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Experience of Using a Bruton Tyrosine Kinase (BTK) Inhibitor in Primary Testicular Diffuse Large B-Cell Lymphoma (DLBCL) with Isolated Central Nervous System (CNS) Metastasis

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ABSTRACT

Background: Primary testicular lymphoma (PTL) is a rare subtype of non-Hodgkin's lymphoma (NHL), most commonly presenting as diffuse large B-cell lymphoma (DLBCL). It primarily affects older men and has a tendency to relapse in the central nervous system (CNS), contralateral testis, and lungs. Although rituximab has improved survival outcomes, its limited CNS penetration is a clinical challenge.

Case Report: We report the case of a 39-year-old man diagnosed with primary testicular DLBCL (PT-DLBCL) (triple expresser). He received six cycles of R-CHOP (rituximab, cyclophosphamide, doxorubicin (hydroxydaunorubicin), vincristine (oncovin), and prednisone) combined with high-dose methotrexate (HD-MTX) and contralateral testicular radiation. After 33 months of disease-free survival, he experienced a CNS relapse. He was subsequently treated with the MAR (methotrexate, cytarabine, and rituximab) regimen, consisting of HD-MTX, cytarabine (Ara-C), and rituximab. Following whole-brain radiotherapy and rituximab maintenance therapy, he achieved complete response and was transitioned to maintenance therapy with acalabrutinib.

Conclusion: This case highlights the successful use of the MAR regimen and acalabrutinib maintenance in a patient with CNS-relapse PT-DLBCL. Further studies are needed to develop standardized treatment protocols for such high-risk cases.

Keywords: DLBCL, extranodal sites, CNS prophylaxis, acalabrutinib, BTK inhibitor.

INTRODUCTION

Among non-Hodgkin's lymphomas (NHL), diffuse large B-cell lymphoma (DLBCL) is the most common subtype, accounting for 30–35% of cases.[1] About 70% of NHLs are nodal in origin, while the remaining one-third arise from sites lacking lymphoid tissue, referred to as extranodal sites. Common extranodal locations include the gastrointestinal tract, spleen, bone, lungs, and skin. Testicular involvement is typically secondary in origin; however, primary involvement occurs in 1–2% of all NHL cases, with DLBCL being the most common pathologically.

The testes and central nervous system (CNS) are considered sanctuary sites due to the limited penetration of systemic chemotherapy. As a result, residual disease and relapses commonly occur in these areas. Primary testicular lymphoma (PTL), although rare, is most commonly seen in elderly males in their sixth decade of life and accounts for 2–9% of all testicular tumors.

The testis is an immune-privileged site, and relapses frequently occur in other extranodal locations such as the contralateral testis, lungs, and CNS. The treatment of PTL is not standardized due to its rarity and is largely based on retrospective data. Currently, most centers manage PTL with surgery of the affected testis, rituximab-based chemoimmunotherapy, radiation therapy to the contralateral testis, and intravenous methotrexate for CNS prophylaxis.[2]

Although the introduction of rituximab has improved survival outcomes, CNS relapses are relatively common in patients treated with this regimen and are associated with poorer outcomes compared to relapses at other sites. Despite the inclusion of methotrexate in treatment protocols, CNS recurrences still occur in 6% of patients, according to data from the International Extranodal Lymphoma Study Group (IELSG-10).[3] Hence, there is a need for an effective maintenance treatment strategy to sustain remission and improve overall survival.

In this report, we present a case of primary testicular lymphoma with isolated central nervous system metastasis. We discuss the challenges encountered during treatment and share our experience using a Bruton tyrosine kinase (BTK) inhibitor, acalabrutinib, to maintain the CNS response. This study was approved by the institutional review board, and informed consent was obtained from the patient.

CASE REPORT

A 39-year-old man initially presented to a local hospital in 2018 with complaints of discomfort and painless swelling in the right testicle, which had persisted for two months. After normal serum tumor marker results, he underwent a right orchiectomy. Histopathological examination revealed a triple-expressor diffuse large B-cell lymphoma of the activated B-cell-like (ABC) subtype (BCL2, MUM1, BCL6) with a Ki-67 index of 80%.

Eager to pursue further treatment, the patient subsequently visited our hospital. Comprehensive investigations, including positron emission tomography-computed tomography (PET-CT) and cerebrospinal fluid (CSF) cytology, were performed and showed no evidence of disease. Following a discussion in the multidisciplinary tumor board, the patient was scheduled to receive R-CHOP chemotherapy (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisolone), along with high-dose methotrexate for CNS prophylaxis. He received four cycles of R-CHOP combined with high-dose (HD) methotrexate, followed by external beam radiation therapy to the contralateral testis at a dose of 30.6 Gy in 17#. He has remained on regular follow-up since then.

After 33 months of disease-free survival, the patient presented with complaints of headache and vomiting. Magnetic resonance imaging (MRI) of the brain revealed a space-occupying lesion in the gangliocapsular region with perilesional edema, causing effacement of the lateral and third ventricles (Fig. 1a).

As this was an isolated CNS metastasis in a known case of PTL, the patient was started on high-dose methotrexate in combination with rituximab and cytosine arabinose (Ara-C) for three cycles. He showed symptomatic improvement, and a response assessment MRI of the brain revealed a reduction in the size of the lesion and associated edema, indicating a favorable response to treatment (Fig. 1b).

Following this initial response, the patient was lost to follow-up for eight months. He later presented to our emergency department with complaints of dizziness, slurred speech, and difficulty walking. MRI of the brain revealed a 5.3 x 5.5 x 3.2 cm hyperintense lesion in the parasagittal white matter with minimal perilesional edema, suggestive of progressive disease (Fig. 1c). At this point, the patient was planned for involved-field radiotherapy (IFRT) targeting the CNS lesions. He received 45 Gy in 25 fractions @ 1.8 Gy per fraction, delivered in two phases using a cone-down technique with three-dimensional conformal radiation therapy (3D-CRT).

After achieving a good partial response following radiation, the patient received six cycles of rituximab and prednisolone to maintain remission. He continued to show symptomatic improvement and was subsequently started on a Bruton tyrosine kinase inhibitor, acalabrutinib, at a dose of 100 mg twice daily, after a thorough discussion of the risks and benefits.

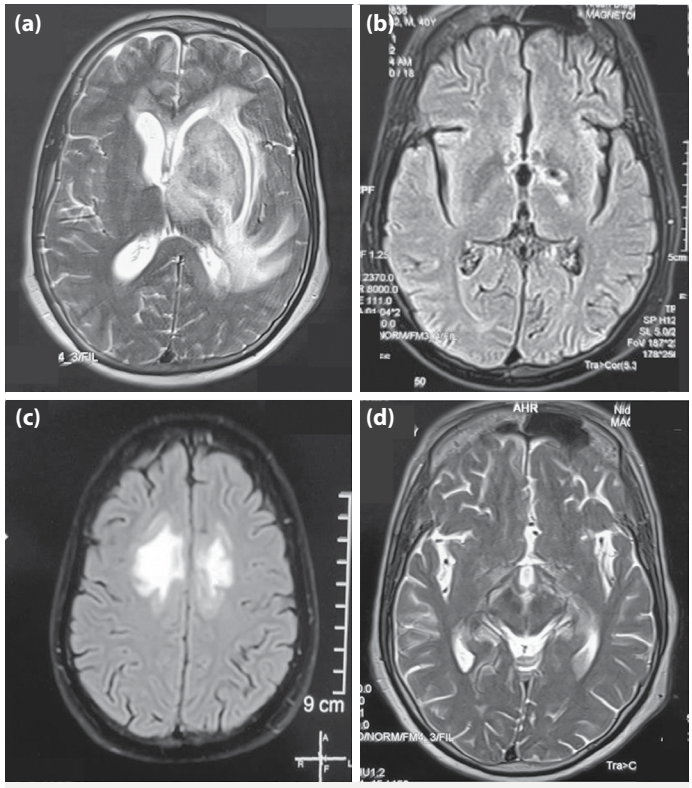

Figure 1. (a) Altered signal intensity lesions in the left basal ganglia and thalamus with associated white matter edema. **(b)** Regression of the lesion with complete resolution of white matter edema. **(c)** Bilateral parasagittal frontal lobe and right thalamic lesions; a focus of calcification in the left globus pallidus is suggestive of recurrence. **(d)** Follow-up imaging showing stable disease with no evidence of recurrence.

The patient has been tolerating maintenance therapy with acalabrutinib well for 12 months, and follow-up scans show no evidence of disease recurrence (Fig. 1d).

DISCUSSION

Primary testicular lymphoma is a rare form of extranodal lymphoma, typically affecting elderly men in their sixth decade of life. It accounts for 1–2% of all NHL cases. Most PLTs exhibit DLBCL histology and are categorized into two main subtypes: germinal center B-cell-like (GCB) and non-germinal activated B-cell-like (ABC).

As the testis is an immune-privileged site, extranodal involvement or relapse is commonly observed, particularly in the contralateral testis and the central nervous system.[4] Therefore, treatment for PTL is generally designed to reduce the risk of relapse at these sites. Although standardized treatment guidelines are lacking, primary testicular lymphomas are typically managed like high-grade lymphomas, based on limited retrospective data.

Table 1. Reported cases of extranodal DLBCL treated with BTK inhibitor maintenance therapy

Extranodal site	BTK inhibitor	Year	Ref.
Primary testicular lymphoma	Ibrutinib	2021	8
Stomach	Zanubrutinib	2023	9
Primary central nervous system (CNS) lymphoma	Zanubrutinib	2023	10
Primary testicular lymphoma	Acalabrutinib	2023	Current case

Ref: Reference; DLBCL: Diffuse large b-cell lymphoma; BTK: Bruton tyrosine kinase.

In most centers, patients with PTL are typically managed with involved-site orchiectomy and rituximab-based immunochemotherapy (anti-CD 20 monoclonal antibody [MAB]) to treat systemic disease. This is usually combined with radiation therapy to the contralateral testis to prevent recurrence. This combined-modality approach is considered the standard of care (SOC), supported by data from a contemporary cohort of 1,897 patients. High-dose methotrexate (HD-MTX) at doses greater than 3.5 g/m^2 is also included in treatment protocols to prevent the risk of CNS relapse. In our case, treatment was administered in line with the SOC protocol, including HD-MTX.

In 1977, the five-year overall survival rate for PTL was only 15.7%, largely due to limited understanding of the disease's biology in this patient subset. However, with the introduction of multimodal systemic treatment strategies, the five-year overall survival has dramatically improved to 74.1%.

The risk of recurrence in PTL is significant, with rates reported to be as high as 55% over ten years, based on a follow-up case series. Recent retrospective data from multiple studies have also questioned the effectiveness of HD-MTX for CNS prophylaxis in high-grade lymphomas (HGL).[5] Hence, there is an unmet need in the treatment of CNS relapse and a lack of consensus regarding the use of methotrexate and Ara-C for CNS prophylaxis and the overall benefit of this approach.

However, based on findings from the IELSG30 study (International Extranodal Lymphoma Study Group 30), the subgroup that benefitted the most from methotrexate and cytarabine was patients with testicular lymphoma. As a result, this has become the standard approach in many centers around the world. Even in the rituximab era, approximately 30% of patients may develop CNS relapse, which is associated with a poor prognosis. The ABC subtype of DLBCL has a higher likelihood of extranodal recurrence and a greater propensity for CNS involvement, largely due to activation of the nuclear

factor kappa-light-chain-enhancer of activated B cells (NF-kB) pathway and B-cell receptor (BCR) signaling. In our present case, the patient was also diagnosed with ABC-subtype DLBCL.

Bruton tyrosine kinase plays a central role in BCR activation, which is why BTK inhibitors have recently been investigated in multiple clinical trials. BTK inhibitors are already approved for use in chronic lymphocytic leukemia and relapsed mantle cell lymphoma; however, their role in PTL-DLBCL is uncertain. Ibrutinib has shown promising clinical benefits in DLBCL, particularly in the ABC subtype.[6] Based on a phase Ib study, acalabrutinib has also demonstrated similar efficacy, with good tolerability and fewer side effects compared to ibrutinib.[7] The most recently reported cases in which BTK inhibitors have been used as maintenance therapy are summarized in Table 1. In our case, acalabrutinib was initiated at a dose of 100 mg twice daily to maintain the CNS response. The patient has been on this medication for one year, with no reported issues related to tolerability or side effects.

CONCLUSION

Primary testicular lymphoma is a rare malignancy, most commonly of the NHL DLBCL subtype. While treatment generally follows protocols for high-grade DLBCL, PTL carries a higher risk of CNS relapse. Despite the use of CNS chemoprophylaxis with high-dose methotrexate and cytarabine, many patients still develop CNS recurrence. Novel Bruton tyrosine kinase inhibitors, such as ibrutinib and acalabrutinib, may play a valuable role in treating refractory or transplant-ineligible patients, as demonstrated in our case. Ongoing phase 3 trials offer hope for demonstrating the effectiveness of novel BTK inhibitors in preventing or treating CNS relapses.

Informed Consent: Written informed consent was obtained from patients who participated in this study.

Author Contributions: Concept – SM, SSP; Design – SM, SSP; Supervision – SSP; Materials – SM, SSP, AKP, DM, RKB, LM, SSM, LS; Data Collection and/or Processing – SM, SSP, AKP, DM, RKB, LM, SSM, LS; Analysis and/or Interpretation – SM, SSP, AKP, DM, RKB, LM, SSM, LS; Literature Search – SM, SSP, AKP, DM, RKB, LM, SSM, LS; Writing – SM, SSP, AKP, DM, RKB, LM, SSM, LS; Critical Reviews – SM, SSP.

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REFERENCES

1. Gang AO, Pedersen MØ, Knudsen H, Lauritzen AF, Pedersen M, Nielsen SL, et al. Cell of origin predicts outcome to treatment with etoposide-containing chemotherapy in young patients with high-risk diffuse large B-cell lymphoma. Leuk Lymphoma 2015;56(7):2039-46. [CrossRef]
2. Kridel R, Telio D, Villa D, Sehn LH, Gerrie AS, Shenkier T, et al. Diffuse large B-cell lymphoma with testicular involvement: Outcome and risk of CNS relapse in the rituximab era. Br J Haematol 2017;176(2):210-221. [CrossRef]
3. Vitolo U, Chiappella A, Ferreri AJ, Martelli M, Baldi I, Balzarotti M, et al. First-line treatment for primary testicular diffuse large B-cell lymphoma with rituximab-CHOP, CNS prophylaxis, and contralateral testis irradiation: Final results of an international phase II trial. J Clin Oncol 2011;29(20):2766-72. [CrossRef]
4. King RL, Goodlad JR, Calaminici M, Dotlic S, Montes-Moreno S, Oschlies I, et al. Lymphomas arising in immune-privileged sites: Insights into biology, diagnosis, and pathogenesis. Virchows Arch 2020;476(5):647-65. [CrossRef]
5. Bobillo S, Joffe E, Sermer D, Mondello P, Ghione P, Caron PC, et al. Prophylaxis with intrathecal or high-dose methotrexate in diffuse large B-cell lymphoma and high risk of CNS relapse. Blood Cancer J 2021;11(6):113. [CrossRef]
6. Wilson WH, Young RM, Schmitz R, Yang Y, Pittaluga S, Wright G, et al. Targeting B cell receptor signaling with ibrutinib in diffuse large B cell lymphoma. Nat Med 2015;21(8):922-6. [CrossRef]
7. Strati P, De Vos S, Ruan J, Maddocks KJ, Flowers CR, Rule S, et al. Acalabrutinib for treatment of diffuse large B-cell lymphoma: Results from a phase Ib study. Haematologica 2021;106(10):2774-8. [CrossRef]
8. Yan Z, Yao S, Wang Y, Liu Y, Yao Z. Primary testicular lymphoma with central nervous system relapse was successfully treated by a chemo-free regimen: A case report and literature review. Cancer Manag Res 2021;13:9489-500. [CrossRef]
9. Zhang CJ, Zhao ML. Rituximab combined with Bruton tyrosine kinase inhibitor to treat elderly diffuse large B-cell lymphoma patients: Two case reports. World J Clin Cases 2023;11(29):7170-8. [CrossRef]
10. Feng L, Gao X, Jiao Z, Wang Z, Min F. BTK inhibitor combined with anti-PD-1 monoclonal antibody for the treatment of CD20-negative primary central nervous system lymphoma: A case report. Oncol Lett 2022;25(2):48. [CrossRef]