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The management and treatment of primary testicular lymphoma

A B S T R A C T

Primary testicular lymphoma (PTL) is an uncommon extranodal lymphoma, with an aggressive clinical course. The majority of PTL cases are diffuse large B-cell lymphoma (DLBCL), but other histological subtypes have been described. Common clinical presentation is unilateral painless scrotal swelling. PTL has a tendency to disseminate to contralateral testis and extranodal sites, such as the central nervous system (CNS). Orchiectomy is mandatory for diagnosis. The complete staging of disease includes total-body computerized tomography, positron emission tomography, bone marrow biopsy and aspirate, and cytological and flow cytometry analysis of cerebral spinal fluid (CSF). PTL has a poor outcome and several prognostic factors have been identified. Orchiectomy is mandatory as the first therapeutic step. A combined treatment with full-course anthracycline-based chemotherapy (i.e. CHOP) with rituximab and CNS prophylaxis with intrathecal methotrexate and contralateral testicular radiotherapy should be considered the standard of care at limited stage. The therapy of advanced stage is the same as that of nodal DLBCL. These patients have a very high risk of CNS recurrence and the addition of systemic CNS prophylaxis with intravenous methotrexate may be the best treatment option. Relapsed PTL has a dismal prognosis. High-dose chemotherapy and autologous stem cell transplantation should be considered when possible, while novel drugs should be considered in elderly patients.

Learning goals
At the conclusion of this activity, participants should:
- understand the histological, biological and clinical features of primary testicular lymphoma (PTL);
- have learnt the standard treatment of PTL;
- be able to discuss issues that remain open concerning the treatment of PTL: CNS prophylaxis, nodal radiotherapy, relapsed patients.

Introduction
Primary testicular lymphoma (PTL) is an uncommon testicular malignancy (3-9%) and represents 1-2% of all non-Hodgkin lymphomas. PTL can be considered a disease of the elderly with a median age at diagnosis of 66-68 years; it represents the most frequent testicular malignancy in men aged over 60 years. At the moment, no specific risk factors for PTL have been clearly defined. Some anecdotal reports suggest an association with testicular traumas, cryptorchidism, chronic infections or filariasis. Other studies raise the possibility of HIV-infection as a predisposing cause. HIV-infection is typically associated with a higher risk of aggressive lymphoma and, in particular, of extranodal disease, such as testicular lymphoma. But in HIV-negative patients, who make up the majority of PTL cases, the causes remain largely unknown.

Histological and biological features
Histologically, PTL could be considered a homogeneous group: between 80% and 90% are diffuse large B-cell lymphomas (DLBCL), even if a variety of other histological subtypes have been described, including plasmablastic and Burkitt lymphoma, mantle cell and rarer low-grade follicular cell and T-cell lymphomas. Plasmacytoid differentiation, shown in some cases of PTL, with somatic hypermutation of immunoglobulin heavy-chain genes (IgH) and the presence of a high T-cell infiltrate, raises the possibility of antigen-driven stimulation, as well as in extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue (EMZL) or MALT. Indeed, other characteristics commonly observed in PTL that may suggest an antigen-driven mechanism in their pathogenesis are a higher frequency of the loss of HLA-DR and DQ expression, associated with homozygous deletions of the corresponding genes, and the frequency of HLA-DRB1-15 and HLA-DRB1-12. PTL has a high tendency to disseminate to contralateral testis and central nervous system (CNS), but also to other extranodal sites, such as lung, pleura, skin, soft tissues and Waldeyer’s ring. The results of some studies suggest that an altered expression of cell surface adhesion molecules may be responsible for this phenomenon, while the relatively high rate of Waldeyer’s ring involvement could be associated with the shared embryonic origin from the endoderm. Another putative biological mechanism studied to explain the
propensity of PTL to disseminate to immune privileged sites, in particular CNS and contralateral testis, is that lymphomas grow under the selective pressure of the immune system and so the most aggressive cells may develop an immune escape phenotype by a downregulation of immunoregulatory genes in both lymphoma and microenvironment cells.11,15,16

Cell of origin, determined by immunohistochemistry and DNA microarray, shows an activated B-cell (ABC) pattern in 60-96%15,17,18-19 that partially explains the poor prognosis of PTL. Despite this poor prognosis, the frequency of ‘double hit’ lymphomas with both MYC and Bcl-2 rearrangements, typically associated with an aggressive course in nodal disease, is low in PTL.20 On the other hand, mutations of MYD88, recently reported to be associated with ABC-type in DLBCL, were found in more than 70% of PTL compared to less than 20% in patients with nodal DLBCL.21 These data suggest the presence of a different pathology and biological pattern between primary testicular and nodal DLBCL.

Clinical features

Typically PTL begins as a painless testicular mass or swelling, rarely with a sharp scrotal pain. On physical examination there is usually a unilateral non-tender firm mass. An associated hydrocele can be observed in 40% of cases. Most patients present a limited stage disease at diagnosis; synchronous bilateral disease occurs in approximately 10% of patients, but up to 35% of cases may have contralateral testis involvement during the course of their disease.12,22 Indeed, monoclonal lymphoid cells have been shown in contralateral tests even in PTL patients without clinical evidence of disease involvement, suggesting that bilateral testicular involvement is more common than expected.10

Systemic B symptoms are usually present in advanced stage disease and present at diagnosis in 25-40% of patients, while they are absent in the majority of localized stage.1

Lymphoma cells can infiltrate epididymis, scrotal skin, spermatic cord or retroperitoneal lymph nodes, but above all, PTL cells have a propensity to diffuse to extranodal sites, such as lung, pleura, skin (0-35%), soft tissues, and Waldeyer’s ring (5%).1 Involvement of these extranodal sites is rare at diagnosis, but occurs frequently during the course of the disease. Moreover, CNS relapses are definitely more common than in other aggressive nodal lymphomas; they have been reported in up to 30% of PTL patients within 1-2 years of diagnosis and warrants routine CSF sampling, even in asymptomatic patients who may often have a subclinical CNS invasion.23 However, occasionally, late relapses have also been described, sometimes as isolated CNS relapse.24-27 The CNS relapse may present as leptomeningeal involvement with positive CSF cytology or parenchymal brain lesions.

Diagnosis and staging

When a PTL is suspected, inguinal orchietomy has historically been considered the gold standard for diagnosis. To study an unknown lesion in the testis, ultrasound-guided core needle biopsy may have a role;28 however, when diagnosis of PTL is made, orchietomy should always be performed. Indeed, orchietomy not only provides a better histological definition (important to define the best therapeutic strategy), but it also removes the main tumor mass, allowing a good local tumor control.29,30

Ultrasoundography (US) may show a focal hypoechoic mass with or without a clear capsule or diffuse hypoechoic enlargement of the entire testis with hypervasculature.31 These findings are not specific for malignant lymphoma. However, hypoechoic striations radiating outward from the center of the testis may be more specific for lymphomatous involvement of the testes because they seem to be due to vascular and lymphatic infiltration by lymphoma cells.32

The complete staging of disease is the same for PTL as for other NHL. At first it includes a physical examination, hematologic and biochemical exams, total-body computerized tomography (CT), and bone marrow biopsy. Positron emission tomography (PET) scan is useful in the initial staging of aggressive lymphomas, but has not been specifically investigated in PTL.33 PET scan appears sensitive and specific for detecting suspected recurrent disease.34-37

Because of the high tendency of PTL to disseminate to particular extranodal sites, some specific diagnostic procedures are required for a complete staging of disease. The presence of pulmonary mass, pleural effusion, skin or Waldeyer’s ring lesions needs a histological definition.

An accurate examination of the skin is recommended because the association with cutaneous “leg-type DLBCL” and testicular DLBCL have been described,38 and on the other hand, skin is a frequent site of extranodal relapse of PTL, in particular in HIV-positive patients.

In order to exclude CNS involvement, diagnostic lumbar puncture with cytological and flow cytometric analysis on CSF is mandatory. Benevolo et al.,39 in their prospective study, compared diagnostic and prognostic value of conventional cytological (CC) examination and flow cytometry (FCM) of base-line sample of cerebrospinal fluid in 174 patients with aggressive NHL. The results show a significantly higher risk of CNS progression in patients with FCM-positive and CC-negative patients, compared to patients who are both FCM- and CC-negative. So FCM is a highly sensitive examination to identify CNS involvement, and it should be recommended in all NHL patients at high-risk of CNS relapse, such as testicular lymphoma. HIV serology should be checked in all cases, as testicular presentations are more frequent in HIV-positive patients.

Ann Arbor system is the standard staging system in PTL, as for other lymphomas. Mono or bilateral involvement of the testes corresponds to stage IE, which represents 50-60% of disease at diagnosis. Stage IIE (20-30% of cases at diagnosis) is defined as the stage IE disease associated with concomitant loco-regional (retroperitoneal and/or iliac) lymph node involvement. Stage III-IV represents mono or bilateral testicular involvement with distant pathological lymph-nodes and/or extranodal sites, and are virtually undistinguishable from a stage III-IV nodal lymphoma.35
Prognostic factors

Historically, PTLs represented a very aggressive disease, with a dismal prognosis. Several prognostic factors have been identified in many different studies on PTL patients: age (>70 years), advanced stage, the presence of B symptoms, performance status, more than one extranodal site involvement, tumor size over 10 cm, high LDH serum level, high beta2-microglobulin serum level, hypoalbuminemia. In the largest retrospective study on 373 PTL patients, performed by the International Extranodal Lymphoma Study Group (IELSG), clinical features significantly associated with a longer overall survival in multivariate analysis were: low/low-intermediate International Prognostic Index (IPI) score, absence of B symptoms, treatment with an anthracycline-containing chemotherapy regimen and prophylactic scrotal radiotherapy. However, at diagnosis, the largest proportion of patients present a localized stage (I-IIE) with typically a low to low-intermediate IPI score, limiting its prognostic value. Some reports have identified a worse prognosis in patients with an involvement of the left testis at diagnosis. Since over 90% of PTL are diffuse large B-cell lymphoma, the impact of different histology on outcome is difficult to determine. In a study on 36 PTL patients, Kuper-Hommel et al. identified patients with a “pure DLBCL” and cases with “DLBCL with mucosa-associated lymphoid tissue (eMZL) features” with the latter pattern associated with more favorable clinical characteristics and with a better outcome. Some other studies also underline pathological features as prognostic factors, such as high histological grade, vascular invasion, and degree of sclerosis.

Treatment

Treatment of limited disease (stage I-II)

Chemotherapy

Orchiectomy remains a mandatory step in the management of PTL. As mentioned above, orchiectomy is indicated both for diagnostic and therapeutic purposes. Orchiectomy provides adequate tissue for histological diagnosis but it also removes a sanctuary site that is potentially resistant to chemotherapy because the blood-testis barrier makes the testis inaccessible to chemotherapy. However, orchiectomy alone should not be considered as single therapy even in patients with stage I disease, because the majority of patients treated with surgery alone relapsed in distant sites within two years. The addition of radiotherapy (RT) alone to paraaortic and iliac nodes after orchiectomy was used in the past to reduce the relapse rate. However, this strategy failed to improve outcome, with more than 70% of patients experiencing relapses in distant sites. Both these experiences suggest that, in PTL, microscopic advanced disease is present at diagnosis making chemotherapy necessary.

The outcome of PTL has been historically dismal with a 5-year survival ranging from 16% to 50%, and a median survival of only 12–24 months was reported with no plateau in progression-free survival (PFS) or overall survival (OS) curves according to the different series of patients (Table 1). The IELSG has reported the largest series of PTL patients so far (373 patients). This retrospective milestone study allowed the key clinical issues of PTL treatment to be clarified: i) the poor outcome due to the high risk of systemic and extranodal relapse; ii) the high risk of contralateral testicular failure; and iii) the high risk of CNS recurrence. In this series, the outcome of patients was extremely poor, with an actuarial 5-year and 10-year OS of 48% and 27%, respectively, and an actuarial 5-year and 10-year PFS of 48% and 33%, respectively, with no evidence of plateau (Figure 1). Although it was not possible to determine the most effective chemotherapy regimen due to the limited number of patients in the reported series and the lack of randomized trials, doxorubicin-containing regimens have been associated with improved relapse-free survival compared with orchiectomy +/- RT. In the IELSG retrospective series, chemotherapy with anthracycline-containing regimens significantly improved the outcome in all patients.
(5-year PFS 55% vs. 35%, P=0.0005; 5-year OS 52% vs. 39%, P=0.02) and the benefit was confirmed also in stage I to II patients. Although other regimens have been reported in small series with increased dose intensity or more intensive strategies such as MACOPB (methotrexate, doxorubicin, cyclophosphamide, vincristine, bleomycin, and prednisone)53 or Hyper-CVAD,54 no clear improvement has been shown over standard CHOP (cyclophosphamide, doxorubicin, vincristine and prednisone), and this remains the standard chemotherapy regimen in PTL. Despite an early favorable report with the use of abbreviated chemotherapy,55 there are well-defined data showing that patients receiving less than 6 courses of chemotherapy have an inferior outcome compared to those who were given a full course of chemotherapy (10-year OS 19% vs. 44% in the IELSG series).2,24

Role of rituximab

Many studies have provided strong evidence of the benefit of adding rituximab to chemotherapy.54,55 As in other DLBCL, the addition of rituximab to CHOP chemotherapy may be useful in PTL, but there is no strong evidence to support this. The most robust evidence of the benefit of rituximab comes from the results of the IELSG10 study.56 IELSG10 was the first phase II prospective multicenter trial in PTL. In this study, 53 patients (median age 64 years) with stage I-II PTL were treated with 6-8 courses of rituximab added to CHOP every 21 days (R-CHOP21) and complete prophylaxis with 4 doses of intrathecal methotrexate (IT-MTX) and RT to the contralateral testis (30 Gy) for all patients +/- RT to regional lymph nodes (30-36 Gy) for stage II disease. All patients received R-CHOP21, 50 received CNS prophylaxis, and 47 received testicular RT. With a median follow up of 65 months, the results showed an improvement over historical outcome of PTL with 5-year PFS and OS rates of 74% and 85%, respectively, no contralateral testis relapses, and a 5-year cumulative incidence of CNS relapse of 6% (Figure 2).

The addition of rituximab to CHOP chemotherapy may have improved the outcome by preventing relapses with better control of microscopic systemic disease that might have been present since the onset of the disease. The benefit of the addition of rituximab in the treatment of PTL was questioned by the SEER population-based retrospective study which showed no difference in the outcome of patients with PTL treated before and after the rituximab era, using the year 2000 as the cut-off point.40 However, the lack of information regarding treatment delivered and the proportion of patients who actually received rituximab-containing chemotherapy regimens has limited the conclusions of this retrospective study. Unlike this study, the MDACC retrospective study showed that the addition of rituximab to anthracycline-containing regimens improved 5-year OS (56% vs. 87%; P=0.019).12 Indeed, the improvement in the outcome observed in the IELSG10 study could have derived not only from the addition of rituximab, but from the whole treatment package that includes contralateral testis and CNS prophylaxis. Table 2 summarizes the few trials conducted with rituximab-containing chemotherapies.

Testicular radiotherapy

Contralateral testicular relapse occurs in 5-35% of the patients.24 In the retrospective IELSG study, contralateral testicular relapses were 15% at three years and 42% at 15 years in patients not receiving prophylactic testicular RT, and the addition of RT to the contralateral testis prevented testicular relapses, which were reduced to 8% (Figure 1B).24 The positive effect of prophylactic RT to the contralateral testis in this trial further supports the inclusion of this strategy into international clinical recommendations for PTL. RT doses are in the range of 25-30 Gy, and below

Table 1. Selected retrospective and prospective studies of PTL containing more than 10 patients in the pre-rituximab era.

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>N pt</th>
<th>Type of study</th>
<th>Therapy</th>
<th>Pre-Rituximab Trial</th>
<th>CNS prophylaxis</th>
<th>Radiotherapy Testis/Nodal</th>
<th>Outcome</th>
<th>CNS relapse</th>
</tr>
</thead>
<tbody>
<tr>
<td>Moller5</td>
<td>1994</td>
<td>39</td>
<td>retrospective</td>
<td>orchiectomy +/- CHT</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>5yr OS 17%</td>
<td>NR</td>
</tr>
<tr>
<td>Fonseca46</td>
<td>2000</td>
<td>62</td>
<td>retrospective</td>
<td>orchiectomy: 97% + CHT: 37% + RT: 45% + both CHT and RT: 16%</td>
<td>IT MTX 4 (6%)</td>
<td>5 (8%)</td>
<td>23 (37%)</td>
<td>median DFS/OS 2.7 yr</td>
<td>13 (32%)</td>
</tr>
<tr>
<td>Seymour2</td>
<td>2001</td>
<td>25</td>
<td>retrospective</td>
<td>orchiectomy alone 4% + CHT: 52% + RT: 24% + both CHT and RT: 20%</td>
<td>IT MTX 2 (3%)</td>
<td>6 (24%)</td>
<td>8 (32%)</td>
<td>3yr EFS 23%</td>
<td>10yr OS 32%</td>
</tr>
<tr>
<td>Linassier55</td>
<td>2002</td>
<td>16</td>
<td>prospective</td>
<td>3 cycles of anthracycline based CHT</td>
<td>IT MTX + brain RT 100%</td>
<td>0</td>
<td>100%</td>
<td>6yr DFS 70%</td>
<td>6yr OS 65%</td>
</tr>
<tr>
<td>Zucca48</td>
<td>2003</td>
<td>373</td>
<td>retrospective</td>
<td>orchiectomy alone 11% + CHT: 36% + RT: 14% + both CHT and RT: 39%</td>
<td>IT CHT 73 (20%)</td>
<td>133 (36%)</td>
<td>92 (25%)</td>
<td>5yr PFS 48%</td>
<td>10yr OS 33%</td>
</tr>
</tbody>
</table>

Selected retrospective/prospective studies in primary testicular lymphomas before rituximab and in rituximab era. NR: not reported; CHT: chemotherapy; RT: radiotherapy; IT: intrathecal; MTX: methotrexate; OS: overall survival; PFS: progression-free survival; EFS: event-free survival; DFS: disease-free survival; R-CHOP: rituximab, cyclophosphamide, vincristine, prednisone; R-CEOP: rituximab, cyclophosphamide, epirubicin, vincristine, prednisone.
this threshold appear to be less effective. RT should be fractionated to minimize acute scrotal skin morbidity. Such treatment is associated with a moderate risk of hypogonadism; screening of testosterone levels and replacement therapy should be considered.

Nodal radiotherapy

Radiation therapy has been used as prophylactic therapy to prevent relapse in the regional lymph-nodes in stage I disease or to treat retroperitoneal lymphadenopathies in patients with stage IIIE disease. Involved field radiation dose in patients with stage II disease depends on the response to primary chemotherapy: 30-36 Gy for patients who achieved complete remission and 36-45 Gy for patients who did not.2,24 However, the lack of well conducted trials makes it difficult to assess the role of RT in this setting. In the IELSG10 study, 9 of 13 stage II patients actually received retroperitoneal lymph node RT. Only one of 13 patients relapsed in both extranodal and nodal sites involving pleura and retroperitoneal lymph nodes within the RT field. On the contrary, the 4 patients who did not receive RT did not experience relapse.56 Indeed, the role of RT after R-CHOP is still controversial in nodal DLBCL.56,59 Recent non-randomized data in nodal DLBCL suggest that PET can guide the use of consolidation RT after rituximab-chemotherapy and in PET-negative CR patients consolidation RT can be omitted without compromising outcome.60 The indication for radiation therapy as single therapy after orchietomy should be kept only for unfit patients with clinical contraindications to systemic treatment.

Central nervous system prophylaxis

The high risk of CNS recurrence is a concern in the management of PTL. In the IELSG retrospective series in 373 patients, the actuarial 5-year and 10-year risk of CNS relapse was 20% and 35%, respectively (Figure 1C).24 With the aim of reducing CNS relapse, intrathecal (IT) chemotherapy has been introduced in many retrospective studies (Table 2).2,3,3,26,24,41,49-50,53 In the prospective IELSG10 study that used IT prophylaxis with 4 doses of methotrexate, the cumulative incidence of CNS relapse at five years was only 6% (Figure 2D).56 However, it is difficult to ascribe these results only to the introduction of CNS prophylaxis because also the addition of rituximab may have played a role. Indeed, there is discordant published evidence on the role of rituximab in preventing CNS relapses in DLBCL.61-63 Recently, Guirguis et al.64 showed that addition of rituximab to CHOP may decrease the incidence of CNS relapse in patients with DLBCL compared with historical rates. Since the blood/brain barrier restricts CNS penetration of rituximab, with CSF levels of rituximab only 0.1% of serum levels, the effect of rituximab in reducing CNS relapse rate may reflect its superior effect in controlling systemic disease.65

The best strategy for preventing CNS relapse in PTL is still a matter of debate. The value of prophylactic intrathecal chemotherapy is controversial because of several limitations: the small sample size in different studies, different IT chemotherapy schedules, the fact that IT was not always applied, and the lack of penetration of IT methotrexate into brain parenchyma. Moreover, CNS relapses occur more frequently in brain parenchyma than in meninges, and also in patients who have received intrathecal chemotherapy. All these issues make the use of high-dose systemic methotrexate, that has a good CNS bioavailability, more appealing. Interestingly, Aviles et al.57 reported no CNS relapse in a series of 38 patients using both IT and systemic methotrexate. However, PTL patients are usually elderly and many of them may not tolerate aggressive CNS prophylaxis such as systemic high-dose methotrexate or cytarabine chemotherapy regimens.

Table 2. Selected retrospective and prospective studies of PTL containing more than 10 patients in the post-rituximab era.

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>N pt</th>
<th>Type of study</th>
<th>Therapy</th>
<th>Post-Rituximab Trial</th>
<th>CNS prophylaxis</th>
<th>Radiotherapy Testis/Nodal</th>
<th>Outcome PFS/OS</th>
<th>CNS relapse</th>
</tr>
</thead>
<tbody>
<tr>
<td>Park53</td>
<td>2007</td>
<td>45</td>
<td>retrospective</td>
<td>orchietomy alone:7%</td>
<td>IT MTX</td>
<td>mPFS 16 months</td>
<td>2/6 IT</td>
<td>5yr OS 85%</td>
<td></td>
</tr>
<tr>
<td>Gundrum46</td>
<td>2009</td>
<td>769</td>
<td>retrospective</td>
<td>orchietomy+ RT 36%</td>
<td>IT MTX</td>
<td>mOS 34 months</td>
<td>7/39 no IT</td>
<td>5yr DSS 62%</td>
<td></td>
</tr>
<tr>
<td>Aviles47</td>
<td>2009</td>
<td>38</td>
<td>prospective</td>
<td>R-CEOP14</td>
<td>mPFS 16 months</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mazloom48</td>
<td>2010</td>
<td>75</td>
<td>retrospective</td>
<td>R-CHOP 32%</td>
<td>IT MTX</td>
<td>5yr OS 70%</td>
<td>9% IT 16% no IT</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vitolo49</td>
<td>2011</td>
<td>56</td>
<td>prospective</td>
<td>R-CHOP21</td>
<td>IT MTX</td>
<td>5yr OS 85%</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Selected retrospective/prospective studies in primary testicular lymphomas before rituximab and in rituximab era. NR: not reported; CHT: chemotherapy; RT: radiotherapy; IT: intrathecal; MTX: methotrexate; OS: overall survival; PFS: progression-free survival; DFS: disease-free survival; R-CHOP: rituximab, cyclophosphamide, vincristine, prednisone; R-CEOP: rituximab, cyclophosphamide, epirubicin, vincristine, prednisone.

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Based on these considerations, and with the aim of further reducing the risk of CNS relapse in PTL, IELSG has designed the ongoing IELSG30 phase II study that includes both IT chemotherapy with liposomal cytarabine, that has a more favorable pharmacokinetic profile, and systemic prophylaxis with a lower dose of methotrexate (1.5 g/m²) to spare toxicity in PTL patients, who are usually elderly (Figure 3).

**Treatment of advanced disease (stage III-IV)**

The therapy of advanced stage PTL does not differ from the standard treatment of advanced stage nodal DLBCL; the standard treatment for these patients is R-CHOP given every 21 or 14 days. Unlike nodal DLBCL, two treatment issues should be incorporated in the therapeutic strategy: prophylactic testicular RT and CNS prophylaxis. As in limited stage PTL, testicular RT is mandatory to prevent contralateral testicular recurrence. Testicular involvement remains one of the most important adverse prognostic factors for CNS relapse in advanced stage DLBCL, both in patients treated without or with rituximab. Bhoeme et al. reported the risk for CNS recurrence in 1693 patients with aggressive NHL treated with 6 courses of CHOP or CHOP and found that younger (<60 years) patients with testicular involvement had a 6-year probability of CNS relapse of 22.1% versus 2.1% of those without testicular involvement (P<0.001). Recently, Zhang et al. in a large meta-analysis showed the presence of testicular involvement as risk factor for CNS recurrence in DLBCL patients treated with rituximab-containing regimens. Overall, in advanced stage DLBCL treated in the rituximab era, the risk of CNS recurrence seems to be lower compared to historical data without rituximab. However, many studies of rituximab-treated DLBCL patients underline that testicular involvement remains one of the most powerful adverse prognostic factors for CNS recurrence.

Indeed, advanced stage DLBCL patients present additional risk factors for CNS recurrence such as intermediate- or high risk IPI, elevated LDH level, or 2 or more extranodal sites. The presence of testicular involvement confers to these patients a very high risk for CNS recurrence, and systemic CNS prophylaxis with intravenous...
methotrexate added to RCHOP may be the best treatment option for these patients. Although this has not been confirmed in randomized studies, Abramson et al., in a cohort of 1283 high-risk DLBCL patients, demonstrated that incorporation of intravenous systemic MTX at a dose of 3.5 g/m² into the standard R-CHOP treatment regimen was associated with a lower incidence of CNS recurrence (3%) compared with the published results in high-risk patients who did not receive it, with a 3-year progression-free survival rate approaching 80%.

**Treatment of relapsed or refractory PTL**

The prognosis of relapsed PTL is usually poor. A standard therapeutic option for these patients has not yet been defined in prospective trials. High-dose chemotherapy and autologous stem cell transplantation should be the best treatment strategy in chemosensitive relapse as in nodal DLBCL, but this option is difficult to apply in many PTL patients, who are usually elderly, with poor performance status and multiorgan dysfunction. Therefore, the inclusion of these patients in clinical trials testing novel drugs is advisable.

**Conclusions**

Primary testicular lymphoma is a rare extranodal lymphoma but with an aggressive clinical course. The excellent results reported by the IELSG10 study with a low toxicity pattern provided evidence that a combined treatment...
References


