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Extranodal Aggressive Lymphomasa - Section 8

Testicular Lymphoma

Annalisa Chiappella

Division of Hematology and Stem Cell Transplantation, Fondazione IRCCS, Istituto Nazionale dei Tumori, Via Venezian 1, Milano, Italy

Take-home messages:

- Primary testicular lymphoma (PTL) represents 5% of testicular malignancies and 1% to 2% of non-Hodgkin lymphomas
- PTL has high tendency to disseminate to extranodal sites
- The first line treatment of PTL includes chemoimmunotherapy plus central nervous system prophylaxis and contralateral testis radiotherapy.

Introduction

Primary testicular lymphoma (PTL) is a rare form of extranodal non-Hodgkin lymphoma (NHL) and represents 5% of testicular malignancies and 1% to 2% of NHL. Median age is in the seventh decade, and 85% of diagnoses of PTL are in men over 60 years old.[*1,2]

The most frequent histotypes in PTL are diffuse large B-cell lymphoma in 90%, Burkitt and Burkitt-like in 5% to 10% (mainly HIV+) and follicular and NK/T-cell in less than 1%. Cell of origin shows an activated B-cell (ABC) profile in 60% to 96%, with frequent CD79B and MYD88 mutations and additional mutations of PIM1 and BTG1. Frequency of double hit lymphomas is low in PTL.[*3,4]

Clinical presentation is characterized by a unilateral painless scrotal swelling; the bilateral involvement is synchronous in 10% and asynchronous in 30% to 35%. B-symptoms are present at diagnosis usually in advanced stage (25%–41%). Local involvement is represented by epididimus and spermatic cord, rarely scrotal skin.

PTLs are staged according to Ann Arbor criteria with few modifications:

- Stage IE: involvement of the testis mono or bilateral
- Stage IIE: mono or bilateral testicular involvement with loco regional lymph nodes (iliac and/or lomboaortic).
- Advanced stage III/IV: mono or bilateral testicular involvement with involvement of distant lymph nodes and/or extranodal sites.

Localized presentation occurs in 70% to 80% of the patients, with 50% to 60% stage I and 20% to 30% stage II. Stage III is rare (3%–5%). Stage IV is undistinguishable from a nodal advanced stage lymphoma with a testicular involvement. The rate of testicular involvement in advanced stage DLCL is less than 20%.

Current state-of-the-art

In the past, orchiectomy and/or radiotherapy, were used as the unique treatment in PTL, with very poor outcome (median survival ranged from 12 to 24 months). In the Eighties, the introduction of doxorubicin-containing regimens, determined an improvement in the relapse-free survival. In a study of BCCA from Vancouver, patients treated with a brief chemotherapy ACOPB or CHOP for three courses after orchiectomy and involved field radiotherapy to scrotum ± pelvic and paraortic lymph nodes, if involved, had a better outcome than a historical control group treated with only orchiectomy ± radiotherapy, with a relapse free-survival and overall survival of 93% vs 50%. However, in other series of PTL patients treated with CHOP-like regimens, the survival was not so good, ranging between 50 to few months. The majority of patients experienced relapses in those series: systemic if treated with orchiectomy ± radiotherapy, at contralateral testis if treated with chemo alone, and in CNS.[5]

Due to the rarity of the disease, in order to better clarify the natural history of PTL and the best treatment, a retrospective international survey of patients with PTL was conducted by the International Extranodal lymphoma study group (IELSG). In the retrospective IELSG study, 373 adult patients with aggressive non-lymphoblastic primary testicular lymphoma treated from 22 tertiary cancer centers and one cooperative group, were analyzed. The median age at presentation was 66 years (range 19–91 years); 79% of the cases had localized Ann Arbor stage I or II. Combination chemotherapy was administered to 279 (75%)

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patients, 255 (68%) including anthracycline. Prophylactic intrathecal chemotherapy was administered to 68 patients (18%). The outcome was extremely poor, with an actuarial 5- and 10-year overall survival (OS) of 48% and 27% and an actuarial 5- and 10-year progression free survival (PFS) of 48% and 33%, respectively. Relapsed occurred in 52% of the patients, mainly in extranodal sites (72%). The most common sites of relapse were: CNS (5 and 10-years risk of CNS relapse 20% and 35%) and contralateral testis (15% at 3 years, 40% at 15 years) in those patients not receiving prophylactic scrotal radiotherapy. Clinical features significantly associated with a longer overall survival in multivariate analysis were: low/low-intermediate IPI score, no B symptoms, anthracyclines containing regimens, prophylactic scrotal radiotherapy. In this retrospective series, only 34 patients received an adequate treatment with CHOP-like chemotherapy with contralateral testis radiotherapy and intrathecal chemotherapy; the outcome in this small group of patients was promising, with a 3-year OS of 88%.[*6]

On this basis, the IELSG and FIL designed an international trial, IELSG10, to address activity of conventional R-CHOP associated with CNS intrathecal prophylaxis and contralateral testis radiotherapy. After diagnostic orchiectomy, patients were planned to receive 6 or 8 courses of R-CHOP21 with 4 intrathecal methotrexate, followed by prophylactic irradiation to the contralateral testis at 25 to 30 Gy. From 2001 to 2006, 53 patients (median age 64 years, range 22–79) with untreated stage I or II PTL were enrolled. At the end of treatment, 52 patients (98%) achieved a complete remission and one died due to progressive disease. At a median follow-up of 65 months, 5-year Progression-Free-Survival (PFS) was 74%, 5-year Overall Survival (OS) 85%, 5-year cumulative incidence of lymphoma progression or death as a result of lymphoma (TTP) 18% and 5-year cumulative incidence of CNS recurrence was 6%. Long term results, at a median follow-up of 9 years, were: PFS 67% (95% CI: 52%–78%), OS 75% (95% CI: 60%–84%); no contralateral testis relapses were observed and 4 patients experienced CNS relapses (meningeal and/or parenchymal). The 9-year cumulative incidence of CNS relapse, considering the competitive risk of death, was 6% (95% CI, 0%–12%). The prospective trial IELSG10 demonstrated that a combined treatment with R-CHOP21, intrathecal prophylaxis and testicular radiotherapy, was associated with a good outcome in patients with PTLs.[*7]

Despite CNS prophylaxis, the risk of CNS relapse was still present; based on these results, FIL and IELSG designed the international trial, IELSG30, with intensified CNS prophylaxis, adding an intrathecal prophylaxis with liposomal cytarabine and at the end of R-CHOP chemotherapy, 2 courses of iv methotrexate, before contralateral testis radiotherapy. The addition of intravenous methotrexate in the treatment plan was introduced because of some parenchymatous relapses in IELSG 10.[8]

In conclusion, the recommended treatment for localized stages PTLs is a complete course of Rituximab-CHOP, with the addition of CNS prophylaxis and prophylactic RT to the contralateral testis. The best strategy to reduce CNS recurrence is still a matter of debate; the two options (intrathecal or systemic methotrexate) can be used as part of overall treatment.[*9]

In relapse setting, high-dose chemotherapy plus transplantation in patients eligible to transplant, or chemoimmunotherapy or clinical trials are recommended.

Future perspectives

The knowledge of the biology of the disease, with the majority of cases with ABC profile and with frequent CD79B and MYD88 mutations, may facilitate the choice of novel therapeutic strategies, including lenalidomide or ibrutinib.[10,11]

Genetic analysis reported frequent 9p24.1 copy number alterations and increased expression of PD-1 ligands in primary central nervous system lymphomas and in primary testicular lymphomas. Based on the activity of PD-1 blockade in other lymphomas with 9p24.1, nivolumab was tested in 4 patients with relapsed/refractory PCNSL and 1 patient with CNS relapse of PTL. The objective responses in this small series of cases was promising, and a phase 2 trial of nivolumab in recurrent and refractory PCNSL and PTL patients (NCT02857426) is ongoing.[12]

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The retrospective IELSG trial represent a milestone in the PTL knowledge.

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