Primary testicular lymphoma (PTL) is an uncommon and aggressive form of extranodal non-Hodgkin's lymphoma (NHL). We aimed to analyse the clinicopathological characteristics and outcomes of our PTL cases. Materials and Methods: A review was made of the medical records of 339 NHL patients who were treated in the Medical Oncology Department between January 2005 and December 2013. Results: 8 PTL patients were identified from the 339 NHL patients. The average age of the patients was 67.7 ± 7.9 years (range 53–79 years). The mean follow-up time was 24.8 months (range 7–98 months). Inguinal orchietomy was performed as a diagnostic and initial therapy and all the patients underwent 4–6 cycles of chemoimmunotherapy consisting of cyclophosphamide, doxorubicin, vincristine and prednisone plus rituximab. 4 of 8 patients received intrathecal prophylactic chemotherapy and 6 of 8 patients continued contralateral testis irradiation. Relapse occurred in only 1 patient in central nervous system after 6 months who had not received intrathecal prophylaxis. No contralateral testis relapse was observed. Conclusions: Primary testicular NHL is an uncommon entity and we evaluated 8 patients; with one relapse in central nervous system and no relapse in the contralateral tests.

Key Words: primary testicular lymphoma, contralateral scrotal irradiation, intrathecal chemotherapy.
in the right testicle and 4 patients had PTL in the left testicle. 6 patients were Ann Arbor stage I or II at the time of diagnosis and 2 patients were stage III. Only 1 patient had B symptoms at stage III. Inguinal orchietomy was performed as a diagnostic and initial therapy and DLBCL was confirmed in all 8 patients after histopathological examination. After orchietomy, all the patients underwent 4–6 cycles of chemotherapy consisting of cyclophosphamide, doxorubicin, vincristine and prednisone (CHOP) plus rituximab (R), followed by intrathecal prophylactic chemotherapy in 4 of 8 patients and irradiation of the contralateral testis in 6 of 8 patients. CR was achieved in 7 patients after R-CHOP chemotherapy, 1 patient was still undergoing chemotherapy during the last follow-up with partial response (patient #2) and 1 patient was continuing chemotherapy and planned contralateral testis irradiation (patient #8).

During the follow-up period, a relapse occurred in only 1 patient (patient #4) in the CNS after 6 months, and it was determined that he had not received CNS prophylaxis. He was treated only with palliative radiotherapy. No contralateral testis relapse was observed. The patient characteristics and follow-up data are presented in Table. Figure shows the OS analysis of the PTL cases.

**Table.** Epidemiological features, clinicopathological characteristics, type of management, and outcome of patients with PTL.

<table>
<thead>
<tr>
<th>Patient no</th>
<th>Age, years</th>
<th>Stage</th>
<th>IPI</th>
<th>Location</th>
<th>Surgery</th>
<th>Chemo-therapy</th>
<th>RT</th>
<th>Response</th>
<th>Relapse</th>
<th>OS</th>
<th>Outcome, alive</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>53</td>
<td>IE</td>
<td>1</td>
<td>Left</td>
<td>Orchiectomy</td>
<td>4 × R-CHOP + -</td>
<td>CR</td>
<td>-</td>
<td>98</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>73</td>
<td>IIIE</td>
<td>4</td>
<td>Left</td>
<td>Orchiectomy</td>
<td>4 × R-CHOP - -</td>
<td>PR</td>
<td>-</td>
<td>7</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>63</td>
<td>III</td>
<td>3</td>
<td>Right</td>
<td>Orchiectomy</td>
<td>6 × R-CHOP + +</td>
<td>CR</td>
<td>-</td>
<td>9</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>68</td>
<td>IIIE</td>
<td>2</td>
<td>Right</td>
<td>Orchiectomy</td>
<td>6 × R-CHOP + -</td>
<td>CR</td>
<td>+ (6)</td>
<td>12</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>79</td>
<td>IE</td>
<td>1</td>
<td>Right</td>
<td>Orchiectomy</td>
<td>4 × R-CHOP + -</td>
<td>CR</td>
<td>-</td>
<td>15</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>66</td>
<td>IIE</td>
<td>1</td>
<td>Right</td>
<td>Orchiectomy</td>
<td>6 × R-CHOP + +</td>
<td>CR</td>
<td>-</td>
<td>36</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>74</td>
<td>IIE</td>
<td>1</td>
<td>Left</td>
<td>Orchiectomy</td>
<td>6 × R-CHOP + +</td>
<td>CR</td>
<td>-</td>
<td>14</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>68</td>
<td>IIE</td>
<td>1</td>
<td>Left</td>
<td>Orchiectomy</td>
<td>6 × R-CHOP - -</td>
<td>CR</td>
<td>-</td>
<td>8</td>
<td>+</td>
<td></td>
</tr>
</tbody>
</table>

**Note:** R-CHOP — rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone; RT — radiotherapy; PR — partial remission.

**Figure.** Kaplan — Meier OS curve for PTL patients.

**DISCUSSION**

In this study, the clinicopathological characteristics and outcomes of 8 PTL cases treated at our department have been reported. In a recent report, Mertsoylu et al. [12] evaluated 802 NHL patients and found only 2 cases of PTL in Southern Turkey. In an other study from South India, Padhi et al. [13] reported 2 PTL patients among 308 NHL cases. Differently we treated more PTL patients in our department.

PTL is a rare and aggressive form of extranodal NHL which accounts for 1–2% of NHL cases in men aged > 60 years [1, 3]. Although outcomes for patients with PTL have historically been poor with no plateau in PFS and OS curves, significant improvements have been achieved with the addition of radiotherapy (RT) to full-course anthracycline-based chemotherapy, R and CNS-directed prophylaxis [14]. Relapses frequently occur in the contralateral tests and CNS [15]. Both these sites are considered to be immunoprivileged sites, where lymphoma cells may escape the host T-cell antitumour response and chemotherapy may have reduced efficacy because of the mechanical blood testis barrier and blood brain barrier [8, 9].

In addition, low levels of p53 expression but high levels of phosphorylated STAT3 (pSTAT3), overexpression of pCXCR4, and upregulation of the nuclear factor kB (NF-kB) pathway were detected in PTL cases by Menter et al. [16] and they reported that expression of both CXCR4 and pCXCR4 was predictive of inferior PFS. Preliminary studies have reported that directed metastasis is mediated by CXCR4 activation and migration toward CXCR12-expressing target organs [14, 17]. Therefore, CXCR4 overexpression may predispose extranodal relapse in PTL. Due to the above-mentioned mechanisms orchiectomy alone is not sufficient even in the early stages. It has been observed that more than 60% of patients treated with simple orchiectomy relapsed mostly in the CNS in the first five years [4, 18].

In the current study, histopathologically all the patients were DLBCL, which was consistent with other reports [19–21]. The most common regimen reported in retrospective studies is R-cyclophosphamide, doxorubicin, vincristine and prednisolone 3 weekly (R-CHOP-21) and there are no data to suggest that any alternative regimen offers a better outcome [3, 7, 22]. In our study, all the PTL patients received R-CHOP. R is a monoclonal antibody against the CD20 antigen expressed on the majority of B-cell lymphomas which has improved the outcome of both high- and low-grade B-cell lymphomas in general. It has also been incorporated into treatment strategies for PTL over the last decade. However, a retrospective analysis of 769 patients with testicular lymphoma from the Surveillance, Epidemiology and End Result database in the USA did not show any improvements in disease-specific survival after 2000, when R came into common usage [4]. In a randomized trial of 399 patients with DLBCL by Feugier et al. [23] the effect of CHOP plus R (R-CHOP) was compared with that of CHOP and it was shown that the addition of R did not reduce the risk of dissemination to the CNS at relapse.

According to the results of these retrospective studies, the International Extranodal Lymphoma Study Group (IELSG) reported a prospective phase II trial [24], in which 53 patients received CHOP-21 plus R followed by prophylactic irradiation of the contralateral testis and intrathecal chemotherapy prophylaxis of 4 doses.
of methotrexate. The patients with stage II disease also received involved-field RT. After a median follow-up of 65 months, the 5-year PFS and OS rates were 74% and 85%, respectively. Only 3 cases demonstrated CNS relapse and no cases demonstrated relapse in the contralateral testis.

In the current series, relapse occurred in only 1 patient in CNS after 6 months who had not received CNS prophylaxis and he died from his disease 6 months after this relapse. The second patient died because of myocardial infarction 14 months after the diagnosis.

Similar to the IELSG study no contralateral testis relapse was observed in the current study group. Neither was any CNS relapse observed in those who received intrathecal methotrexate but the current study population was small and the follow-up period was not long enough for some patients.

As CNS prophylaxis after anthracycline-based combined chemotherapy and RT, Aviles et al. [25] treated 34 PTL patients with high-dose methotrexate (6 g/m²). More recently Lokesh et al. [26] reported their PTL series but none of them received CNS prophylaxis nor contralateral testis irradiation so the survival is poor. In another report Ichikawa et al. [27] confirmed that combined modality treatment suggests a better PSF similar to our findings.

On the other hand, new potential therapeutic approaches are necessary because of the poor prognosis for relapsed patients especially in CNS. If CXCR4 is found to have a pathophysiologic role in mediating extranodal relapse, development of the CXCR4 inhibitor may prove attractive as a therapeutic adjuvant to chemotherapy. In addition, overactivation of the NF-κB and STAT3 signalling pathways may be exploited as a target, but rigorous testing is required in prospective clinical trials in PTL patients.

In conclusion, PTL is a rare condition and prospective randomised controlled trials have been difficult to establish. However, collective international experience based on a number of retrospective analyses has led to the evolution of therapeutic protocols that offer a significantly improved prognosis for PTL. The best outcome is achieved from combined treatment with orchiectomy, R-CHOP and CNS prophylaxis with intrathecal chemotherapy and irradiation of the contralateral testis. Despite notable improvement in the PFS and OS, CNS relapse remains a devastating condition. Ongoing IELSG30 phase II trials with modified CNS prophylaxis (intrathecal injections of cytarabine) could yield essential information. In the future, the development of biological therapeutic agents should be considered for this rare but aggressive disease.

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CONFLICT OF INTEREST
The authors report no conflicts of interest.

REFERENCES


