CR. Patients' characteristics, treatment modalities and outcomes are shown in Table 1.

Discussion

Bone lymphoma is an uncommon disease. Therefore, classification, staging, treatment, and prognosis of bone lymphoma are controversial. In our study, we evaluated 18 patients with NHL involving the bone, retrospectively. In this series, the median age of patients was 56.5 years, and this is similar to that in the literature [3,8-14]. Although a slight male preponderance has been reported in some studies [3,8], we found a female predominance as reported in other studies [10,11,14].

Previous studies have emphasized a predominance of long bone involvement [3]; however, the most recently reported study of a large series with 131 patients with primary bone lymphoma showed that long bones and flat bones were equally affected [15]. Bone pain, soft tissue swelling and pathologic fracture are the most common symptoms of the disease, and B symptoms are reported as in other lymphomas [3,10,12]. Our series also demonstrated an equal involvement of long and flat bones, as in the previous huge series.

Diffuse large B cell lymphoma is the most common histological type reported in many studies [3,5,6,8-18]. We also established this data in our study. Gianelli et al. [18] reported a study of 28 cases with primary bone lymphomas and 26 cases with systemic lymphomas involving the bone. Two main histo-

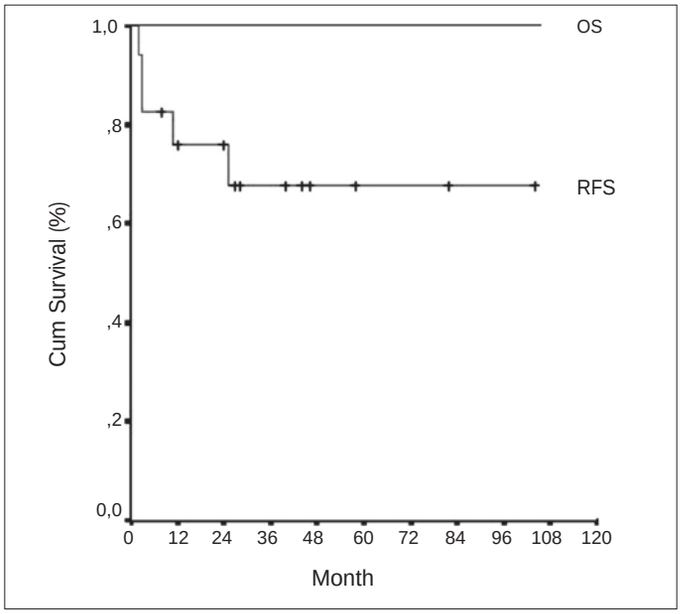

Figure 1. Kaplan-Meier estimate of overall survival and relapse-free survival of all patients

logical types were established: DLBCL and CD30 (+) anaplastic large cell lymphomas. A retrospective study with a large series by Ramadan et al. [15] showed that the most common diagnosis was DLBCL, determined in 79% of all patients.

Traditionally, treatment choice of localized stages IE and IIE, according to the Ann Arbor classification, was radiation therapy alone [3]. Recently, combined therapy with chemotherapy was also recommended for localized stages of disease [6,19]. In our series, all patients except one were treated with anthracycline-containing regimens. Radiation therapy were applied to nine (50%) patients. At the end of the treatment, we observed a complete response in 17 patients; one patient was lost to follow-up. The median follow-up was 37 months. Relapses were observed in only five patients during follow-up. The five-year RFS was 73.5% . Charousset et al. [13] reported a retrospective analysis of 22 patients with primary bone lymphoma. Twelve patients were treated with chemotherapy alone and eight patients with combined therapy. The mean five-year Kaplan-Meier survival was 83.3% for the chemotherapy group and 82.5% for the combined therapy group, and the mean follow-up was 48 months. They found no significant OS difference between the chemotherapy and combined therapy groups.

Recently, there has been a trend toward better survival with combined therapy with chemotherapy and radiotherapy. There have been studies demonstrating an improvement in survival in patients with primary bone lymphoma with the combined treatment [8,14,16,17].

Most recently, Ramadan et al. [15] retrospectively studied 131 patients with primary bone lymphoma and compared chemotherapy alone and combined modality with radiation. In that study, patients with advanced-stage disease who received chemotherapy plus radiotherapy actually had a poorer outcome compared with chemotherapy alone (10-year OSs were 25% and 56% , respectively). Their results did not support the routine use of irradiation in the treatment of primary bone lymphoma. They also revealed that the addition of rituximab to chemotherapy improved the outcome. They showed that three-year progression-free survival for patients who received rituximab-CHOP chemotherapy was 88% compared with 52% for those who received standard CHOP chemotherapy without rituximab (p=0.025).

In our series, eight patients (44.4%) also received rituximab in addition to chemotherapy; all of them achieved CR and none relapsed. There are other studies in the literature showing the effectiveness of rituximab in improving the outcome in patients with bone lymphoma, especially in patients who had resistant disease [20,21]. Recently, Beal et al. [12] published a study including 82 patients with bone lymphoma. They compared CHOP and CHOP plus rituximab, and demonstrated that rituximab was likely to be effective not only in chemoresistant patients but also in untreated patients.

In conclusion, anthracycline-containing chemotherapy regimens, especially with rituximab and radiotherapy, seem to be effective in the treatment of NHL of bone. However, randomized, controlled large prospective clinical trials will determine the role of radiotherapy and combined therapy.

Conflict of interest

No author of this paper has a conflict of interest, including specific financial interests, relationships, and/or affiliations relevant to the subject matter or materials included in this manuscript.

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