Case Report

Open Access

Intrathecal Rituximab for Treatment of Leptomeningeal Non-Hodgkin's Lymphoma: A Case Report

Vikas Kumar*, Shaha Nabeel*, Thuy-Hong Le*, Martin Barnes* and William LiPera*

*The Donald and Barbara Zucker School of Medicine at Northwell, USA

SUMMARY

Introduction: Standard therapy for central nervous system (CNS) Non-Hodgkin's lymphoma (NHL) is still to be determined and varies in clinical practice. Leptomeningeal metastasis (LM) is more common as compared to parenchymal disease in CNS NHL. We present a case of Leptomeningeal NHL which was found to be resistant to treatment with intrathecal (IT) Methotrexate, Cytarabine and whole brain radiation therapy (WBRT). Our patient achieved a complete remission only after treatment with IT Rituximab.

Case Presentation: 74-year-old male presented to us with cough with purulent sputum. Upon thorough investigation including biopsy of axillary lymphadenopathy and a staging MRI, the patient was found to have low grade I/III B cell follicular lymphoma with LM. The patient was refractory to treatment with intrathecally administered Methotrexate, intrathecal (IT) Cytarabine and WBRT. After administration of IT Rituximab, patient showed clinical improvement and subsequent cerebrospinal fluid (CSF) cytology revealed complete elimination of clonal B-cell population.

Conclusions: In LM where cure is generally not expected, administration of IT Rituximab showed a favorable efficacy and safety profile. Prospective trials are needed to establish the role of IT Rituximab as a standard of care for treatment of LM involvement in B-cell lymphomas.

*Corresponding author

Vikas Kumar, The Donald and Barbara Zucker School of Medicine at Northwell, New York, USA. E-mail: vikkumar@gmail.com

Received: February 11, 2021; **Accepted:** February 18, 2021; **Published:** February 24, 2021

Keywords: Leptomeningeal Metastasis, Non-Hodgkins Lymphoma, CNS lymphoma, Meningeal Carcinomatosis, Intrathecal Chemotherapy

Introduction

Standard therapy for central nervous system (CNS) Non-Hodgkin lymphoma (NHL) is still to be determined and varies in clinical practice. Leptomeningeal metastasis (LM) is more common as compared to parenchymal involvement in CNS NHL. Due to different histopathological types of lymphoma, the incidence of LM varies from 2.8 to 24.4% [1,2]. LM typically has a poor prognosis and no optimal treatment has been established. However, a wide range of overall survival is observed depending upon type of primary malignancy and response to treatment. Treatment is typically continued until cerebrospinal fluid (CSF) cytology becomes negative and the goal is usually to improve quality of life. We present a case of LM NHL resistant to treatment with intrathecal (IT) methotrexate (MTX), IT cytarabine and whole brain radiation therapy (WBRT). Our patient achieved complete remission only after treatment with IT rituximab.

Case report

Our patient is a 74-year-old male with a medical history of tobacco dependence and monoclonal gammopathy of undetermined significance (MGUS) who presented to us with complaints of cough with purulent sputum. A chest computed tomography (CT) scan revealed the presence of a right lung upper lobe nodule as well as right axillary lymphadenopathy. A biopsy of an axillary lymph

node showed monoclonal lambda, CD10 and CD20 positive B cells consistent with follicle-center B cell immunophenotype. Upper lobe lobectomy of the right lung and subsequent cytopathology were also found to be consistent with diagnosis of low grade I/III B cell follicular lymphoma. Staging brain magnetic resonance imaging (MRI) suggested LM (Figure 1). Subsequent lumbar puncture (LP) and CSF flow cytometry were positive for B-cell lymphoproliferative disease lacking CD5, CD10, and bright CD11 with CD20 positive lambda clonal excess. An Ommaya reservoir was placed, and the patient was treated initially with high dose (HD) IT methotrexate for six cycles over a period of 3 months, to which he exhibited a partial response determined by CSF cytology.

Patient was subsequently treated with IT methotrexate and cytarabine. CSF analysis continued to be positive for B-cell lymphoproliferative disease and repeat MRI revealed worsening leptomeningeal NHL. Our patient went on to develop episodes of severe headaches, intractable hiccups, ataxia and tremors. His neurological symptoms improved with WBRT, however despite all the above-mentioned treatments, CSF cytology remained positive for clonal B cell population. We started treatment with 50 mg IT rituximab for a total of five weekly treatments. After the second cycle of IT rituximab, CSF studies were negative for clonal B cell population and consistently remained negative thereafter. His brain MRI showed significant improvement of leptomeningeal involvement, and head positron emission tomography (PET) scan showed no fluoro-deoxyglucose (FDG) uptake. After successful IT rituximab treatment, patient's LM remained in remission for 5 years.

Discussion

The incidence of leptomeningeal NHL is rising due to prolonged survival of patients and poor penetration of chemotherapeutic agents into the CNS [2]. Prognosis is grim and optimal treatment is yet to be established as per our literature review. Currently, National Comprehensive Cancer Network (NCCN) recommendations include combination of high dose methotrexate based regimen, WBRT and supportive care based on patient and disease related factors. At this time, IT chemotherapy is a grade 2b recommendation as per NCCN guidelines [3]. The addition of intravenous (IV) rituximab to standard chemotherapy has shown to improve complete response and survival rates in primary CNS lymphoma [4]. Some clinical studies have also shown that addition of rituximab to the standard therapy of NHL leads to a reduced incidence of CNS metastasis [5,6]. Due to its large molecular size, rituximab has a low blood brain barrier (BBB) penetration. Levels in CNS are up to only 0.1% of matched plasma levels after IV administration [7]. Therefore, there has been an increased interest in administering rituximab intrathecally for CNS lymphomas. Moreover, IT rituximab was found to be well tolerated with minimal and manageable side effects in adults as well as children [8]. Our case lays emphasis on the efficacy of this emerging modality in the treatment of leptomeningeal involvement in NHL. The patient tolerated five sequential weekly treatments of IT rituximab without experiencing any serious toxic effects. In LM where cure is generally not expected, IT rituximab appeared to have a suitable risk-benefit profile. Complete remission of disease with progression free survival of a few years was observed which calls attention to the lack of studies to explore the use of IT rituximab. Future clinical trials may determine optimal routes of delivery, such as intrathecal vs intraventricular, in order to achieve effective outcomes in leptomeningeal NHL.

Conclusion

Rituximab is standard of care in treatment of various B cell lymphomas. IT administration has shown to have a favorable result for managing CNS NHL. Prospective trials are needed to establish the role of IT rituximab as an effective treatment option for leptomeningeal involvement in B-cell lymphomas.

References

1. Hollender, S. Kvaloy, O. Nome, E. Skovlund, K. Lote, and H. Holte (2002) "Central nervous system involvement following diagnosis of non-Hodgkin's lymphoma: a risk model," *Annals of Oncology* 13: 1099-1107.
2. Meng, X., Yu, J., Fan, Q. et al. (2018) Characteristics and outcomes of non-Hodgkin's lymphoma patients with leptomeningeal metastases. *Int J Clin Oncol* 23: 783-789.
3. National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology. Central Nervous System Cancers Version 3.2019. 2019 Oct. 18; National Comprehensive Cancer Network.
4. Holdhoff M, Ambady P, Abdelaziz A, et al. (2014) High-dose methotrexate with or without rituximab in newly diagnosed primary CNS lymphoma. *Neurology* 83: 235-239.
5. Herr MM, Mohile NA, Barr PM et al. (2016) Survival of secondary central nervous system lymphoma patients in the rituximab era. *Clin Lymphoma Myeloma Leuk* 16: e123-e127.
6. Boehme V, Schmitz N, Zeinalova S, Loeffler M, Pfreundschuh M (2009) CNS events in elderly patients with aggressive lymphoma treated with modern chemotherapy (CHOP-14) with or without rituximab: an analysis of patients treated in the RICOVER-60 trial of the German High-Grade Non-Hodgkin Lymphoma Study Group (DSHNHL). *Blood* 113: 3896-3902.
7. Batchelor TT, Grossman SA, Mikkelsen T, Ye X, Desideri S, et al. (2011) Rituximab monotherapy for patients with recurrent primary CNS lymphoma. *Neurology* 76: 929-930.
8. Ceppi F, Weitzman S, Woessmann W et al (2016) Safety and efficacy of intrathecal rituximab in children with B cell lymphoid CD20+malignancies: an international retrospective study. *Am J Hematol* 91: 486-491.