Malignant Lymphomas of the Testis

Testisin Malign Lenfomaları

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ABSTRACT Objective: Testicular lymphomas are similar to that of testicular germ cell tumors and account for approximately 9% of all testis tumors and represent 1-2% of all lymphomas. We evaluated clinical features, management and survival of 10 patients with primary testicular non-Hodgkin's lymphoma presented to our hematology unit between January 2001 and July 2006, retrospectively. **Material and Methods:** The median age of patients was 53 years at presentation (range 51-72 years) and all of them were >50 years old. In all of cases, orchidectomy was performed as diagnostic and first-line therapeutic procedures. **Results:** Dominant histological subtype was diffuse large B-cell non-Hodgkin's lymphoma. Six patients out of 10 (60%) were Ann Arbor stages I-II and, the remaining four patients (40%) were stages III and IV. All of the patients received doxorubicin-based chemotherapy and achieved complete remission. All patiens consolidation treatment received four cycles of MINE treatment. The addition of rituximab and central nervous system prophylaxis with intrathecal combined chemotherapy containing methotrexate, cytarabine and dexamethasone were applied to three patients who were recently admitted. No patient had elevated AFP and HCG or a history of undescended testis. The rate of relapse within references was 8% and progression-free survival (PFS) at 5 years was 88%. But all patients are alive and in case remission median duration of response was 62 months (range 10-62 months), median 72 months of follow-up. **Conclusion:** Testicular lymphomas tends to occur in middle ages. Tumor markers AFP and BHGC are in normal limits. Development in cryptorchid testis is extremely rare. An early systemic therapy is indicated.

Key Words: Lymphoma; antineoplastic protocols; prognosis

ÖZET Amaç: Testiküler lenfomalar, testiküler germ hücreli tümörlere benzerler ve bütün testis tümörlerinin yaklasık %9'unu ve bütün lenfomaların yaklasık %1-2'sini oluştururlar. Ocak 2001 ve Temmuz 2006 tarihleri arasında hematoloji birimimize başvuran primer testiküler non Hodgkin lenfomalı 10 hastanın klinik özelliklerini, takibini ve sağkalımlarını değerlendirdik. **Gereç ve Yöntemler:** Sunulan hastaların ortalama yaşları 53 (51-68) olmakla birlikte hepsi 50 yaşından büyüktü. Bütün olgularda, tanı ve tedavi prosedürü olarak orşiektomi uygulanmıştı. **Bulgular:** Baskın histolojik subtip, diffüz büyük B hücreli non Hodgkin lenfoma idi. Ann-Arbor evrelemesine göre 10 hastadan 6 (%60)'sı evre 1-2, geri kalan 4 (%40) hasta evre 3 ve 4'tü. Bütün hastalar doksorubisin tabanlı kemoterapi aldı ve tam remisyon elde edildi. Hastalara konsolidasyon tedavisi olarak MINE protokolü uygulandı. Yakın zamanda kabul edilen 3 hastaya rituksimab ve santral sinir sistemi profilaksisi olarak metotreksat, sitarabin ve deksametazon içeren intratekal kombine kemoterapi eklendi. Hastaların hiçbirinde AFP ve BHCG yüksekliği ya da inmemiş testis öyküsü yoktu. Literatürde 5 yıllık relaps oranı %8 ve 5 yıllık nükssüz sağkalım %88 oranında belirtilirken, hastalarımızda nüks görülmedi. Ortalama cevap süresi 62 aydı. Bütün hastalarımız hayatta ve remisyonda idi. **Sonuç:** Testiküler lenfomalar. testiküler germ hücreli tümörlere benzerler ve orta yaşlarda görülme eğilimindedirler. AFP ve BHCG tümör belirteçleri normal sınırlardadır. Kriptoorşit testis gelişimi son derece nadirdir. Erken sistemik tedavi endikasyonu vardır.

Anahtar Kelimeler: Lenfoma; antineoplastik protokoller; prognoz

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Primary testicular lymphoma (PTL) accounts for about 1-2% of all lymphomas and is the most common testicular malignancy in men aged >60.[1] The diagnosis is usually obtained after orchiectomy, and the dominant histological subtype is diffuse large B-cell lymphoma (DLBCL).[2-4] PTL shows a tendency to spread to several extranodal sites at presentation or relapse, including the contralateral testis, central nervous system (CNS), skin, lung, pleura, Waldeyer's ring and soft tissues.[2,3] Because of the low incidence of the disease and absence of prospective studies, the most appropriate therapy for PTL remains controversial. Early retrospective studies indicated that local treatment with surgery alone or surgery plus radiotherapy (RT) and chemotherapy without antracycline provides suboptimal disease control even in localized disease.[4-6] Recently, combined modality treatment with systemic doxorubicin-based chemotherapy, prophylactic intrathecal (IT) chemotherapy and scrotal RT has been recommended because of the relapse risk to extranodal sites such as the CNS and contralateral testis. Despite these more aggressive treatment modalities, prognosis is often poor, even in the localized disease, with the two-year relapse rate exceeding 50%.[1,2,4,7-9] In this retrospective study, we aimed to evaluate the clinical and histological characteristics of PTL and effectiveness of the treatment modality administered in our center. The average incidence of testis tumors is in the range of 2,1 to 2,3 per 100.000 males. Rarely, primary lymphoma of the testis occurs in children.[3,6]

MATERIAL AND METHODS

We evaluated clinical features, management, outcome and survival of 10 adult male patients with primary testicular lymphoma presented to the Ankara Oncology education and Research hospital hematology unit between January 2001 and July 2006. We retrospectively searched 812 non-Hodgkin's lymphoma (NHL) cases registered between 1999 and 2006 and included in this study those with a histopathologically verified testicular lymphoma. We used data from the available clinical files concerning patient age, symptoms, disease extension, histopathological subtypes according to the World Health Organization (WHO) classification, level of lactate dehydrogenase (LDH) at presentation, and treatment modalities, response rate, relapse pattern and survival time. Pretreatment staging evaluations consisted of a medical history; physical examination; laboratory investigation of hemoglobin, hematocrit, white blood cell, platelet count and LDH levels; computed tomography (CT) scan of the neck, thorax and abdomen; and a staging bone marrow (BM) biopsy. During the treatment period, all patients were reevaluated at the third or fourth cycles of chemotherapy for the signs of disease or any additional new involvement site for the progressive disease. Patients who have bone marrow infiltration at presentation were also reevaluated with bone marrow biopsy at the third or fourth cycle of chemotherapy for the treatment response. The clinical stage of the disease was designated by the Ann Arbor classification system.[6] B symptoms were defined as a recurrent fever of >38°C temperature, nightsweats and unexplained weight loss of >10% of bodyweight within six months prior to diagnosis. Patients were retrospectively classified into four risk groups according to an International Prognostic Index (IPI) score low (IPI score of 0-1), low-intermediate (IPI score of 2), high-intermediate (IPI score of 3), high-risk (IPI score of 4-5).[7] All patients had a diagnosis of lymphoma by orchidectomy. All pathological slides were reviewed at our institution, and disease was described according to WHO classification.[10] Histopathological specimens patients who were administered after 2004 were investigated for the positivity of some prognostic factors such as MUM-1, Ki-67 and bcl-2. All patients were treated with doxorubicin-based chemotherapy. Complete remission 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 for patients in complete remission. Overall survival was calculated from time of diagnosis to time of death or last follow-up. Progression-free survival (PFS) was measured from time of diagnosis to time of treatment failure, relapse/progression or death from lymphoma.

TABLE 1: Patients clinical and laboratory findings.

Patient n=10	Age (Years)	Location (Testis)	Stage	B Symptoms	Extranodal Sites	IPI	Histology (WHO)
1	53	Right	III	(-)	(-)	L-I	DLBCL
2	51	Left	IV	(+)	Bone Marrow	L-I	DLBCL
3	61	Bilateral	II	(-)	(-)	L-I	DLBCL
4	50	Left	III	(-)	(-)	L-I	Peripheral T-cell
5	68	Bilateral	II	(-)	(-)	H-1	DLBCL
6	63	Right	II	(-)	(-)	L-I	DLBCL
7	51	Left	I	(-)	(-)	L-I	DLBCL
8	72	Right	IV	(+)	(-)	H-1	DLBCL
9	55	Bilateral	II	(-)	(-)	L-1	DLBCL
10	58	Right	I	(-)	(-)	L-1	DLBCL

IPI: International Prognostic Index; DLBCL: Diffuse Large B Cell Lymphoma.

RESULTS

PATIENT CHARACTERISTICS

Ten patients with a median age of 53 years (range 51-72 years) at presentation were included in the study. Patients clinical and laboratory findings summarized Table 1. Majority of patients were histologically diagnosed as DLBCL, one was diagnosed as peripheral T-cell lymphoma. All the patients admitted with a complaint of painless testicular swelling. Three patients had involvement of the left testis, four of the right. Three patients had bilateral testicular involvement. Median duration of symptoms from initiation to diagnosis was three months (range 1-8 months) and two patients (25%) had B symptoms, patient suffered from fever and weight loss. Six patients (60%) were Ann Arbor stages I and II, the remaining four (40%) were stages III and IV Bone marrow infiltration. Bulky disease was not recognized in patients. Four patients had anemia at presentation; median hemoglobin level was 13 g/dL (range 10-16 g/dl). Six patients, presented with high serum LDH levels with a median LDH of 378 U/L (range 141-819 U/L). Some histopathological features of the biopsy samples such as MUM-1and Ki-67 for DLBCL patients were excluded since only two patients applied after 2004.

TREATMENT

All patients were treated with 6 cycles (6-8 cycles) of doxorubicin-based chemotherapy, CHOP-21 (the standard dose of cyclophosphamide 750 mg/m^2 D;l, hydroxydaunorubicine 50 mg/m^2 D;1vincristine 1.4 mg/m^2 D;I, and prednisone 100 mg/dayD; I-5 chemotherapy. All patient consolidation treatment received four cycles of MINE (mitoxantrone 8 mg/m^2 D;I-3, etoposide 65 mg/m^2 D;1-3, ifosfamide 1.330 mg/m^2 D;I-3 and mesna equal dose to ifosfamide) chemotherapy and achieved complete remission. Rituximab was added to all cycles of chemotherapy with the dose of 375 mg/m^2 and CNS prophylaxis within trathecal combined chemotherapy containing methotrexate, cytarabine and dexamethasone were applied to three patients who were recently admitted in different clinical protocols.

OUTCOME

Complete remission was achieved in all patients. He has been followed-up in complete remission for two years. At median 42 months (range 15-62 months) of follow up, all of the patients are still alive. The rate of relapse within references was 8%, and PFS at 5 years was 88%. Median duration of response was 42 months (range 15-62 months). The ten identified cases of PTL correspond to 1-2% of all NHL patients diagnosis our hematology unit between January 2001 and July 2006. The median age of all patients 53 years with PTL was younger than the reported series.[2,4,7] Ages of patients ranged from 51-72 years, but most were aged>50 years old. This may be due to regional differences, but as there is no population-based large cohort studies related to the geographical occurrence of testicular lymphomas, this point is still unexplained.

In our patients, the first symptom of the testis lymphomas was painless testicular swelling, and diagnosis was generally performed by orchidectomy. Histological diagnosis showed the dominance of B-cell type and the major lymphoma subtype as DLBCL, which is consistent with previously published reports.[2,10]

Published series reported that testicular lymphoma is associated with the involvement of the skin and subcutaneous tissues in 6-13%, of the Waldeyer's ring and upper airway in 4-6%, of the CNS in 3-6%, and of the contralateral testis in up to 50% at presentation.[2,7,8,11-14] In our patients at presentation, spreading to extranodal organs other than the testis was seen less than these reports. Bilateral testicular involvement at presentation was 33%, which is similar to previous reports.[2,14-16] At presentation, predilection for the right site involvement of testis is common findings[4,17] as seen in our series; right site involvement was 42%. Rate of involvement of bone marrow (10%) was higher than the previously reported series.[2,11,18] In our patients, more than half of the patients (58%) had stage IE and IIE and favorable IPI score.

DISCUSSION

The ten identified cases of PTL correspond to 1-2% of all NHL patients diagnose our hematology unit between January 2001 and July 2006. The median age of four patients 53 years with PTL was younger than the reported series.[2,4,7,19] Ages of patients ranged from 51-72 years, but most were aged>50 years old. This may be due to regional differences, but as there is no population-based large cohort studies related to the geographical occurrence of testicular lymphomas, this point is still unexplained. In our patients, the first symptom of the testis lymphomas was painless testicular swelling, and diagnosis was generally performed by orchidectomy. Histological diagnosis showed the dominance of B-cell type and the major lymphoma subtype as DLBCL, which is consistent with previously published reports.[2,20] Published series reported that testicular lymphoma is associated with the involvement of the skin and subcutaneous tissues in 6-13%, of the Waldeyer's ring and upper airway in 4-6%, of the CNS in 3-6%, and of the contralateral testis in up to 50% at presentation.[2,3,11,13,14,16,21] In our patients at presentation, spreading to extranodal organs other than the testis was seen less than these reports. Bilateral testicular involvement at presentation was 33%, which is similar to previous reports.[2,14] At presentation, for the right site involvement of testis is common as seen in our series; right site involvementwas 42%. Rate of involvement of bone marrow (10%) was higher than the previously reported series.[2,4,11] In our patients, more than half of the patients (58%) had stage IE and IIE and favorable IPI score, which issimilar to previous reports.[2,4,8,22,23] It was reported that, even when present in early stages (stages IE and IIE), relapse is common at extranodal sites and prognosis is poor.[6,19,23] Although testicular lymphoma was identified more than 100 years ago, it remains a subset of interest because it follows a unique biological and clinical course, and optimal treatment continues to be controversial. Orchidectomy is the established diagnostic and first therapeutic procedure in cases of PTL. The choice of further treatment is still controversial because ofthe rare incidence of the disease and lack of prospective, randomized series. There is only one prospective phase-TI study related to treatment ofthe early stages (IE and IIE) of PTL; Aviles et al. 25 treated patients with PTL with six cycles of systemic chemotherapycontaining 1.250 mg/m^2 cyclophosphamide, 2 mg vincristine, 120 mg/m^2 epirubicine, 100 mg prednisone and 10 IU/m^2 bleomycine followed by radiotherapyto contralateral testis, iliac and pelvic lymph nodes. After complete remission, four cycles of CNS prophylaxis with 6 g/m^2 methotrexate intravenously in every 28 days was applied to treatment. They achieved complete remission in 97% of patients, but actuarial curves at five years showed that EFS was as little as 32% and also overall survival at five years was 30%. They conclude in this prospective study that prognosis of patients with even early-stage PTL is poor. Antracycline-based systemic chemotherapy and prophylactic treatment to CNS and contra-lateral testis did not improve patient's outcome. Multicenter or single-

center retrospective series also report that outcome for primary testicular lymphoma is poor. The International Extranodal Lymphoma Study Group's 2 reported that of 373 retrospectively evaluated patients with PTL from 21 institutions treated with different modalities, the overall survival rate was 81% and PFS was 68% at five years. At a median follow-up of 7.6 years, 195 patients (52%) hadrelapsed; most frequent sites of involvement at relapse included CNS and contralateral testis. In our retrospective study, all patients were treatedwith. 6 cycles of doxorubicin-based chemotherapy. At a median 62 months of follow-up, all the patients are alive and in complete remission. At 5 years, PFS was 88% and median duration of response was 47 months (range 12-200 months).The prognosis of patients with PTL presented and treated in our center was not poor, as reported in previous studies. This may also be related to racial and regional characteristics of the disease. Also the young age ofthe affected patients may have had a positive impact on the outcome of the disease. Early retrospective studies indicate a high rate of late relapses in patients with localized disease treated by surgery alone or surgery plus local radiotherapy.[4,6,21]

Radiation therapy alone is not considered effective, even stage-I disease failure to contralateral testis occurs in 5-35%.[7,8,14,18,24,25] Doxorubicin-based systemic chemotherapyhas been recommended because of the unique spreading behavior of PTL.[1,3,4,6,21] The treatment recommendation was recently changed to a combined modality of systemic doxorubicin-based chemotherapy, prophylactic IT chemotherapy and scrotal radiotherapy.[4] For Liang et al and Tondini et al prophylactic irradiation of un involved testis is pointless if aggressive chemotherapy is used.

In summary, patients admitted to our center have different characteristics; the presence of extranodal involvement other than the testis was not as common as previously reported. They were younger and showed relatively better prognosis than the reported series. In the management of PTL systemic treatment with doxorubicin-based chemotherapy with or without CNS prophylaxis and radiotherapy to other testis seems to produce good results. Application of rituximab to the combined modality may improve outcomes. The young age of our patients may have had a positive effect on outcomes as compared to the general patient population.

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