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Review

Primary Testicular Lymphoma: Single Center Experience

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Abstract. *Background/Aim: Primary testicular lymphoma (PTL) is an exceedingly rare and aggressive form of non-Hodgkin's lymphoma; the most common subtype is diffuse large B-cell (DLBCL). Standard treatment includes orchiectomy, chemotherapy, central nervous system (CNS) prophylaxis, and prophylactic radiation to the contralateral testis. PTL can reoccur years after complete remission. Treatment to immune sanctuary sites, CNS and contralateral testis, is crucial in preventing relapse. There are limited data characterizing this entity and this study aimed to add to existing literature. Patients and Methods: This descriptive retrospective study characterized twelve patients with PTL from years 2010-2021 at Allegheny Health Network. Their demographic data, prognostic factors, treatment regimens, and relapse sites (if any) were tabulated. The mean progression-free survival (PFS) was calculated to describe our experience in treating PTL. Results: Twelve patients were diagnosed with PTL; 10/12 (83.33%) patients were diagnosed with ABC PTL-DLBCL. Median age of diagnosis was 67 years. Eight of the 12 (66.66%) were African American, 4/12 (33.33%) were Caucasian. At the time of diagnosis, 8/12 (66.66%) patients presented with an elevated lactate dehydrogenase (LDH) and 8/12 (66.66%) presented with a left testicular mass. Most were treated with R-CHOP (9/12), intrathecal methotrexate (IT-MTX) (10/12), and radiation to the contralateral testis (9/12). Three of the twelve (25%) patients relapsed. Median time to relapse was 8 months. Mean PFS was 50.417 months. Conclusion: We discuss our experience in treating PTL with RCHOP, IT-MTX, and irradiation to the contralateral testis and add to the limited pre-existing data that exist.*

Primary testicular lymphoma (PTL) is a rare type of extra nodal Non-Hodgkin's lymphoma (NHL), accounting for 1-2% of all malignant lymphomas and 1-5% of all primary testicular malignancies (1). It has an annual incidence of 0.09 to 0.26 per 100,000 (2) and typically affects elderly men. The median age of diagnosis for PTL is between 66-68 years of age (3). It commonly presents as a painless unilateral testicular mass without any constitutional symptoms for weeks or months. An orchiectomy is imperative for pathological diagnosis, cell of origin identification, and optimal disease control. The most common histological subtype of PTL is diffuse large B-cell lymphoma, 88-98% (4). Rare histological types of PTL include extranodal mantle cell lymphoma, peripheral T-cell lymphoma, and activin receptor-like-kinase-1 negative anaplastic large cell lymphoma (5-7). Although PTL has an innocuous presentation, it follows an aggressive clinical course with poor overall survival (OS) and progression-free survival (PFS). PTL-DLBCL has a strong predilection to grow in immune sanctuary sites, the testis, and central nervous system (CNS). These areas are outside the cancer suppressing actions of the immune system due to specific interface barriers such as the blood brain barrier or central nervous system barrier. PTL has shown a pattern of continuing relapses, even 15 years after initial treatment (8).

Currently standardized treatment regimen guidelines do not exist for PTL due to paucity of cases and lack of large prospective trials. However, stage I/II PTL patients treated with rituxumab, cyclophosphamide, doxorubicin, vincristine, and prednisone (RCHOP), radiation to the contralateral testis, and intrathecal methotrexate have shown 65% PFS in a five-year period and 74% overall survival in an International Phase II prospective trial (9). This retrospective

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study aimed to evaluate patients at our institution with a diagnosis of PTL and subsequently describe patterns regarding response to various chemotherapy regimens and intrathecal prophylaxis. This information will be utilized to contribute to the limited pre-existing data and improve the clinical practice of PTL.

Patients and Methods

We conducted a retrospective analysis using data accessed from the electronic health records (EHR) from January 1st, 2010, to January 1st, 2021. We included patients with a diagnosis of primary testicular lymphoma who were greater than 18 years old. The following demographic data were collected; age, race, body mass index (BMI), Eastern Cooperative Oncology Group (ECOG) performance status, and Charlson comorbidity index. Pertinent lab values at the time of diagnosis that were collected include serum alpha fetoprotein (AFP), serum lactate dehydrogenase (LDH), tumor laterality, and presence of B symptoms. We excluded patients with missing lab values or treatment regimens. Exploratory analysis of the patient groups was performed. Summary statistics are presented as percentages for categorical data and median with interquartile range (IQR) for quantitative data. Survival estimates were performed using the Kaplan–Meier method, and survival differences were assessed using the log-rank test (10, 11). Adjusted effect size estimates and 95% confidence intervals are reported using an alpha level of 0.05 to indicate statistical significance. All statistical analyses were conducted with SPSS Statistics Version 23 (IBM, Armonk, NY, USA).

Table I. *Baseline characteristics of patients diagnosed with primary testicular lymphoma.*

Baseline characteristics	Median	IQR
Age (years)	67	64.75-74.75
BMI (kg/m^2)	31.7	29.01-35.05
Serum AFP (ng/ml)	3.4	2.52-7.12
Charlson Comorbidity Index	4	4-7
Serum LDH (U/l)	263.65	205.25-291.25
	Number of patients	Percentage (%)
Race		
Caucasian	4	33.33
African American	8	66.66
Other	0	0.00
Insurance		
Medicare	8	66.66
Medicaid	0	0.00
Private	4	33.33
B symptoms		
Yes	0	0.00
No	12	100
Laterality		
Left	8	66.66
Right	4	33.33
ECOG performance status		
0-1	12	100.00
≥2	0	0.00

BMI: Body mass index; AFP: alpha fetoprotein; LDH: lactate dehydrogenase.

Results

Baseline demographics. Eighteen male patients were diagnosed with primary testicular lymphoma in our center from 2010-2020. However, based on our inclusion and exclusion criteria, 6 patients were excluded. Our final study cohort size was 12 as shown in Table I. Our cohort had a median age of diagnosis of 67 years (IQR=64.75-74.75). African Americans [8/12 (66.66%)] were the majority, while Caucasians [4/12 (33.33%)] constituted the rest. At the time of diagnosis, none of our patients (0%) presented with constitutional B symptoms, fever, chills, night sweats or weight loss. All our patients reported a good ECOG performance status of 0 or 1. At the time of diagnosis, 8/12 (66.66%) patients presented with elevated LDH levels (median 263.55; IQR=205.25-291.25). Most of our patient cohort presented with a left sided testicular mass [8/12 (66.66%)]. In addition, 10/12 (83.33%) of the patients were diagnosed with DLBCL-ABC, whereas 1/12 (8.33%) patients had DLBCL-GCB. One patient had an unknown lymphoma subtype.

Treatment and survival outcomes. Two thirds of our patients, 8/12 (66.66%), were treated with RCHOP. Alternatively, 3/12 (25%) were treated with lenalidomide, rituximab, cyclophosphamide, doxorubicin, and prednisone (R2CHOP), and 1/12 (8.33%) was treated with rituximab, cyclophosphamide, vincristine, and prednisone (R-CVP). Of the patients treated with R-CHOP, half of those patients, 4/8 (50%) received a total of 6 cycles of chemotherapy. Intrathecal methotrexate (IT-MTX) was given to 10/12 (83.33%) for CNS prophylaxis and 6/12 (50%) patients received prophylactic radiation therapy to the contralateral testis. A total of 3/12 patients, who were followed, relapsed post treatment. Of the three relapsed patients, two (66.66%) received R-CHOP, as their initial chemotherapy regimen, and one (33.33%) received R2-CHOP (Table II). Median time to relapse was 8 months. Mean PFS was 50.417 months with a 95%CI=36.11-64.72, as depicted in Figure 1.

Discussion

The majority of PTL's (80-90%) are DLBCL (4). Distinguishing cell of origin is an important prognostic factor, in addition to identifying DLBCL tumor histology. The two distinct molecular subtypes are activated B-cell like (ABC) and germinal center B-cell (GCB). ABC accounts for 60-96% of PTL-DLBCLs and carries a worse prognosis and poorer outcomes compared to the germinal center subtype (3, 12). It is postulated that traditional chemoimmunotherapy

Table II. *Treatment regimens and outcomes of patients diagnosed with primary testicular lymphoma.*

Patient number	Orchiectomy	Lymphoma subtype	Chemotherapy	Number of cycles	Radiation to contralateral testis	Intrathecal methotrexate	Number of cycles	Relapse	Time to relapse (months)
1	Unknown	ABC	R-CHOP	7 cycles	No	Yes	4 cycles		
2	Yes	ABC	R-CHOP	6 cycles	No	Yes	2 cycles	Yes	4 (R Orbit)
3	Yes	ABC	R-CHOP	------	Yes	Yes	4 cycles		
4	Yes	ABC	R-CHOP	4 cycles	No	---			
5	Yes	GCB	R-CHOP	6 cycles	Yes	Yes	4 cycles		
6	Yes	ABC	R2-CHOP	6 cycles	Yes	Yes	6 cycles		
7	Yes	Unknown	R-CVP	------	Yes	---			
8	Yes	ABC	R-CHOP	6 cycles	Yes	Yes	6 cycles		
9	Yes	ABC	R-CHOP	6 cycles	Yes	Yes	4 cycles	Yes	8 (Right pleural effusion + LAD thorax)
10	Yes	ABC	R-CHOP	------	Yes	Yes	5 cycles		
11	Yes	ABC	R2-CHOP	6 cycles	Yes	Yes	6 cycles		
12	Yes	ABC	R2-CHOP	6 cycles	Yes	Yes	6 cycles	Yes	8 (Tongue)

ABC: Activated B-cell; GCB: germinal center B cell; R-CHOP: rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone; R2-CHOP: revlimid + R-CHOP; R-CVP: rituximab, cyclophosphamide, vincristine, prednisone.

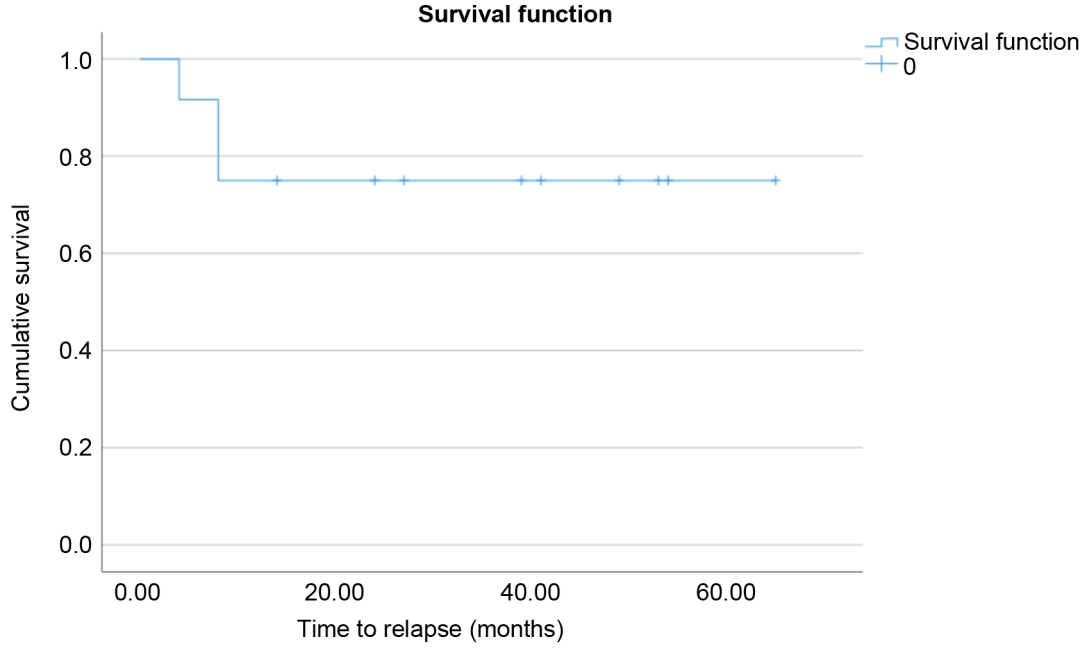

Figure 1. *Kaplan–Meier curve depicting time to progression in primary testicular lymphoma patients.*

(RCHOP) is not as effective in the ABC subtype due to chronic activation of B-cell receptor signaling and constitutive NF-κB and PI3K activation. Studies show a 3 year OS of 85% in GCB patients versus 69% in non-GCB patients with treatment with RCHOP (13-15). Other prognostic factors that have been correlated with worse outcomes are age greater than seventy, ECOG score greater than 1, left sided mass at presentation, presence of B-constitutional symptoms, increased LDH, and extranodal tumor metastasis (3). In our cohort, 10/12 (83.33%) patients were diagnosed with DLBCL ABC subtype and 8/12 (66.6%) had a left sided mass presentation and increased LDH on presentation, implying our patients had high risk disease.

The current multimodal approach in treating PTL-DLBCL

is orchiectomy, chemotherapy, IT-MTX, and radiation to the contralateral testis. As PTL is microscopically advanced at diagnosis, it requires chemotherapy irrespective of stage due to high risk of relapse (16). Anthracycline containing regimens, such as RCHOP, are the chemotherapy of choice. In the International Extranodal Lymphoma Study Group (IELSG-10), a phase II trial, patients with Stage II disease received 6-8 cycles of R-CHOP, IT-MTX, radiation to the contralateral testis (30 Gy) and radiation to regional lymph nodes (30-36 Gy) with a 5-year PFS of 74%, and OS of 85% (17). Our study cohort, with differing stages of disease, primarily was treated with RCHOP (9/12), with only two patients experiencing relapse within one year. Our cohort had a mean PFS of 50.4 months.

Prophylactic IT-MTX for the CNS is used as treatment of PTL as relapses are commonly found in this immune-sanctuary site. In the IELSG retrospective series analyzing 381 patients with PTL, the 5- and 10-year actuarial risks of CNS involvement were 19% and 34%, respectively (18). The 5-year cumulative incidence of CNS relapse was 6% (3/53) with IT-MTX (17). The 64% of CNS relapses involved the brain parenchyma as opposed to leptomeningeal spread (18). Two prospective trials that prophylactically treated with IT MTX reported a CNS relapse rate of 6% (9, 19). While the use of IT MTX is currently the accepted prevention modality, there is conceptual appeal to use HD-MTX in lieu of IT MTX, as HD- MTX can achieve greater drug concentrations within the parenchyma (20). However, of the patients in our study that received IT MTX, none of them experienced CNS relapse.

The contralateral testis is the second immune sanctuary site in PTL with high rates of relapse, therefore requiring prophylactic radiation. In the IELSG series, the 15-year actuarial incidence of contralateral testicular relapse was 42% in the absence of scrotal irradiation (17). There was no testicular relapse after irradiating the contralateral testis (17). A retrospective analysis by Seymour *et al*. showed that prophylactic scrotal radiation was associated with significant reduction in the incidence of testicular relapse. No testicular relapses were seen in 6/25 patients that received prophylactic radiation (21). In our cohort, 9/12 patients received radiation to their contralateral testis. None of our patients experienced testicular relapse.

Active research into novel therapeutic strategies to combat PTL continues. The addition of Lenalidomide to RCHOP (R2CHOP) had garnered some attention in recent years as an effective treatment for ABC- DLBCL. Lenalidomide is an oral immunomodulatory drug that targets the E3 ubiquitin ligase cereblon (22). In xenograft models of DLBCL, lenalidomide had a pronounced effect on ABC-DLBCL subtype by down-regulating transcription factor IRF4 (23) and consequently down-regulating B-cell receptor dependent NF-KB. Therefore, there is some evidence to state that lenalidomide combined with RCHOP (R2CHOP) would yield far more robust results against both ABC and GCB subtypes (24). These results were corroborated with a study performed at the Mayo Clinic, which compared 64 elderly patients with newly diagnosed DLBCL treated with R2CHOP to 87 matched patients treated with RCHOP (25). The 2 year PFS in the RCHOP and R2CHOP cohorts was 28% and 60%, respectively. OS was 46% and 83%, respectively, showing a benefit in regard to PFS and OS with R2CHOP treatment. We treated three patients with R2CHOP due to their poor prognostic factors, hoping to achieve similar results. One patient relapsed to the base of their tongue eight months after completion of treatment.

ROBUST, a phase III randomized control trial that examined R2CHOP *vs*. Placebo added to RCHOP in previously untreated DLBCL lymphoma patients, disproved the efficacy reported by prior studies. After randomizing and treating 560 DLBCL-ABC patients, the primary endpoint, defined as at least a 37.5% risk reduction in disease progression in a 24-month period, was not reached (24). As a result, further research is being undertaken to try to optimize administration, pharmacokinetics, and dosing of lenalidomide to optimize its efficacy. R2CHOP was looked upon less favorably after the ROBUST trial results were published.

Conclusion

Primary testicular lymphoma is an aggressive malignancy with a high relapse rate. Even with the standard chemotherapy regimen, RCHOP, appropriate CNS prophylaxis, and radiation therapy to the contralateral testis, it has been shown to relapse, years in the future. Our study sought to add to pre-existing data to further the knowledge base of this rare entity. The small sample size and retrospective nature of our study remain to be its greatest limitations. Further research needs to be done to find an effective strategy in treating and preventing relapse. Our study, while limited, adds to the existing literature, and reinforces the limitations of the current treatment strategy.

Conflicts of Interest

The Authors confirm that they have no financial or non-financial conflicts of interest to disclose in relation to this study.

Authors' Contributions

Shivani Shah: Conceptualization, data collection and writing/editing of the original manuscript. Sushanth Sreenivasan: Conceptualization, data collection and writing/editing of the original manuscript. Pragnan Kancharla: Conceptualization, writing/editing of the original manuscript. Cyrus Khan: Conceptualization and methodology. Yazan Samhouri: Conceptualization, methodology, editing/reviewing the manuscript.

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