Primary testicular lymphoma

Chan Y Cheah\textsuperscript{1,2}, Andrew Wirth\textsuperscript{2,3} and John F Seymour\textsuperscript{1,2}

1. Department of Haematology, Peter MacCallum Cancer Centre, East Melbourne, Melbourne, Victoria, Australia
2. University of Melbourne, Parkville, Melbourne, Victoria, Australia
3. Division of Radiation Oncology, Peter MacCallum Cancer Centre, East Melbourne, Melbourne, Victoria, Australia

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Corresponding author
Prof John F Seymour
Head of Department, Haematology
Peter MacCallum Cancer Centre
Locked Bag 1, A'Beckett St
East Melbourne 8006
Victoria, Australia
Email: john.seymour@petermac.org
Phone: +61 3 9656 1076
Fax: +61 3 9656 1408
Abstract

Primary testicular lymphoma (PTL) is a rare, clinically aggressive form of extranodal lymphoma. The vast majority of cases are histologically diffuse large B-cell lymphoma, but rarer subtypes are clinically important and must be recognised. In this review we discuss the incidence, clinical presentation and prognostic factors of PTL and present a summary of the recent advances in our understanding of the pathophysiology which may account for the characteristic clinical features. Although outcomes for patients with PTL have historically been poor, significant gains have been made with the successive addition of radiotherapy, full-course anthracycline-based chemotherapy, rituximab and CNS-directed prophylaxis. We describe the larger retrospective series, prospective clinical trials and critically examine the role of radiotherapy. Although 3-weekly RCHOP with intrathecal methotrexate and locoregional RT is the current international standard of care, a substantial minority of patients progress, representing an unmet medical need. Finally, we discuss new treatment approaches and recent discoveries which may translate into improved outcomes for patients with PTL.
Introduction

Primary testicular lymphoma (PTL) is an uncommon and aggressive form of extranodal non-Hodgkin lymphoma (NHL) accounting for <5% of testicular malignancies and 1-2% of NHL. The median age at diagnosis 66-68 years and it is both the commonest testicular malignancy in men aged >60 years and the most common bilateral testicular neoplasm. Population based studies have estimated the annual incidence at 0.09 - 0.26 per 100,000 population.

Clinical features, risk factors and etiology

The typical presentation is with a firm, painless testicular mass without preference for either side, inseparable from the affected testis, with median tumor size at presentation 6cm. There is an associated hydrocele in ~40% of cases. Synchronous bilateral involvement occurs in 6-10% of cases. Constitutional symptoms at diagnosis are uncommon but if present strongly suggest systemic disease, present in 20-30% of patients. PTL has marked extranodal tropism and relapses frequently involve sites including central nervous system (CNS), skin, contralateral testis and pleura. Although there are limited data regarding specific risk-factors for PTL, HIV infection is a known risk factor for aggressive NHL, with lymphomas in HIV-infected patients more commonly presenting with extranodal primary sites, including the testis. HIV-positive patients with PTL are younger (median age 36) with immunoblastic, plasmablastic or Burkitt-like histology more frequent, with median OS <6 months prior to use of combined antiretroviral therapy (CART). Although data are scarce, it is likely that since the introduction of CART outcomes for HIV-positive patients with PTL have improved in line with nodal DLBCL.
There are several putative mechanisms for the link between PTL and CNS relapse. This may in part reflect the biological characteristics of tumors arising in an immune privileged site. Lymphomas arising under the selective pressure of immune surveillance may develop an immune escape phenotype.\textsuperscript{16} Common to both PTL and primary CNS lymphoma (PCNSL) are high levels of IgVH somatic hypermutation\textsuperscript{17} and loss of HLA expression resulting from gene deletions\textsuperscript{18,19} which may assist evasion of the host anti-tumor response. In addition, a nascent PTL clone may benefit from developing in an immune privileged site behind the blood-testis barrier, which has several components designed to shield developing gametocytes. These include: 1) a mechanical barrier formed by the tight junction between Sertoli and endothelial cells preventing the passage of large/hydrophilic molecules,\textsuperscript{20} 2) an efflux pump (P-glycoprotein, MRP1) for smaller/lipophilic molecules, 3) an immunological barrier formed by Sertoli cells hindering passage of antibodies\textsuperscript{21} and 4) local production of anti-inflammatory cytokines.\textsuperscript{22}

Menter \textit{et al} studied 45 cases of PTL using immunohistochemistry (IHC) and FISH, finding low levels of p53 expression but high levels of phosphorylated (p)STAT3, overexpression of pCXCR4, and upregulation of the NF-\kappa b pathway.\textsuperscript{23} Although few patients had clinical outcome data available, expression of both CXCR4 and pCXCR4 was predictive of inferior progression-free survival (PFS) ($P=0.007$). Little is known about the role of CXCR4 expression in lymphoma, though the chemokine receptor has myriad biological functions including trafficking of lymphocytes to sites of inflammation, hematopoetic cell homing, trafficking of tumor cells to target organs, proliferation and directed migration of neuronal cells, and infiltration of activated monocytes to areas of ischemic injury.\textsuperscript{24} Preclinical models have shown directed metastasis is mediated by CXCR4 activation and migration toward CXCR12 expressing target organs.\textsuperscript{24} Thus overexpression of CXCR4 may predispose PTL toward extranodal relapse.
**Diagnosis and staging**

Imaging modalities which may assist in diagnosis include ultrasonography, which demonstrates focal or diffuse areas of hypoechogenicity with hypervascularity in an enlarged testis and magnetic resonance imaging (MRI) which allows simultaneous evaluation of both testes, paratesticular spaces and spermatic cord; typical findings include T2 hypointensity and strong heterogeneous gadolinium enhancement. When PTL is suspected, inguinal orchiectomy is required for achievement of optimal disease control and adequacy of pathological specimen. In view of the rarity of PTL and frequent presentation to non-hematologists, it is important that the appropriate immunohistochemistry be performed (see “Pathology” below) and expert pathology review sought for difficult cases, as distinguishing some cases from seminoma can be difficult.

Recommended staging is as for other forms of aggressive NHL (PET-CT, bone marrow biopsy) with the addition of specific CNS staging with lumbar puncture for CSF analysis by cytology and flow cytometry (as there is evidence to support improved sensitivity) and brain MRI. We recommend thorough examination of the skin as cutaneous “DLBCL, leg type” and testicular DLBCL have been concurrently reported and the skin is a potential site of extranodal recurrence. HIV serology should be performed. As with other forms of NHL, the Ann Arbor system is used for staging, although this was not specifically designed for extranodal lymphomas. Patients with isolated bilateral involvement of the testes have similar prognosis to stage I/II disease, and therefore we agree with existing recommendations that such cases be considered stage I. In the largest series, 60-79% of patients were stage I/II at presentation although from a pragmatic perspective, patients with stage III/IV “primary” testicular lymphoma can be considered identical to systemic nodal DLBCL with secondary testicular involvement. Making distinctions between the two entities is difficult and somewhat arbitrary, as usually it cannot be determined in
retrospect whether the testicular mass was truly the initial site of disease and the
prognoses are similar.\textsuperscript{7}

**Pathology**

The large majority of PTL (80-98%) are diffuse large B-cell lymphoma (DLBCL) although patients with HIV infection often present with more aggressive variants. DLBCL-type PTL typically expresses B-cell markers CD19, CD20, CD79a and PAX5; Bcl-2 protein is expressed in 70% of cases; Bcl-6 is rarely positive.\textsuperscript{23} The median MIB1 proliferative index is 40% and in the non-HIV population EBV is usually negative.\textsuperscript{23} Rare histologies include mantle cell lymphoma,\textsuperscript{35-37} extranodal NK-cell lymphoma,\textsuperscript{38} peripheral T-cell lymphoma,\textsuperscript{39} extranodal marginal zone lymphoma\textsuperscript{40} and ALK1-negative anaplastic large cell lymphoma.\textsuperscript{41}

*Pediatric follicular lymphoma (FL) of the testis*

This rare entity deserves special mention, as it appears to have characteristics distinct from nodal follicular lymphoma and requires a distinct management approach. Of the 15 cases reported typical features include grade 3A morphology, stage IE disease, expression of CD10 and Bcl-6 by IHC but lack of Bcl2 protein expression or *BCL2* gene rearrangement and indolent clinical behaviour.\textsuperscript{42-46} In contrast, adults with primary follicular lymphoma of the testis are reported to bear the *BCL2* gene rearrangement and overexpress Bcl-2 protein.\textsuperscript{42} The optimal therapy is unclear, with most patients treated with orchiectomy plus abbreviated anthracycline-containing chemotherapy. However, two patients have been managed with surgery alone, and remained in ongoing clinical remission at 30 and 96 months.\textsuperscript{46,47} Although data are scarce, outcomes appear favorable without reports of CNS relapses to date.

*Cell of origin studies and chromosomal translocations*
In PTL of DLBCL histology, cell of origin determined either by IHC-based algorithms and/or DNA microarray is activated B-cell (ABC)-type in 60-96% of cases. The variation in frequency is dependent on both the proportion of patients with advanced stage disease (where it is difficult to distinguish PTL from nodal DLBCL with testicular metastases) and the IHC algorithm employed. The true proportion of cases which are ABC-type is likely to be at the higher end of the published estimates, as although 6-36% of cases are CD10+ in published series are classified as GCB-type by the Hans algorithm, many also express the B-cell activation marker MUM1. Some scoring systems consider such cases to be ambiguous, fitting neither ABC nor GCB-subtype. Booman et al determined cell of origin using both IHC and gene expression profiling. By IHC, 14 (64%) were clearly ABC-type (CD10- Bcl6 +/- MUM1+) however 8 (36%) were classified as ‘ambiguous’ (CD10+ Bcl6+ MUM1+), and 7/8 (88%) of these ambiguous cases were re-classified as ABC-type by gene expression analysis. This predominance of ABC-type may partially account for the historically poor outcomes from PTL. Recent data in nodal DLBCL suggest that the adverse outcome conferred by ABC-subtype may be attributable to chronic active B-cell receptor signalling, constitutive NF-κB and PI3K activation. Interestingly, a large international consortium found that co-expression of MYC and Bcl-2 protein contributed to the inferior survival of ABC-type nodal DLBCL. However, the limited data available suggests the frequency of either proteomic or cytogenetic “double hit” with MYC and Bcl-2 in PTL is low. Bernasconi et al performed cytogenetic analyses using split signal FISH probes in 16 patients with PTL, finding 3 cases (19%) bearing MYC translocations. Menter et al found only 5/38 (13%) PTL cases expressed c-myc protein, but all five also expressed Bcl-2 protein. Finally, the dependence of ABC-type DLBCL on MYD88, an adaptor protein which acts through toll and IL-1 receptor, was recently described. Kraan et al found mutations in MYD88 in >70% of PTL and PCNSL, but <20% of patients with nodal DLBCL, providing further evidence for differences in pathophysiology.
Prognostic factors and patterns of relapse

Numerous prognostic factors for PTL have been described, largely derived from small retrospective series, often including patients with disseminated disease including testicular involvement. Thus although IPI and its components have been frequently reported as prognostic factors they are surrogate markers of high tumor burden and disseminated disease. For the majority of patients with PTL who present with limited stage disease the IPI is typically <2 and therefore has limited prognostic utility. The adverse prognostic markers for PFS are summarised in Table 1; those for OS are similar with one study also identifying infiltration of adjacent tissues. The impact of non-DLBCL histology is difficult to determine because of the rarity of such cases. A Dutch series found evidence of transformed extranodal marginal zone lymphoma was associated with smaller tumor size, less frequently elevated LDH, absence of B-symptoms, more frequent stage IE disease and lower IPI than “pure” DLBCL and non-significant trend toward improved survival.

A particular characteristic of PTL is the temporal pattern of continuing relapses, even >15 years after initial treatment which frequently involves sanctuary sites such as the contralateral testis and CNS. Often relapses occur at multiple extranodal sites including lung, soft tissue, adrenals, liver and bone marrow. The crude incidence of CNS involvement in PTL has been reported in smaller series as up to 44%, although estimates vary widely and use of CNS-directed prophylaxis was typically non-uniform. The best estimate of risk in the pre-rituximab era is the large, retrospective International Extranodal Lymphoma Study Group (IELSG) series of 381 patients with PTL. The 5- and 10-year actuarial risks of 19% and 34% are substantially greater than nodal DLBCL. As is the case in nodal DLBCL, CNS parenchymal relapse is more frequent than leptomeningeal; in the IELSG series 64% of CNS relapses involved brain parenchyma and 61% were isolated to the CNS, consistent with other series.
Treatment and outcomes

Systemic therapy (chemotherapy and rituximab)

Historically the outcome of PTL has been inferior to nodal DLBCL with no plateau in PFS and OS curves in retrospective studies (Table 2).4,5,9,11,12,33,64 As previously outlined, orchiectomy alone is indicated both for diagnostic and therapeutic purposes. However, outcomes of patients treated with orchiectomy and/or radiation alone are poor.7,65 Many chemotherapy strategies have been used; the rarity of the tumor has prevented the conduct of prospective randomised comparisons between chemotherapy strategies. Thus the available data are drawn from either non-randomised phase II studies or retrospective series.

The outcome of patients with PTL has gradually been improving. A retrospective MD Anderson Cancer Centre (MDACC) series showed incremental improvements in PFS and OS over time with refinement of treatment strategy (Figure 1).11 This trend is mirrored by the SEER registry in which analysis by ‘treatment era’ (defined by 5-year intervals) showed incremental improvements in OS, with the median OS 1.8 years for patients diagnosed in 1980-1985 but median not yet reached for those diagnosed 20 years later (5-year disease-specific survival 62.4%).7 Based on nodal DLBCL, CHOP at 3-weekly intervals was the most widely used regimen for PTL prior to the introduction of rituximab, achieving 5-year OS of 30-52%.11,66 Attempts to improve on this with the addition of bleomycin,10,67 increasing dose density10 or use of more intensive strategies such as Hyper-CVAD64 have been limited to small retrospective series with no appreciable improvements demonstrated. Also the deliverability of such dose-intensive strategies is limited, given the demographic features of the majority of patients with PTL.

The impact of rituximab on outcomes in PTL remains unclear, but appears less definitive than in nodal DLBCL. A retrospective analysis from the British Columbia
Cancer Agency (BCCA) of 88 patients with PTL treated with CHOP either with \( n=48 \) or without \( n=40 \) rituximab found after a median follow up of 60 months, there was no difference in 5-year rates of progression or OS.\(^6^8\) However, the RCHOP group contained more patients with adverse prognostic factors and multivariate analysis found use of rituximab to be a favourable prognostic factor for both TTP \( (P=0.006) \) and OS \( (P=0.009) \). Rituximab had no evident impact on CNS relapse in this study. The improvement in outcome was also noted in the MDACC retrospective series, in which the addition of rituximab to anthracycline-based chemotherapy resulted in significant improvements in 5-year OS \( (56\% \text{ vs } 87\%, \; P=0.019) \) despite no such improvement in PFS \( (52\% \text{ vs } 59\%, \; P=0.138) \), suggesting improved salvage therapies may have been responsible.\(^1^1\)

**CNS prophylaxis**

The apparent lack of impact of rituximab on CNS relapse risk in the BCCA series is unsurprising, given that CSF levels of rituximab are only 0.1\% that of serum levels\(^6^9\) and a recent meta-analysis suggested only minor reduction in CNS relapse in nodal DLBCL.\(^6^2\) In an attempt to ameliorate the high risk of CNS relapse, IT chemotherapy has been used in many retrospective series.\(^3^-^5,^1^1\) However, given the non-uniform application inherent to retrospective case series, drawing firm conclusions about the efficacy of IT methotrexate is difficult. Of the prospective clinical trials outlined below, two used IT chemotherapy alone and reported CNS relapse rates of 6\%\(^5^9,^7^0\) whilst one used both IT and systemic methotrexate, reporting no CNS relapses among 38 patients.\(^7^1\) In all three studies, the crude incidence of CNS relapse was significantly less than historic controls. Given that many relapses are parenchymal rather than leptomeningeal and the penetration into brain parenchyma and distribution around the neuroaxis of methotrexate injected by lumbar puncture is limited\(^7^2\), there is conceptual appeal to the use of high-dose systemic methotrexate for CNS prophylaxis, as it achieves higher drug levels in brain parenchyma.\(^7^3\) Furthermore in
nodal DLBCL the addition of high-dose systemic methotrexate appears to lower CNS relapse risk. The merits of this approach are reflected by treatment guidelines, and the ongoing IELSG-30 prospective protocol incorporates IV methotrexate (1.5g/m²) in addition to IT liposomal cytarabine. (ClinicalTrials.gov identifier: NCT00945724) Dose reductions should be made for patients with renal impairment and the elderly.

Prospective clinical trials in PTL

Few prospective clinical trials in PTL have been conducted (Table 3). The GOELAMS study used three cycles of VCAP (vindesine, cyclophosphamide, doxorubicin and prednisolone) in patients aged 18-60, or VCEP-Bleo (vindesine, cyclophosphamide, epirubicin, prednisolone and bleomycin) in patients aged 61-75. All patients received radiotherapy (RT) to inguinal, iliac, and para-aortic lymph nodes, whole brain RT and IT prophylaxis. With a median follow up of 73.5 months, the DFS and OS were 70% and 65% respectively, with one CNS relapse (6%).

Aviles et al conducted a single-arm, open-label study using 6 cycles of R-CEOP (rituximab, cyclophosphamide 1500mg/m², epirubicin 120mg/m², vincristine and prednisolone) dosed at 14-day intervals, with patients achieving complete response (CR) receiving 30 Gy RT to the scrotum and contralateral testis. CNS prophylaxis comprised four cycles of high-dose intravenous methotrexate (6g/m²) with leucovorin rescue. Of the 38 patients enrolled, 86% achieved CR and the actuarial 5-year EFS and OS were 70% and 66%, respectively. No CNS relapses were reported in this study.

Finally, the IELSG-10 study was a phase-II multicentre study which evaluated RCHOP delivered at three weekly intervals followed by locoregional irradiation. Fifty-three patients with stage I/II DLBCL type PTL were included (patients with bilateral
testicular involvement were considered stage I); 98% achieved CR and after median follow up of 65 months, the 5-year PFS and OS were 74% and 85%, respectively. The 5-year actuarial incidence of CNS relapse was 6%. The excellent results in this study established RCHOP Q21 with IT methotrexate and locoregional radiation as the reference treatment for patients with limited stage PTL, including those with bilateral testicular involvement. Thus we regard RCHOP Q21 with IT methotrexate with scrotal RT after completion of chemotherapy as the recommended treatment for these patients also.

There are limited data regarding the use of abbreviated chemotherapy in PTL. An early report from BCCA treated 15 patients with stage I/II PTL with either three cycles of CHOP or a six-week regimen modified from MACOP-B termed ACOB (cyclophosphamide, doxorubicin, vincristine, bleomycin and prednisolone). They reported a remarkable 4-year PFS and OS of 93%, with no CNS relapses. This result should be taken in the context of the small numbers and has not been replicated. Conversely, data exists suggesting abbreviated chemotherapy compromises outcomes. Seymour et al in a retrospective series of 25 patients reported a shorter median time to treatment failure (1.2 v 8.4 years, \( P=0.03 \)) in patients who received <6 cycles of chemotherapy. Supporting this, the IELSG retrospective series, patients receiving \( \geq 6 \) cycles of chemotherapy had a better long-term outcome than those treated for a shorter period (10-year OS, 44% v 19%; \( P=0.03 \)).

**Radiotherapy**

Early studies of PTL included patients treated with orchiectomy and locoregional RT only, and were associated with uniformly high rates of relapse. The use of radiation alone for PTL would only be considered in patients who refuse, or are unfit for, systemic chemotherapy. Recent efforts to improve the management of PTL have focused on prophylactic therapy for sanctuary sites such as the CNS and contralateral testis.
Testicular irradiation

Patients treated by orchiectomy and anthracycline-based chemotherapy have an appreciable risk of relapse in the contralateral testis. In the IELSG series, testicular relapse was a component of 43/195 (45%) treatment failures, with 15-year actuarial incidence of contralateral testicular relapse 42% in the absence of scrotal irradiation. Prophylactic scrotal radiation was associated with significant reduction in the incidence of testicular relapse (P=0.011) and improvement in both 5-year PFS (70 v 36%, P=0.00001) and OS (66 v 38%, P=0.00001). Other studies have also suggested the addition of adjuvant RT improves survival, although it is uncertain to what extent this reflects patient selection for adjuvant irradiation.

In the IELSG-10 study, adjuvant testicular radiation (median 30, range 24-40 Gy) was used routinely with no testicular relapses observed. RT should thus be considered mandatory in stage I-II disease. Adjuvant scrotal radiation may have more value in limited stage disease, as in the IELSG series, testicular relapse occurred in 28% of treatment failures for stage-I and was sole initial site of failure in 10%, whereas for patients with initial stage III-IV, testicular relapse occurred in 16% of failures but was sole site of failure in only 2%. Nonetheless given the relatively low morbidity of this treatment, it should be considered standard care for all patients having potentially curative chemotherapy. Despite this, the SEER data showed only 30-40% of patients received RT, without apparent improvement over time.

Nodal Irradiation

In Stage I PTL there is no role for adjuvant irradiation to uninvolved para-aortic or pelvic nodes. In stage II PTL, the benefit of RT to involved nodes in patients treated with RCHOP is uncertain. For example, in the IELSG-10 study, of 13 stage II patients, nine received nodal RT and the single relapse occurred in one of these patients, within the radiotherapy field. The four patients not treated with RT were all
in remission at the time of reporting – however the small number and non-randomized allocation of RT means that this question remains open. There are limited data to suggest benefit of regional nodal irradiation in stage III/IV disease, and as such this is not recommended.

Toxicity

Testicular irradiation causes acute cutaneous toxicity, which may last several weeks. The major long-term toxicities of scrotal irradiation are dose dependent and include infertility and hypogonadism. The acute toxicities of abdominal and pelvic irradiation include lethargy, nausea, disturbance of bowel function and cytopenias whilst late toxicity primary consists of increased risk of second primary malignancies.

Management of relapsed disease

The prognosis of patients with PTL who experience relapse is poor. The median survival after relapse is infrequently reported but was <2 months in the Danish series. The narrow gap between reported PFS and OS in most other studies suggests that this estimate is probably accurate. The likely explanations for this dismal outlook are the high frequency of CNS relapse and the average patient being elderly, with comorbidities precluding aggressive salvage strategies and/or stem cell transplantation.

It is difficult to make robust evidence based recommendations for the optimal approach for patients with relapsed PTL. Four of 18 (22%) patients with relapsed lymphoma in the MDACC series underwent autologous stem cell transplantation, but their outcomes were not reported. Interestingly, of the nine patients with relapsed lymphoma in the IELSG-10 study, four (44%) remained alive in second remission after unspecified salvage therapy, perhaps suggesting that prevention of CNS relapse may result in greater potential to salvage patients in the future.
Future Directions

New insights into the distinctive pathophysiology of PTL may facilitate novel therapeutic strategies. There is evidence that both lenalidomide and the inhibitor of Bruton’s tyrosine kinase ibrutinib are active in ABC-type DLBCL. Several groups are exploring RCHOP in combination with lenalidomide (R²CHOP) and ibrutinib in nodal DLBCL. The data available so far suggests these combinations to be well tolerated and effective, although to our knowledge patients with PTL are not specifically being studied. The presence of lenalidomide has been demonstrated in the semen of male patients, and a case of multiple myeloma invading the testis was successfully treated using lenalidomide and dexamethasone, suggesting penetration of the blood-testis barrier. Data regarding the CNS penetration of lenalidomide are lacking, however two phase I studies in patients with refractory CNS tumors have demonstrated low toxicity but poor response rates. Pomalidomide, another immunomodulatory drug has demonstrated both synergistic enhancement of antigen-dependent cellular cytotoxicity with rituximab and excellent CNS penetration and impressive activity against a Raji xenograft model of PCNSL. Thus, given the promising activity of R²CHOP, combining pomalidomide with rituximab and/or chemotherapy in patients with PTL may have appeal.

If CXCR4 is found to have a pathophysiological role in mediating extranodal relapse, development of the CXCR4 inhibitor plerixafor (currently licensed for peripheral blood stem cell mobilization) may prove attractive as a therapeutic adjuvant to chemotherapy. Finally, the overactivation of NF-κB and STAT3 signalling pathways may be exploited as a target; a small molecule inhibitor of JAK-STAT signalling has shown in vitro activity against ABC DLBCL cell-lines and is synergistic with NF-κB pathway inhibitors. Further improvements in the outcome of patients with PTL are likely to be achieved only by collaborative enrolment of patients into thoughtfully designed, prospective clinical trials.
Conclusion

Significant gains have been made in PTL with the successive addition of RT, anthracycline-based chemotherapy, rituximab and CNS-directed prophylaxis. Although 3-weekly RCHOP with intrathecal methotrexate and locoregional RT is the current international standard of care there is unmet medical need for patients failing this approach. A greater understanding of the pathophysiologic processes underlying the characteristic tropism of PTL has the potential for further improvements in treatment for this rare but aggressive disease.

Disclosures

The authors declare no conflicts of interest.

Contributions

CYC, AW and JFS performed literature review, wrote and approved the manuscript.

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References


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### Tables and Figures

**Adverse prognostic factors for progression free survival in studies of primary testicular lymphoma**

<table>
<thead>
<tr>
<th>Factor</th>
<th>References</th>
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<td>Age &gt;70 years</td>
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<tr>
<td>Advanced stage</td>
<td>7, 11, 12, 64</td>
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<tr>
<td>B symptoms</td>
<td>11, 12, 93</td>
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<tr>
<td>ECOG performance status &gt;1</td>
<td>12, 93</td>
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<tr>
<td>&gt;1 extranodal site</td>
<td>68</td>
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<tr>
<td>Involvement of extranodal sites other than testis</td>
<td>12, 68</td>
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<tr>
<td>Tumor diameter &gt;10cm</td>
<td>12</td>
</tr>
<tr>
<td>Raised serum LDH</td>
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<tr>
<td>Raised serum β2-microglobulin</td>
<td>11, 12</td>
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<tr>
<td>Hypoalbuminemia</td>
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<tr>
<td>Involvement of the left testis</td>
<td>7, 93, 94</td>
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Table 1. Prognostic factors for PFS identified in primary testicular lymphoma. Abbreviations: ECOG = Eastern Cooperative Group; LDH = lactate dehydrogenase
<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>n</th>
<th>Median age, years (range)</th>
<th>DLBCL</th>
<th>CNS prophylaxis</th>
<th>Adverse prognostic factors</th>
<th>CNS relapse</th>
<th>Outcome</th>
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<tr>
<td>Moller</td>
<td>1994</td>
<td>39</td>
<td>stage I/II 73 (10-86)</td>
<td>NR</td>
<td>-</td>
<td>stage III/IV poor ECOG PS LDH B sx</td>
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<td>5-yr OS 17%</td>
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<td>Fonseca</td>
<td>2000</td>
<td>62</td>
<td>68</td>
<td>76%</td>
<td>IT MTX 4 (6%)</td>
<td>stage III/IV ECOG PS &gt;1 Bsx LDH</td>
<td>13 (32%)</td>
<td>median DFS/OS 2.7y</td>
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<tr>
<td>Seymour</td>
<td>2001</td>
<td>25</td>
<td>69</td>
<td>100%</td>
<td>IT MTX 2 (3%)</td>
<td>albumin &lt;35 g/L</td>
<td>0/2 IT</td>
<td>3-yr EFS 23%</td>
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<td>Zucca</td>
<td>2003</td>
<td>373</td>
<td>66 (19-91)</td>
<td>100%</td>
<td>IT chemo 73 (20%)</td>
<td>stage III/IV ECOG PS &gt;1 Bsx LDH EN sites other than testis CNS involvement b2m bulk &gt;10 cm IP I high no anthracycline &lt;4 cycles IT chemo no proph scrotal RT</td>
<td>19% at 5 yrs 34% at 10 yrs</td>
<td>5-yr PFS 48% 5-yr OS 48%</td>
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<tr>
<td>Park</td>
<td>2007</td>
<td>45</td>
<td>59 (40-81)</td>
<td>91%</td>
<td>IT MTX 6 (13%)</td>
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<td>2/6 IT</td>
<td>mPFS 1.3y mOS 2.8y</td>
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<td>68</td>
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<td>Unknown</td>
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Table 2. Selected retrospective studies of patients with testicular lymphoma containing ≥10 patients. Abbreviations: S: surgery; RT = radiotherapy; C = chemotherapy (various); IT = intrathecal; MTX = methotrexate; LDH = serum lactate dehydrogenase; Dx = diagnosis; IPI = International Prognostic Index; R-CEOP: rituximab, cyclophosphamide, epirubicin, vincristine, prednisolone. Abbreviations: DLBCL = diffuse large B-cell lymphoma, RCEOP = rituximab, cyclophosphamide, epirubicin, vincristine, prednisolone; CEOP-B = cyclophosphamide, epirubicin, vincristine, prednisolone, bleomycin; VCAP = vindesine, doxorubicin, cyclophosphamide, prednisolone; VEGP-bleo = vindesine, epirubicin, cyclophosphamide, prednisolone, bleomycin; EFS = event-free survival; DSS = disease specific survival; RFS = relapse free survival; PFS = progression free survival; OS = overall survival; ECOG PS = Eastern Cooperative Oncology Group performance status; NR = not reported *histological subtype based on older classification systems; SEER: Surveillance, Epidemiology and End Results database; MDACC = MD Anderson Cancer Centre; IELSG = International Extranodal Lymphoma Study Group.

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
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<th>LDH</th>
<th>IPI</th>
<th>Treatment</th>
<th>Stage</th>
<th>Rx other than surgery and RT</th>
<th>OS 5yr</th>
<th>Rx other than surgery and RT</th>
<th>IT%</th>
<th>Rx other than surgery and RT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gundrum 2</td>
<td>1995, 2010</td>
<td>75</td>
<td>62 (22-82)</td>
<td>100%</td>
<td>IT chemo 30 (40%)</td>
<td>stage III/IV</td>
<td>stage III/IV</td>
<td>RCHOP 87%</td>
<td>stage III/IV</td>
<td>RCHOP 87%</td>
<td>RCHOP 87%</td>
</tr>
<tr>
<td>MDACC Tourotoglou 5 and Mazloom 11</td>
<td>1995, 2010</td>
<td>75</td>
<td>62 (22-82)</td>
<td>100%</td>
<td>IT chemo 30 (40%)</td>
<td>stage III/IV</td>
<td>stage III/IV</td>
<td>RCHOP 87%</td>
<td>stage III/IV</td>
<td>RCHOP 87%</td>
<td>RCHOP 87%</td>
</tr>
</tbody>
</table>

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Table 3. Prospective studies in primary testicular lymphoma. Abbreviations: DLBCL = diffuse large B-cell lymphoma, RCEOP* = rituximab, cyclophosphamide (1500mg/m²), epirubicin (120mg/m²), vincristine, prednisolone; CEOP-B = cyclophosphamide, epirubicin, vincristine, prednisolone, bleomycin; VCAP = vindesine, doxorubicin, cyclophosphamide, prednisolone; VECP-bleo = vindesine, epirubicin, cyclophosphamide, prednisolone, bleomycin; EFS = event-free survival; PFS = progression free survival; OS = overall survival; MTX = methotrexate; RT = radiotherapy.

<table>
<thead>
<tr>
<th>author</th>
<th>year</th>
<th>n</th>
<th>median age, years (range)</th>
<th>DLBCL</th>
<th>treatment</th>
<th>CNS prophylaxis</th>
<th>prognostic factors</th>
<th>CNS relapse</th>
<th>outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Linassier⁷⁰ (2002)</td>
<td>2002</td>
<td>16</td>
<td>62 (29-73)</td>
<td>100%</td>
<td>18-60: VCAP 61-75: VECP-Bleo regional RT</td>
<td>IT MTX all</td>
<td>NR</td>
<td>1 (6%)</td>
<td>6-yr OS 65%</td>
</tr>
<tr>
<td>Aviles⁵¹ (2009)</td>
<td>2009</td>
<td>38</td>
<td>51.8 (53-70)</td>
<td>100%</td>
<td>R-CEOP14 *</td>
<td>6g/m² MTX IV x 4 Q28</td>
<td>NR</td>
<td>0%</td>
<td>5-yr EFS 70%</td>
</tr>
<tr>
<td>Vitolo⁵⁴ (2011)</td>
<td>2011</td>
<td>56</td>
<td>64 (22-79)</td>
<td>100%</td>
<td>RCHOPO21</td>
<td>IT MTX x 4</td>
<td>NR</td>
<td>6%</td>
<td>5-yr PFS 74%</td>
</tr>
</tbody>
</table>
Figure 1. Overall survival of patients with primary testicular lymphoma treated at MD Anderson Cancer Centre, by chemotherapy strategy. Reproduced with permission from Mazloom et al.11
Figure 2. Time to CNS recurrence in the IELSG retrospective study, demonstrating ongoing risk of late CNS relapses. With permission from Zucca et al.\textsuperscript{12}
Primary testicular lymphoma
Chan Y. Cheah, Andrew Wirth and John F. Seymour