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Overview

Primary Testicular Lymphoma

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Abstract

Primary testicular non-Hodgkin lymphoma (PTL) comprises around 9% of testicular cancers and 1–2% of all non-Hodgkin lymphomas. Its incidence is increasing and it primarily affects older men, with a median age at presentation of around 67 years. By far the most common histological subtype is diffuse large B-cell lymphoma, accounting for 80–90% of PTLs. Most patients present with a unilateral testicular mass or swelling. Up to 90% of patients have stage I or II disease at diagnosis (60 and 30%, respectively) and bilateral testicular involvement is seen in around 35% of patients. PTL demonstrates a continuous pattern of relapse and propensity for extra-nodal sites such as the central nervous system and contralateral testis. Retrospective data have emphasised the importance of prophylactic radiotherapy in reducing recurrence rates within the contralateral testis. Recent outcome data from the prospective IELSG-10 trial have shown far better progression-free and overall survival than historical outcomes. This supports the use of orchidectomy followed by Rituximab- cyclophosphamide, doxorubicin, vincristine and prednisolone (R-CHOP), central nervous system prophylaxis and prophylactic radiotherapy to the contralateral testis with or without nodal radiotherapy in patients with limited disease. Central nervous system relapse remains a significant issue and future research should focus on identifying the best strategy to reduce its occurrence. Here we discuss the evidence supporting combination chemotherapy and radiotherapy in PTL.

Key words: Chemotherapy; extra-nodal lymphoma; primary testicular lymphoma; radiotherapy

Statement of Search Strategies Used and Sources of Information

Literature including PubMed, Medline and the Cochrane Library was searched for articles from 2000 to 2011 published in the English language. The key words used for the search were 'primary', 'testis', 'testes', 'testicular', 'lymphoma', 'chemotherapy', 'radiotherapy', 'therapy' and 'outcome'. Publications before 2000 were also considered if they were commonly referenced or highly regarded older publications. The search also included the reference list for these articles and selected additional articles and web pages that were judged to be relevant.

Introduction and Clinical Features

Primary testicular non-Hodgkin lymphoma (PTL) is an uncommon entity that has an annual incidence of 0.26 cases per 100,000 person-years. It accounts for 3–9% of testicular cancers and 1–2% of all non-Hodgkin lymphomas. It is, however, the most common testicular malignancy in men aged over 60 years and the incidence is increasing. The median age of presentation in the largest reported series was between 66 and 68 years [1,2].

Most patients with limited stage disease present with a testicular mass or swelling [3]. Bilateral involvement may not be clinically evident at diagnosis, but up to 35% of patients may have involvement of the contralateral testis during the course of their disease [4]. Indeed, monoclonal lymphoid cells in an apparently unaffected contralateral testis may be found, indicating early asynchronous involvement [5]. Scrotal pain or lymphocele may also occur. B symptoms are usually present only in patients with advanced stage disease. Rarely, patients with retroperitoneal

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node enlargement may present with abdominal pain and ascites [6]. PTL has a propensity for multiple other extra-nodal sites, including the central nervous system (CNS), skin, subcutaneous tissue, Waldeyer's ring, lung and pleura [7–11].

No definitive risk factors have been established to date, although anecdotal reports associate the development of PTL with a range of testicular pathologies, including direct trauma, cryptorchidism and filiarasis.

Diagnosis and Staging

Orchidectomy has historically been preferred for diagnosis above fine needle aspiration or testicular biopsy, as it may also confer a therapeutic advantage by gaining better local control of disease and removing a possible sanctuary site for relapse [3]. There may, however, be some role for ultrasound-guided core needle biopsy for evaluating focal indeterminate lesions in the testis [12]. Concerns regarding needle-tract seeding have not been borne out in published studies and therefore biopsy may spare an otherwise normal testis. Staging should be completed as for other high-grade lymphomas, including a full staging computed tomography scan of chest, abdomen and pelvis, and bone marrow aspiration and trephine. Cerebrospinal fluid examination should also be carried out in view of the high risk of CNS relapse. Positron emission tomography and positron emission tomography–computed tomography are now widely used in the initial staging of high-grade lymphoma, but their use in PTL specifically has not been reported.

By definition, most PTL present with stage I and II disease, 50–60% and 20–30%, respectively [1,13]. Stage III or IV disease may be indistinguishable from, and are thus treated as, disseminated nodal diffuse large B-cell lymphoma (DLBCL) with testicular metastases.

Pathology

PTL can be morphologically distinguished from germ cell tumours of the testis with relative ease and immunohistochemistry can help clarify the diagnosis if not immediately apparent. Between 80 and 90% of PTL are diffuse large B-cell type with most displaying an activated B-cell (ABC) phenotype that is CD10−, BCL-6+/− and MUM1+ on immunohistochemistry [4,14,15]. The ABC phenotype is associated with a significantly poorer prognosis than the germinal cell phenotype DLBCL, which is characteristically CD10+/−, BCL-6+ and MUM1−. Although some immunophenotypic heterogeneity has been reported [16], molecular analysis with cDNA microarray and somatic hypermutation analysis of immunoglobulin heavy chain genes has shown that primary testicular DLBCLs have uniform ABC subtype characteristics [17].

Various case series and reports have also shown a variety of other histological subtypes of lymphoma that may also occur in the testes, including mantle cell, plasmablastic and Burkitts lymphoma, as well as rarer T-cell and low-grade follicular types. These tend to arise in specific population groups, for example Burkitts-like lymphoma in HIV-positive men and testicular follicular lymphoma in children and young adolescents. These rare presentations fall outside the scope of this review [18–21].

PTL may have a unique tumour biology [22], in keeping with its ability to relapse not only in the contralateral testis, but also other extra-nodal sites, such as lung, Waldeyer's ring and soft tissues, but also particularly the CNS [10]. The relatively high rate of Waldeyer's ring involvement (5%) is not yet fully understood. It is believed to be associated with a shared embryonic origin given that the testis, nasopharynx and oropharynx are derived from the endoderm. It is postulated that particular patterns of cell surface adhesion molecule expression may lead to lymphoma cells adhering poorly to the extracellular matrix [23]. Recent studies have also hinted that differences in the genomic alterations and gene expression may exist between testicular and nodal DBLCL [24]. Finally, PTL does not clinically display the clear survival plateau of other high-grade lymphomas, owing to the occurrence of late relapses [2,25], as outlined below.

Poor prognostic markers reported include older age, advanced stage, elevated lactate dehydrogenase, B symptoms, high International Prognostic Index (IPI) score and not having surgery or radiotherapy. Curiously, involvement of the left testis also confers a worse prognosis [2,26].

Pattern of Relapse and Prognosis

Multiple studies have shown a continuous pattern of relapse, even up to 10–14 years after initial therapy. Relapse presents predominantly at extra-nodal sites, most commonly in the CNS and contralateral testis [27]. 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 [28,29]. Multidrug resistance through P-glycoprotein expression within the blood–brain and blood–testis barrier significantly reduces the penetration of chemotherapy agents [30]. The risk of relapse in the contralateral testis is reported to be around 15% at 3 years and 42% at 15 years without scrotal irradiation. CNS relapse rates at 5 and 10 years have been reported at 20 and 35%, respectively [1]. The clear propensity for CNS parenchymal involvement is in contrast to nodal DLBCL, where the CNS relapse rate is less than 5% and leptomeningeal disease is more common. Most CNS, and other site, relapses occur within the first 2 years, although later recurrences have been reported [31].

Historically, PTL has been considered to have an extremely poor prognosis compared with its nodal counterpart [32,33]. Even those with stage I disease or favourable IPI have been reported as having a worse outcome than for DLBCL at other sites [1]. However, a multimodal therapeutic approach has led to significant improvements in prognosis. Five-year overall survival increased from 56.3 to 86.6% for patients treated after 2000 compared with those treated between 1977 and 1999 [26]. The improvement in prognosis is significant to the extent that recent studies have shown that as a group, patients with testicular DLBCL have a better overall prognosis earlier in their disease than nodal DLBCL,

although they do remain at a higher risk for late disease-related deaths and the survival advantage disappears at around 6 years owing to late relapses of PTL [2].

The management of testicular lymphoma remains a challenge, particularly because many sufferers are of an age that may reduce their tolerance of aggressive chemotherapy.

Treatment: Chemotherapy

PTL is uncommon and randomised controlled trials have been impossible to establish. Most data come from retrospective case series comparing different modalities of treatment. No standard of care has been ascertained until the recent publication of a phase II prospective study IELSG-10, which has shown encouraging outcomes [34].

Locoregional therapies alone, such as orchidectomy or local radiotherapy, yield very short progression-free survival (PFS) compared with regimens that include systemic chemotherapy [35–37]. Anthracycline-based therapies have shown their efficacy in DLBCL and have similarly formed the basis of treatment in PTL [1,9,34,38]. Chemotherapy without anthracyclines has been shown to produce inferior outcomes [8,11] with patients treated without doxorubicin-based therapies in the 1970s having a 5 year overall survival of around 15% [26].

A range of anthracycline-based regimens have been used with variable efficacy and toxicity. In addition, a range of specific strategies have been used, including CNS prophylaxis with intrathecal chemotherapy and irradiation of contralateral testis in combination with systemic chemotherapy to try and reduce the risk of relapse in PTL and improve PFS. The role of radiotherapy is considered in detail later, but cumulative international experience suggests that the use of a multimodal approach to treatment with systemic chemotherapy combined with locoregional radiotherapy and CNS prophylaxis may improve the outcome for these patients [39].

The first reported prospective trial in which the treatment of PTL was mandated used three cycles of 4 weekly vindesine/cyclophosphamide/adriamycin/prednisone (VCAP) with locoregional irradiation and intrathecal chemotherapy with brain radiation for CNS prophylaxis. All 16 patients achieved a complete remission. Relapse in CNS and contralateral testis occurred in one patient each, with an overall survival of 65% at 74 months [40].

Rituximab – a monoclonal antibody against the CD20 antigen expressed on the vast majority of B-cell lymphomas – has improved the outcome of both high- and low-grade B-cell lymphomas in general and 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 appear to show an early improvement in disease-specific survival after 2000 when rituximab came into common use for B-cell lymphomas. However, this study suffers from several limitations inherent to population-based studies, including not being able to ascertain the proportions of patients who actually received rituximab. Recently published evidence from British Columbia presented at the American Society of Hematology meeting in 2011 also suggests that CNS relapse rates at 5 years are still around 25% – similar to those of the pre-rituximab era – although the use of intrathecal or systemic methotrexate (MTX) was limited in this patient cohort [41]. However, a smaller review of the outcomes of 75 patients with PTL showed a significantly improved prognosis in the post-2000 rituximab era [26]. Given the evidence that rituximab has limited CNS penetration [42], it may not have an effect on reducing late CNS relapse. Longer-term follow-up is needed to clearly establish its role [2].

By far the most common regimen reported in retrospective studies is Rituximab- cyclophosphamide, doxorubicin, vincristine and prednisolone 3 weekly (R-CHOP21) and there are no data to suggest that any alternative regimen offers a better outcome [26,27,33]. A phase II study of R-CEOP14 (rituximab-cyclophosphamide/epirubicin/vincristine/prednisone) in 38 patients with untreated stage I/II PTL showed a relative risk of 85% with 5 year event-free survival and overall survival of 70 and 66%, respectively. Toxicity was mild and the regimen was well tolerated [43]. The use of more aggressive regimens, such as R-CHOP14, R-EPOCH, hyper CVAD and CHOP-B, has also been reported as part of retrospective studies of small numbers of patients, but none has shown a clear advantage over six cycles of Rituximab-cyclophosphamide, doxorubicin, vincristine and prednisolone (R-CHOP) [3,44].

IELSG-10 is the largest international prospective trial examining the efficacy and tolerability of multimodal therapy in PTL [34]. Fifty-three patients were recruited, all of whom received R-CHOP21, 50 received four doses of intrathecal MTX and 47 radiotherapy to the contralateral testis. After a median follow-up of 65 months, the investigators reported 5 year PFS and overall survival rates of 75 and 85%, respectively. There were no cases of relapse in the contralateral testis, but three patients relapsed with CNS disease, indicating the need for further investigation of more effective CNS prophylaxis.

Central Nervous System Prophylaxis

Intrathecal prophylaxis has shown a reduction in the level of CNS relapse [45], although it has not eliminated it altogether [34,44]. A significant number of CNS relapses occur in the brain parenchyma rather than the leptomeninges and may occur up to 10 years after initial diagnosis.

This has led some investigators to consider high-dose MTX with doses of 3.0 g/m^2 as a strategy to allow better penetration of the CNS parenchyma [46]. In a study of 34 patients treated with high-dose MTX in combination with six cycles of anthracycline-based chemotherapy and local radiotherapy there was no evidence of CNS relapse, with a median follow-up of 74 months [47]. However, combination chemotherapy can present problems with tolerability in the elderly population, in which PTL is most common [1]. The current IELSG-30 phase II study is attempting to reduce the risk of CNS relapse with a more intensive CNS

prophylaxis regimen comprising four intrathecal cytarabine injections in the treatment phase and two cycles of systemic intermediate dose MTX (1.5 g/m^2) as consolidation.

Similarly, there is currently no evidence to support the role of prophylactic whole brain radiotherapy to reduce CNS relapse. On the contrary, given that whole brain radiotherapy has been associated with excessive neurotoxicity in patients with primary CNS lymphoma [48,49], its use is not routinely recommended.

Treatment: Radiotherapy

In current clinical practice, radiotherapy continues to play an important role in the radical treatment of patients with PTL. Prophylactic scrotal radiotherapy can reduce recurrence in the contralateral testis. Radiotherapy to regional lymph nodes can be used in stage II disease to prevent nodal relapse or to treat regional retroperitoneal nodes.

Although no randomised controlled trial data are available in PTL, a number of retrospective case series have supported the efficacy of radiotherapy, particularly in reducing the risk of recurrence in the contralateral testis. The largest of these case series reports a clear advantage to prophylactic scrotal irradiation [1]. Within the 373 patients analysed, 133 patients received prophylactic scrotal irradiation (36%). This was associated with a highly statistically significant difference in contralateral testicular relapse (Log-rank test $P = 0.0011$). This translated into an overall survival benefit (median overall survival, 5.9 versus 2 years; $P = 0.0008$). There was also a benefit in PFS in patients who received radiotherapy (5 year PFS, 36% versus 70%; $P = 0.00001$). Moreover, the study showed an advantage in receiving a locoregional radiotherapy dose of at least 30 Gy. Patients receiving the higher dose had a significant improvement in overall survival ($P = 0.02$). Notably, the investigators also found that anthracycline-based chemotherapy reduced contralateral testis recurrence ($P = 0.02$).

There are obvious limitations to these retrospective data. Most patients who received prophylactic irradiation had a more favourable IPI score. Most importantly, there is a high level of heterogeneity in the dose, delivery and indication of radiation treatment not accounted for within the analysis. Doses ranged from 18 to 50 Gy and fields from scrotal only to a variety of extended fields with or without the contralateral testis and analysis included patients with stage III and IV disease. This particularly leads to conclusions regarding the effectiveness of nodal radiotherapy being limited.

The benefit of radiotherapy has been supported by other smaller case series [26]. A retrospective review of PTL patients treated at the MD Anderson Centre showed that in the 45 of 72 patients treated with prophylactic scrotal radiotherapy at a median dose of 30.6 Gy (range, 24.0–56.0 Gy) only two relapsed in the testis (4%). This compares with 11% in patients who did not receive radiotherapy, which is low compared with previous studies and potentially related to the use of more effective systemic chemotherapy [50].

The US population-based Surveillance, Epidemiology, and End Results programme also supports the use of radiotherapy in PTL [2]. Researchers analysed a total of 769 patients with DLBCL. Patients who received both surgery and radiation had a median disease-specific survival time of 14.3 years compared with 9.4 years ($P = 0.03$) for patients not receiving both treatments. This retained statistical significance on multivariate analysis ($P = 0.026$). Notably, there was significant underutilisation of prophylactic testicular irradiation. Less than 40% of patients received radiotherapy and this was shown to be relatively unchanged over the previous 25 years [51].

Radiotherapy therefore forms a part of the recommended treatment algorithm for stage I and II PTL investigated in the IELSG-10 trial [34]. This non-randomised phase II feasibility study recently reported its long-term outcomes. Within the trial, all patients had a diagnostic orchidectomy. Subsequent treatment consisted of a standard dose of R-CHOP21, which consisted of 375 mg/m^2 rituximab day 0 or day 1, 750 mg/m^2 cyclophosphamide day 1, 50 mg/m^2 doxorubicin day 1, 1.4 mg/m^2 (maximum 2 mg) vincristine day 1 and 100 mg prednisone days 1–5. All patients were restaged after three courses of R-CHOP21. A complete response, an unconfirmed complete response and a partial response were defined according to Cheson's 1999 criteria [52]. Stage I patients received six courses of R-CHOP21. Stage II patients received a total of six courses of R-CHOP21 if there had been a complete response after the third cycle; if not they received eight courses.

All patients were planned to receive CNS prophylaxis with intrathecal MTX, 12 mg total dose, weekly for four doses, during the first two R-CHOP21 courses. At the end of chemotherapy, prophylactic irradiation to the contralateral testis at 25–30 Gy was delivered to all patients. Patients with stage II disease at diagnosis, alongside prophylactic testicular radiotherapy, received involved field radiotherapy (IF-RT). This included the entire involved lymph node region with or without an adjacent lymph node region. Patients with a complete response after R-CHOP21 received IF-RT at 30–35 Gy; IF-RT at 35–45 Gy was administered to those with an unconfirmed complete response or a partial response at the end of the chemotherapy programme.

In total, 47 of the 53 patients (89%; 36 stage I and 11 stage II) received radiotherapy after R-CHOP21 and intrathecal MTX. Six patients did not receive prophylactic testicular radiotherapy because of bilateral orchidectomy at diagnosis (one patient), disease progression (one patient) and refusal (four patients). Nine stage II patients were treated with retroperitoneal lymph node radiotherapy. The median delivered dose of testicular radiotherapy was 30 Gy (range 24–40 Gy) and the median delivered dose of IF-RT to the lymph nodes was also 30 Gy (range 23–45 Gy). At a median follow-up of 65 months there were no testicular relapses. Two patients relapsed in lymph nodes alone. Only one of the 13 patients with stage II disease relapsed with both extranodal and in-field retroperitoneal lymph node recurrence. This patient had received a total dose of 38 Gy of IF-RT.

Radiotherapy Technique

Prophylactic scrotal radiotherapy is usually started about 3 weeks after chemotherapy and is well tolerated. The

clinical target volume is the contralateral testis and should be defined clinically by palpation in the treatment position. The contralateral testis can be treated with a direct anterior beam with an electron beam energy of 9–12 MeV. Alternatively, 6 MV photons can be used with bolus; 260 kV can also provide a suitable dose distribution. Care should be taken to avoid unnecessary radiation to the perineum or legs. Dose-fractionation schedules of 25 Gy in 10–15 fractions or 30 Gy in 10–20 fractions are generally acceptable. Most frequently a dose of 30 Gy in 15 daily fractions is used.

The lymphatic drainage of the testicle has been extensively studied in the management of testicular seminoma [53,54]. It is important to note that the testes' lymphatic drainage is to the para-aortic lymph nodes and occasionally to the ipsilateral pelvis, whereas the scrotum drains to the inguinal nodes. The ipsilateral renal hilar nodes should be included [55]. The clinical target volume in IF-RT for stage II disease should include the entire involved nodal region and may also contain an adjacent nodal region. The minimum IF, for patients with limited para-aortic lymph node involvement only, should extend from T10-11 to L5-S1 and include at least an 8 cm wide field to provide an adequate margin. The maximum IF should include a 'dog leg' field covering the para-aortic lymph node region and ipsilateral pelvic lymph nodes. Patients should be treated on a linear accelerator with energies $\geq$6 MV using equally weighted anterior and posterior fields.

In patients receiving pelvic radiotherapy, the inferior border should be at the superior border of the obturator foramen in patients without inguinal lymph node involvement, and 5 cm below the involved inguinal lymph nodes in patients with inguinal lymph node involvement. Ipsilateral renal hilar lymph nodes should be included in patients with a testicular presentation. Both kidneys should be located by planning computed tomography and appropriate blocks should be used to prevent including more than 25% of renal parenchyma in the para-aortic field [55]. IF-RT dose in patients with stage II disease has been varied depending on the response to primary chemotherapy: 30–35 Gy (conventional fractionation) for patients who achieved complete remission and 35–45 Gy in those who did not [34]. However, a recent study showed no evidence of dose response above 30 Gy in patients treated for DLBCL at a variety of sites [56]. Radiation therapy as exclusive treatment after orchidectomy should be kept for patients with clinical contraindications to systemic treatment: the vast majority of patients with stage IE or IIE who receive radiotherapy to the retroperitoneum experience systemic recurrence as opposed to an in-field relapse.

Testicular Recurrence

Although rare, in-field recurrence is significant particularly given the improvements in the prognosis of PTL due to better systemic therapies. A recent literature review concluded recurrence rates in irradiated contralateral testes to be in the order of 10% or more. The time to recurrence varied from 13 to 120 months [57]. Approaches to improve upon on this include prophylactic orchidectomy and the use of chemotherapy agents that may cross the blood–testis barrier, e.g. MTX [58]. For the purpose of our review, testicular recurrence rates have been updated based on more recently published literature and this appears to be lower at around 4% (Table 1) [1,10,26,27,34,38,43–45]. This estimate suffers from the fact that patients received vastly differing radiotherapy schedules and systemic therapies. Evidence to support nodal radiotherapy is lacking in the literature, primarily due to a fewer number of patients treated and significant heterogeneity in radiotherapy dose and fields.

The role of prophylactic orchidectomy is debatable. An advantage to testicular radiotherapy is the chance of preserving gonadal function. However, germinal epithelium is very sensitive to radiotherapy damage and doses of more than 6 Gy can deplete the spermatogonial stem cell pool leading to permanent infertility [59,60]. Moreover, fractionation of radiotherapy increases germ cell toxicity. This is hypothesised to be due to repeated hits first activating and then depleting the reserve stem cell population [60]. Consequently, virtually all patients become sterile after prophylactic scrotal irradiation and sperm banking should be offered.

Table 1
Testicular relapse rates in large published series of patients with primary testicular lymphoma. Updated with permission from [57]

Reference	*n*	Testicular relapse among those who received radiation	Median follow-up among survivors (months)	Time to relapse (months)	Comments
[1]	373	4 of 45 (8.9%)	91	All <60	Radiation dose not reported
[10]	62	1 of 5 (20%)	103	120	Radiation dose not reported
[26]	72	2 of 45 (4%)	31	Not reported	Median 30.6 Gy (24–56)
[27]	25	0 of 6 (0%)	36	NA	Median 30 Gy (25–40)
[34]*	53	0 of 47 (0%)	65	NA	Median 30 Gy (24–40)
[38]	43	2 of 20 (10%)	49	24, 72	40 and 32 Gy, respectively
[43]*	38	0 of 33 (0%)	65	NA	30 Gy
[44]	45	0 of 10 (0%)	32	NA	Radiation dose not reported
[45]	35	0 of 12 (0%)	45	NA	Median 24 (24–40)
Pooled analysis		9 of 223 (4%)			

* Prospective studies.

Leydig cells are also affected by radiotherapy, although to a lesser extent [61]. Evidence from patients with carcinoma *in situ* of the testis suggests that doses ≥18 Gy cause a reduction in serum testosterone levels [62]. This occurred after a median period of 3.2 months (0.6–13.9) and a continuous decrease in testosterone was seen more than 5 years after treatment. Most patients are therefore hypogonadal after radiotherapy. However, despite this, prophylactic orchidectomy is principally reserved for poorer performance status patients unable to tolerate systemic chemotherapy.

Other Indications for Radiotherapy

Prophylactic scrotal radiotherapy may be considered in advanced stage III and IV disease. There is no available evidence to support prophylactic whole brain radiotherapy. Management of CNS lesions from PTL should follow guidelines for other aggressive lymphomas with CNS involvement at relapse.

Advanced Stage Disease and Relapsed or Refractory Primary Testicular Non-Hodgkin Lymphoma

Patients with stage III and IV disease should be treated as per the guidelines for the management of advanced stage nodal DLBCL. In such cases it is impossible to identify whether the testicular lesion is a primary or metastatic lesion. Standard therapeutic options are conventional-dose anthracycline-containing chemotherapy plus rituximab with the addition of prophylactic scrotal radiotherapy and intrathecal chemotherapy. As previously discussed, the addition of high-dose MTX may improve CNS prophylaxis, especially in younger patients. High-dose chemotherapy supported by autologous stem cell transplantation may be an investigational option in such patients.

Relapsed PTL should be treated similarly to other relapsed aggressive non-Hodgkin lymphomas [33]. Therapeutic decision making is influenced by age, performance status and previous treatments. Most patients with relapsed PTL are elderly and have a high tumour burden and therefore may be unsuitable for aggressive treatments. In younger patients with chemo-sensitive relapse, high-dose chemotherapy with supportive autologous stem cell transplant should be considered.

Conclusions

PTL is a rare condition resulting in a paucity of robust, randomised data to help guide its treatment. 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 – to the extent that PTL now has a better prognosis compared with its nodal counterpart. The best outcome data support the use of orchidectomy, R-CHOP and CNS prophylaxis with intrathecal chemotherapy in combination with irradiation of the contralateral testis. Further international experience may establish this regimen as a standard of care.

Despite improvements in local and systemic disease control, CNS relapse remains a devastating complication. Strategies that may reduce its risk may further improve the prognosis of patients with PTL.

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