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Primary testicular lymphoma

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Contents

Abstract

Primary non-Hodgkin's lymphoma of the testis (PTL) accounts for about 9% of testicular neoplasms and 1–2% of all non-Hodgkin's lymphomas. It is the most common testicular malignancy in elder men. Anecdotal reports associated PTL development with trauma, chronic orchitis, cryptorchidism, or filariasis exist, but no case-control studies have confirmed their etiologic significance. Diffuse large B-cell lymphoma (DLBCL) is the most common histotype in primary forms; aggressive histologies, especially Burkitt's lymphoma, are prevalent in cases of secondary involvement of testis. The most common clinical presentation is a unilateral painless scrotal swelling, sometimes with sharp scrotal pain or hydrocele. Systemic B symptoms are present in 25–41% of patients with advanced stage. Less frequently, abdominal pain, and ascites can be seen in patients with involvement of retroperitoneal lymph nodes. Bilateral testicular involvement is detected in up to 35% of patients. Although good results with doxorubicin-containing chemotherapy, followed or not by radiotherapy, have been reported, a high proportion of patients with stage I–II diseases experience aggressive relapses, and patients with advanced disease have a very poor prognosis. PTL has a propensity to disseminate to other extranodal organs, including the controlateral testis, CNS, skin, Waldeyer's ring, lung, pleura, and soft tissue. Orchidectomy followed by R-CHOP combination, with CNS prophylaxis, and prophylactic irradiation of the contralateral testis is the recommended first-line treatment for patients with limited disease. Management of patients with advanced or relapsed disease should follow the worldwide recommendations for nodal DLBCL.

Keywords: Diffuse large B-cell lymphoma; Central nervous system lymphoma; Waldeyer's ring; Testicular neoplasm

1. Definition, incidence, and risk factors

Primary non-Hodgkin's lymphoma of the testis (PTL) is an uncommon disease. It accounts for about 9% of testicular neoplasms and 1–2% of all non-Hodgkin's lymphomas,

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with an estimated incidence of 0.26/100,000 per year [1]. Despite this low overall incidence, however, it is the most common testicular malignancy in men older than 50 years of age; 85% of all PTLs are diagnosed in men over 60 years of age [2]. PTL has a rather high incidence of bilateral involvement and a propensity for extranodal spread to the skin, subcutaneous tissue, central nervous system (CNS), lung, and Waldeyer's ring. Diffuse large B-cell lymphoma (DLBCL) is the most common histotype in primary forms, while in secondary involvement of testis, other aggressive histologies, especially Burkitt's lymphoma, are prevalent. Although good results with doxorubicin-containing chemotherapy, followed or not by radiotherapy, have been reported, a high proportion of patients with stage I–II diseases experience aggressive relapse, and patients with advanced disease have a very poor prognosis. CNS and residual testicle are often involved in relapsing patients [2,3]. There are not well-documented predisposing causes for PTL. Anecdotal reports associated with trauma, chronic orchitis, cryptorchidism, or filariasis exists [4–6]. To date, no case-control studies proving their etiologic significance have been published.

2. Pathology

For pathological diagnosis, orchiectomy is the method of choice to obtain tissue samples, which better results with respect to fine needle ultrasound guided biopsy. Orchiectomy not only provides a better histological definition but it also removes the main tumour mass allowing a good local tumour control [7]. Moreover, orchiectomy also removes a potential sanctuary site, as the blood–testis barrier makes testis tumours a chemotherapy sanctuary [8]. Most of PTLs display a B-cell immunophenotype, being DLBCL in 80–90% of cases. Other histological subtypes, mostly Burkitt's and Burkitt's-like types, have been reported in 10–20% of cases, mostly in HIV+ patients. Rarely T-cell or follicular lymphomas involving the testes have been reported [9–11]. Immunophenotypic features in PTL are similar to those reported for the same histological categories arising in lymph nodes or other extranodal organs. Monoclonal lymphoid cells have been shown in controlateral testis in PTL patients, suggesting that bilateral testicular involvement is a pattern of a disease of the same origin [12]. Similarly to those reported for extranodal marginal zone lymphoma, somatic hypermutations of immunoglobulin heavy-chain gene have been described in PTL, indicating a possible antigen-driven stimulation in these lymphomas [13].

3. Clinical features

PTL present in adult patients, with a median age in the sixth decade. The most common clinical presentation is a unilateral painless scrotal swelling, sometimes with sharp scrotal pain. Systemic B symptoms such as fever, night sweats, and weight loss are usually present only in advanced stage, in 25–41% of patients [8,14,15]. Less frequently, abdominal pain, and ascites can be seen in patients with enlarged retroperitoneal lymph nodes [16]. Hydrocele is observed in 43% of cases, requiring ultrasound of the testis to detect the parenchymal mass. Lymphomatous mass has a sonographic appearance of a focal hypoechoic mass without a definable capsule or diffuse enlargement and decreased echogenicity of the entire testis that contrasts with the hyperechoic aspect of normal testis. On physical examination, there is usually a monolateral firm mass. Bilateral testicular involvement may be synchronous at diagnosis or, more frequently, asynchronous during the course of the disease, and has been detected in up to 35% of patients [14,15]; lymphoma is the most common bilateral tumour of the testis [17,18].

Lymphoma can infiltrate epididymus, spermatic cord, scrotal skin, and retroperitoneal lymph nodes. PTL has a propensity to disseminate systematically to several extranodal sites including the controlateral testis, CNS (6–16%), skin (0–35%), Waldeyer's ring (5%), lung, pleura, and soft tissue. Involvement of Waldeyer's ring is enigmatic. This may be because of a common embryonic origin, since both the testis and the oropharynx and nasopharynx are derived from the endoderm. Involvement of these sites may occur either concurrently or subsequently during the course of the disease.

The rarity of non-germ cell testis tumours can jeopardize their correct diagnosis and is an important reason for the failure to recognize them reliably, especially in young patients. Diagnostic errors in this setting, though small in number, can be clinically tragic because treatment and prognosis of PTL are very different from the germ cell tumours. Testicular lymphoma in most cases should be easily distinguishable from germ cell cancer on morphologic grounds. However, the differential diagnosis with seminoma in some cases may not be straightforward; immunohistochemistry is very helpful in this setting.

4. Staging

Complete staging work-up for PTL is the same that routinely used for other NHL. It includes an accurate physical examination, complete haematological and biochemical exams, total-body computerized tomography, and bone marrow aspirate and biopsy. Some particular sites of disease frequently involved by PTL, that is CNS, skin, Waldeyer's ring, and the contralateral testis, require especially diagnostic procedures; brain MRI, CSF examination, and screening ultrasound of the contralateral testis are advisable. The presence of pulmonary masses or pleural effusions should be histologically assessed. Bone marrow assessment should follow the general statements for all NHL. CSF flow cytometry has been recently showed to detect occult CNS disease in aggressive B-cell lymphomas [19] and PET scan increases accuracy in lymphoma staging [20]. Such new staging procedures may be worthwhile to be incorporated into staging

work-up of PTL, but so far only anecdotal reports exist on the use of PET in PTL [21].

The standard staging system used for PTL is the same one proposed for Hodgkin's lymphoma at the Ann Arbor Conference in 1971 [22], but with a few modifications. Fifty to 60% of all patients with testicular lymphoma present with stage-IE disease, which consists of the mono or bilateral involvement of the testes. Stage-IIE disease represents the mono or bilateral testicular involvement associated with concomitant involvement of loco-regional (retroperitoneal and/or iliac) lymph nodes; 20–30% of patients have this stage at presentation. Stage III–IV disease is defined by mono or bilateral testicular involvement with involvement of distant lymph nodes and/or extranodal sites [23]. Stage III disease is very rare (3–5%), whereas the precise incidence of stage IV is not easy to assess. A stage IV testicular lymphoma is virtually undistinguishable from an advanced stage nodal lymphoma with testicular involvement. The rate of testicular involvement in advanced stage DLBCL is 10–18% and 10–29% in Burkitt's lymphoma. In order to separate these two entities, a testicular lymphoma is usually defined if the testicular mass is the primary site of the disease or the main site of involvement.

5. Prognosis

PTL are very aggressive malignancies, with a poor outcome. In spite of initial complete remission, most patients with stage I/II disease experience relapse [1,11,24–26]. Most relapses occur within the first 2 years of follow-up, but late relapses have been also reported [27]. The pattern of relapse depends on the first-line treatment; after chemotherapy both systemic and regional relapses are seen, while systemic relapses are more common than local ones in irradiated patients. In most cases, relapses occurred in extranodal sites such as: CNS, skin, lung, pleura, soft tissue, Waldeyer's ring [28,29]. Five-year relapse rate in patients with limited disease treated with orchiectomy and chemotherapy, followed or not by radiotherapy, oscillates between 42% and 66% [30,31]. Relapse in the controlateral testis occurs in 5–35% of the patients, with a 3- and 15-year risk of 15% and 40%, respectively [15,23]. This form of relapse occurs mostly in patients who did not receive prophylactic scrotal radiotherapy [23]. CNS relapses both in brain parenchyma and meninges, are definitely more common than in other aggressive lymphomas. This complication is usually observed during the first 2 years of follow-up, but late relapses involving exclusively the CNS have also been reported [3,30]. In the largest reported series of patients with PTL ($n = 373$), the International Extranodal Lymphoma Study Group (IELSG) observed a 5- and 10-year risk of CNS relapse of 20% and 35%, respectively [23]. Five-year survival ranges from 16% to 50%, and median survival is 12–24 months according to the different series of patients [7,14]. In the largest series of PTL patients reported so far [23], outcome was very poor, with a 5- and 10-year OS of 48% and 27%, respectively. The overall and progression-free survival curves showed no clear evidence of plateau, suggesting no cure for patients with PTL, even for those with stage I–II disease. Five- and 10-year OS for patients with stage I PTL was 58% and 29%, and with stage II PTL was 46% and 29%, respectively [23]. Disseminated lymphomas involving the testis (stage IV disease) show a very aggressive behaviour with a relapse rate >90% and a 5-year survival of 20–25%. Patterns of relapse and dissemination are similar to those described for patients with limited disease [3,23]. In the final phase of disease infiltration of any organ may occur, and a leukemic phase has also been reported [26].

Several variables have been reported as prognostic factors in patients with PTL; among others: age, performance status, systemic symptoms, tumour burden > 9 cm, spermatic cord involvement, LDH serum level, histologic grade, vascular invasion, degree of sclerosis, and stage of disease [5,15,25,32]. In the IELSG series of 373 PTL patients, the variables associated with a longer overall survival were: low/low-intermediate risk, according to the International Prognostic Index, absence of B symptoms, anthracycline-based chemotherapy, and prophylactic scrotal radiotherapy [23].

6. Treatment

6.1. Treatment of PTL patients with limited disease (stage I–II)

Standard treatment for patients with PTL has not been yet established [15]. Orchiectomy not only provides histological tissue for diagnosis but it also removes a potential sanctuary site, as the blood–testis barrier makes testicular tumours inaccessible to systemic chemotherapy. Although occasionally long-term survival may be achieved with orchiectomy alone, surgery should not be considered as the exclusive treatment even in patients with stage I disease. In fact, most of these patients treated with surgery alone experience relapse within 2 years, suggesting that widespread microscopic disease is present at diagnosis in PTL [33]. Thus, orchiectomy followed by complementary anthracycline-containing chemotherapy is a widely accepted option as suitable for individual clinical use on a type 3 level of evidence. The use of anthracycline-based chemotherapy has been associated with a 5-year survival of 30–75% [3,24,26,30,34]. Although it is not possible to individuate the most efficacious chemotherapy regimen due to the limited number of patients in the reported series and the lack of randomised trials, doxorubicin-containing regimens have been associated with an improvement in the relapse-free survival compared with orchiectomy ± radiotherapy. However, the advantage on survival time varied greatly among the different series published so far. The most common chemotherapy regimen used was standard CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone) in the most recent studies and less frequently CHOP-like regimens such as MACOP-B

(methotrexate, doxorubicin, cyclophosphamide, vincristine, bleomycin, and prednisone) [3] or VCAP (vindesine, doxorubicin, cyclophosphamide, and prednisone) [35].

As in nodal DLBCL, the addition of rituximab to CHOP chemotherapy may be useful in PTL as suggested by preliminary data of the recently reported IELSG #10 trial [36]. In this study, 49 patients with stage I–II PTL were treated with 6–8 cycles of CHOP and rituximab and complete prophylaxis with intrathecal methotrexate and scrotal radiotherapy ± loco-regional radiotherapy for stage II. The preliminary results suggest an improvement in the outcome with a 3-year OS and 3-year PFS of 87% and 84%, no contralateral testis relapses and 2.5% actuarial risk of CNS relapse at 3 years [36]. In a preliminary study conducted by IELSG and MDACC, 27 patients were treated with the same regimen (CHOP + intrathecal methotrexate and scrotal radiotherapy ± loco-regional radiotherapy for stage II) but without rituximab. The 5-year PFS and OS were 78% and 66%, respectively, without an apparent plateau. There were no testicular relapses and the actuarial risk of CNS relapse was still high at 16% [37]. It is difficult to assess from these studies if the addition of rituximab may prevent CNS relapses. The differences in results may be merely due to different follow-up time or to a true reduced risk of systemic relapse in rituximab-treated patients that might prevent CNS recurrences. On the other hand, as demonstrated by Feugier et al. in a randomized trial on 399 patients with DLBCL comparing R-CHOP versus CHOP chemotherapy regimen [38], the addition of rituximab did not reduce the risk of CNS dissemination at relapse. In fact, CNS dissemination rate was 5.4% and 4.5% ($p = 0.68$) for patients treated with R-CHOP and CHOP, respectively. Effectively, there are several doubts about the capacity of rituximab to cross the whole blood–brain barrier and, as consequence, to prevent CNS dissemination. Larger studies with a more mature follow-up will show the role of rituximab in PTL treatment.

Routine CNS prophylaxis is recommended in PTL patients of any stage since the high rate of CNS recurrence. The best strategy to prevent CNS relapse is still a matter of debate. The value of prophylactic intrathecal chemotherapy is controversial because CNS relapses occur more frequently in brain parenchyma than in meninges and also in patients who had received intrathecal chemotherapy [23,29]. Perhaps, the use of drugs with a higher CNS bioavailability, like methotrexate or cytarabine administered at high doses, could reduce the incidence of this dismal complication. This type of chemotherapy could however be associated with severe toxic side effects in elderly patients, such as PTL usually are.

Radiation therapy can be used as prophylactic therapy to prevent relapse in the regional lymph nodes or in the controlateral testis in patients with stage-IE disease or to treat lymphomatous lesions, mostly retroperitoneal lymphadenopathies, in patients with stage-IIE disease. Patients should be treated on linear accelerator with energies ≥6 MV and by anterior and posterior equally weighted fields, both fields being treated daily 5 days per week. The clinical target volume in involved field (IF) irradiation for stage II disease should include the entire involved nodal region and may include an adjacent nodal region. Minimum IF, for patients with limited para-aortic lymph node involvement only, should include the cm wide field. Maximum IF should include inverted "Y" or "dog leg" field and include para-aortic lymph node region and bilateral pelvic lymph nodes. For patients receiving pelvic irradiation, the inferior border should be at the superior border of the obturator foramen in patients with inguinal lymph node involvement, and 5 cm below the involved inguinal lymph nodes in patients with inguinal lymph node involvement. Left renal hilar lymph nodes must be included in patients with left testicular presentation. Both kidneys should be located by planning CT and appropriate blocks should be used to prevent including more than 25% of renal parenchyma in the para-aortic field. IF radiation dose in patients with stage II disease depends on the response to primary chemotherapy: 30–35 Gy (conventional fractionation) for patients who achieved complete remission and 35–45 Gy for patients who did not. The indication for radiation therapy as exclusive treatment after orchidectomy should be kept for patients with clinical contraindications to systemic treatment. Almost all patients with stage-IE or -IIE irradiated to the retroperitoneum experience systemic dissemination, with a very few cases of in-field relapses.

Prophylactic irradiation (25–30 Gy; standard fractionation) prevents relapses in the contralateral testis, with excellent tolerability [1,24,25,34,39]. The clinical target volume in scrotal irradiation should be defined clinically by palpation. The contralateral testis should be treated with the direct anterior beam with electron beam 9–12 MV or direct anterior cobalt field or 6 MV field bolus should be placed for patient who are treated with 6 MG linear accelerator. Care should be taken to avoid unnecessary radiation to the perineum or the legs. Other uses of radiation therapy could be related to the control of CNS disease. With the current evidence, CNS prophylactic irradiation was not addressed in reported literature while the irradiation of CNS lesions from PTL should follow the general rules for other aggressive lymphomas with CNS involvement at relapse.

In conclusion, PTL patients with limited disease should be managed with primary orchidectomy followed by R-CHOP treatment, CNS prophylaxis (high-dose methotrexate ± intrathecal chemotherapy), and prophylactic scrotal radiotherapy. In patients with stage-IIE disease, irradiation of involved lymph nodes is advisable.

6.2. Treatment of advanced disease (stage III–IV)

These patients should be treated according to the guidelines for the treatment of advanced stage nodal DLBCL. Standard therapeutic option for patients with stage III–IV disease is conventional-dose anthracycline-containing chemotherapy plus rituximab with the addition of prophylactic scrotal radiotherapy and intrathecal chemotherapy. The addition of high-dose methotrexate might improve CNS pro-

phylaxis, especially in the younger patients but this has never been formally demonstrated [40]. High-dose chemotherapy supported by autologous stem cell transplantation may be an investigational option in these patients.

6.3. Treatment of relapsed or refractory PTL

Standard therapeutic option for patients with relapsed PTL has not been yet defined in prospective trials. However, therapeutic strategy should be the same as for other relapsed aggressive NHL. Therapeutic decision is influenced by age, performance status, and previous treatments. At the time of therapeutic decision it is important to take into account that many of patients with relapsed PTL are elderly, have a large tumour burden, poor performance status, weight loss, and multiorgan dysfunction. In patients <65 years with chemosensitive relapse, high-dose chemotherapy supported by autologous stem cell transplantation is recommended.

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START METHODOLOGY

START is an evidence-based instrument. This means that statements on main clinical "options" are codified and accompanied by a codified "type of basis", as follows, according to a classification originally devised for the **START** project. The **START** Editorial team is glad to receive comments on this (please, address them to the START Secretariat). The background has been detailed in *Ann Oncol 1999; 10: 769-774.*

TYPE of OPTION

START provides the following diagnostic and treatment options. The "standard" and the "individualised" options are coupled with ranked types of basis,

- ***STANDARD ("standard", "recommended" [or "not recommended"])***
  This can be considered a conventional choice for the average patient.
- ***INDIVIDUALIZED ("suitable for individual clinical use")***
  This is not a standard option, but it can be a reasonable choice for the individual patient. The patient should be informed that the option is not standard and the decision must be shared with the patient.
- ***INVESTIGATIONAL ONLY ("investigational")***
  This is something which, in principle, can be offered to the patient only within a clinical study.

TYPE of BASIS for available options

START provides an appropriate basis for each clinical option. Types of basis are ranked in five levels.

- There is a widespread consolidated consensus. Randomised trials have not been carried out or have been inadequate, but the issue is settled without major controversy: currently, no (further) experimental evidence is felt to be needed
- ***"TYPE 1 evidence" (Randomised trial(s) available, strong evidence)***
  Consistent results have been provided by more than one randomised trials, and/or a reliable meta-analysis was performed. In some instances, one randomised trial can be considered sufficient to support this type of evidence. Further confirmatory trials do not seem necessary.
- ***"TYPE 2 evidence" (Randomised trial(s) available, weak evidence)***
  One or more randomised trials have been completed, but the evidence they provide is not considered definitive (their results are not consistent, and/or they are methodologically unsatisfactory, etc.). Some controlled evidence has therefore been provided, but confirmatory trials would be desirable.
- ***"TYPE 3 evidence" (External controlled comparisons available)***
  Evidence is available from non-randomised studies, with external controls allowing comparisons. Some uncontrolled evidence has therefore been provided, but trials would be desirable.
- ***"TYPE R basis" (Rational inference)***
  Little or no direct evidence from clinical studies is available. Yet clinical conclusions can be rationally inferred from available data and knowledge (e.g. by rationally combining pieces of information from published studies and observations; for a rare neoplasm, or presentation, through analogy with a related, more common tumour, or presentation; etc.). The inference can be more or less strong, and trials may, or may not, be desirable (although sometimes unfeasible).