

# Intravenous Methotrexate Prophylaxis of CNS Recurrence with B-Mobileular Lymphoma

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## Abstract

The final results of sufferers with systemic diffuse big B-mobileular lymphoma (DLBCL) had stepped forward over the last decade with the addition of monoclonal antibody remedy. Unfortunately, about five% of those sufferers nonetheless advanced a secondary vital anxious system (CNS) recurrence observed continuously with the aid of using speedy loss of life. This fee is notably expanded in sufferers with positive excessive-threat capabilities. Although prophylaxis in opposition to CNS recurrence with both intrathecal or intravenous methotrexate is generally used for such sufferers, to the authors' expertise, there may be no popular of care. Retrospectively evaluated changed into the position of excessive-dose systemic methotrexate blended with popular cyclophosphamide, doxorubicin, vincristine, and prednisone with rituximab (R-CHOP) chemotherapy to lower CNS recurrence in excessive-threat sufferers.

**Keywords:** B-mobileular lymphoma • CNS recurrence • Prophylaxis

## Introduction

A general of sixty five sufferers with DLBCL and CNS threat elements had been recognized on the look at group among 2000 and 2008 who obtained intravenous methotrexate as CNS prophylaxis concurrent with popular systemic remedy with healing motive. CNS recurrence fee, development-unfastened survival, and ordinary survival had been calculated. Patients obtained an average of three cycles of methotrexate at a dose of three.five gm/m<sup>2</sup> with leucovorin rescue. The whole reaction fee changed into 86%, with 6% partial responses. At an average follow-up of 33 months, there had been simplest 2 CNS recurrences (3%) on this excessive-threat population. The three-12 months development-unfastened and ordinary survival prices had been 76% and 78%, respectively. Complications related to methotrexate remedy blanketed temporary renal disorder in 7 sufferers and a put off in systemic chemotherapy in eight sufferers. Intravenous methotrexate may be correctly administered simultaneously with R-CHOP and is related to a low threat of CNS recurrence in excessive-threat sufferers.

The fee of secondary involvement of the vital anxious system (CNS) in lymphoma varies broadly with the aid of using histology however is sort of usually devastating. CNS dissemination in Burkitt and lymphoblastic lymphomas tactics 30%,<sup>1</sup> necessitating the habitual incorporation of intravenous and intrathecal (IT) prophylaxis in opposition to secondary CNS ailment withinside the remedy applications for those histologies. The threat of CNS involvement and next want for prophylaxis are much less properly defined for diffuse big B-mobileular lymphoma (DLBCL), the maximum not unusualplace non-Hodgkin lymphoma, and there may be no popular of care.

DLBCL contains a fee of secondary CNS involvement of about three% to five%, however the fee is extensively better in sufferers with positive excessive-threat scientific capabilities gift on the time of prognosis.<sup>1-3</sup> These threat elements encompass the involvement of particular extranodal webweb sites (bone marrow, testes, and paranasal sinuses, in addition to possibly the

kidneys, adrenal glands, liver, and breast).<sup>1</sup> four-10 Multivariate threat fashions have similarly recognized the mixture of an multiplied lactate dehydrogenase (LDH) and involvement of  $\leq 2$  extranodal webweb sites as conferring a threat of CNS recurrence as excessive as 34%.<sup>1</sup> eleven A big Norwegian retrospective evaluation recognized five unbiased threat elements for CNS recurrence: multiplied LDH, age  $>60$  years, involvement of  $>1$  extranodal site, retroperitoneal lymph node involvement, and hypoalbuminemia.<sup>three</sup> When  $>three$  of those threat elements had been gift at prognosis, the threat of CNS recurrence surpassed 25%. The scientific final results of CNS recurrence in sufferers with DLBCL is poor, with speedy morbidity and loss of life inside 2 to five months.

Identification of DLBCL sufferers at excessive threat for next CNS recurrence offers the possibility to provide prophylactic remedy on the time of prognosis. High-dose methotrexate is uniformly blanketed in regimens for the remedy for Burkitt lymphoma and lymphoblastic lymphoma and is the maximum energetic unmarried agent withinside the remedy of number one CNS DLBCL. Despite those implications, to our expertise there may be no clean popular for CNS prophylaxis in excessive-threat DLBCL sufferers. IT methotrexate has been maximum generally used historically, however proof of gain has been equivocal, and not using a shielding gain determined in 2 big randomized managed remedy trials of DLBCL. By contrast, the mixture of systemic and IT methotrexate has tested powerful discount in CNS recurrence in DLBCL, sixteen suggesting that intravenous methotrexate can be in most cases accountable for the threat discount; however, the protecting gain of intravenous excessive-dose methotrexate without concurrent IT chemotherapy has by no means been officially evaluated. In the present day look at, we gift what to the pleasant of our expertise is the primary document of excessive-dose systemic methotrexate blended with popular chemoimmuno therapy to lower CNS recurrence in excessive-threat DLBCL sufferers.

We queried our Institutional Review Board-accepted clinicopathologic database, derived from complete tumor registry statistics on the Massachusetts General Hospital, for all sufferers aged  $\geq 18$  years who had been recognized with DLBCL among 2000 and 2008. A general of 1283 sufferers with DLBCL had been recognized with inside the database, sixty five of whom (five%) met inclusion standards and are blanketed with inside the evaluation. Patients had been decided on for inclusion in the event that they had been dealt with with healing motive with cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP), without or with rituximab (R-CHOP), plus as a minimum infusion of systemic intravenous methotrexate at a dose of 3.5 gm<sup>2</sup> for CNS prophylaxis. CHOP and R-CHOP had been administered with the aid of using popular protocol on a 21-day cycle.<sup>17</sup> Patients had been now no longer blanketed in the event that they offered with number one DLBCL of the CNS, or concurrent CNS and systemic involvement with the aid of using DLBCL

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**Date of Submission:** 01 September, 2022, Manuscript No. aso-22-74018; **Editor assigned:** 03 September, 2022, PreQC No. P-74018; **Reviewed:** 15 September, 2022, QC No. Q-74018; **Revised:** 20 September, 2022, Manuscript No. R-74018; **Published:** 27 September, 2022, DOI: 10.37421/2471-2671.2022.8.22

at prognosis. CNS involvement changed into decided with the aid of using neuroimaging or cerebrospinal fluid (CSF) exam in symptomatic sufferers on the discretion of the treating physician. Patients had been now no longer blanketed if their pathology changed into steady with Burkitt lymphoma or excessive-grade B-mobileular lymphoma with intermediate capabilities among DLBCL and Burkitt lymphoma. All sufferers had been taken into consideration excessive threat for CNS recurrence primarily based totally on posted threat fashions, together with involvement of >2 extranodal websites plus an multiplied LDH, Hollender five-factor criteria; or excessive-threat places together with bone marrow, paranasal sinuses, testes, epidural ailment, liver, adrenal, renal, or orbit. Discordant bone marrow involvement with the aid of using a low-grade lymphoma changed into now no longer taken into consideration a demonstration for CNS prophylaxis. Progression-unfastened and ordinary survival prices with 95% self-assurance intervals (95% CI) had been calculated from date of prognosis to ailment development or loss of life, or loss of life, respectively, and had been plotted with the aid of using the approach of Kaplan and Meier. Sixty-5 sufferers met inclusion standards and had been blanketed with inside the evaluation. The median age at prognosis changed into 60 years (variety, 25-seventy nine years), and 63% of sufferers had been male. The majority of sufferers had Ann Arbor degree IV ailment (73%). Using the revised International Prognostic Index (IPI) rating, forty four (68%) sufferers had been excessive threat (rating of three-five), predicting for a four-12 months ordinary survival fee of 55%. One affected person had human immunodeficiency virus infection. LDH changed into multiplied in 73% of sufferers, and sixty four of sixty five sufferers had extranodal involvement in their DLBCL. Lumbar punctures (LPs) had been done at prognosis in sufferers, all of which had been poor with the aid of using mobileular counts. Seventeen LPs underwent cytologic exam and 14 underwent waft cytometry, none of which had been superb for malignant cells, despite the fact that waft cytometries had been believed to be equivocal because of paucity of cells, and had poor accompanying cytology and mobileular remember and are blanketed withinside the evaluation. These LPs had been done on the discretion of the treating physician. Cytogenetic records changed into to be had on sufferers, of whom had a BCL rearrangement, three sufferers had a c-MYC rearrangement, and five had complicated karyotypes. Two sufferers had concurrent rearrangements of c-MYC and BCL. Ki-sixty seven staining changed into done on forty six instances at prognosis, amongst which the median Ki-sixty seven proliferation index changed into 78% (variety, 15-100%). Fourteen instances (30%) had a proliferation index of >90% [1-5].

Sixty-3 sufferers obtained R-CHOP, and a pair of sufferers obtained CHOP without rituximab. CHOP/R-CHOP changed into given for an average of 6 cycles, with forty four sufferers receiving 6 cycles, 12 receiving 7 to eight cycles, and nine receiving three to four cycles. Methotrexate changed into administered to all sufferers at a dose of three.five g/m<sup>2</sup> intravenously for an average of three cycles (variety, 1-eight cycles). Methotrexate changed into maximum generally administered on Day 15 of alternating cycles of R-CHOP (ie, with Cycles 2, four, and 6), as an inpatient with leucovorin rescue. Four sufferers obtained a unmarried dose of IT methotrexate on the time of diagnostic LP. Sixteen sufferers obtained consolidative worried discipline radiotherapy [6].

Most prophylactic remedy changed into given to sufferers with a couple of extranodal webweb sites plus an multiplied LDH (forty six%), observed with the aid of using involvement of bone marrow (22%); epidural ailment (22%); a Hollender rating of four or five (17%); and involvement of the kidney or adrenal gland (14%), orbit (14%), liver (12%), paranasal sinuses (nine%), testes (eight%), and breast (2%). Patients regularly had >1 of the above threat elements gift at prognosis.

The median follow-up is 33 months. The ordinary systemic reaction fee changed into 92%, with fifty six sufferers (86%) attaining a whole reaction, four sufferers (6%) attaining a partial reaction, and five (7%) growing ailment development all through induction remedy. There had been eleven systemic recurrences outdoor of the CNS at an average of 14 months (variety, three-fifty one months) from prognosis. The three-12 months development-unfastened survival fee changed into 76% (95% CI, 62-86%), and the general survival fee changed into 78% (95% CI, sixty four-88%) (Fig. 1). Among all sufferers with recurrent ailment, the median Ki-sixty seven proliferation index of diagnostic

biopsy specimens changed into 70% (variety, 50-90%). Among eleven sufferers with recurrent systemic ailment, the median follow-up is two years with four sufferers last alive at remaining follow-up [7].

CNS recurrence took place in simplest 2 sufferers (at four months and nine months, respectively from prognosis), yielding a CNS recurrence fee of three% on this excessive-threat population. Both sufferers died in their CNS recurrence at 32 days and 127 days from recurrence, respectively. One affected person had obtained IT methotrexate on the time of preliminary diagnostic LP, which changed into equivocal with the aid of using waft cytometry and poor with the aid of using cytology and mobileular remember. The different affected person did now no longer have an LP at prognosis. Both sufferers obtained R-CHOP. One affected person advanced ailment recurrence all through remedy completely with inside the leptomeninges after receiving three cycles of R-CHOP and 1 infusion of systemic methotrexate. The different affected person finished 6 cycles of R-CHOP and five infusions of systemic methotrexate, and offered forty eight days after finishing chemotherapy with CNS recurrence with inside the mind parenchyma and leptomeninges, in addition to systemic ailment recurrence. The indication for CNS prophylaxis changed into bone marrow involvement with the aid of using DLBCL in each sufferers. LDH changed into markedly multiplied in each sufferers at prognosis (2764 U/L and 798 U/L; regular variety for our laboratory, 110-210 U/L). Ki-sixty seven staining at preliminary prognosis changed into to be had in simplest this sort of sufferers and changed into 70%. Neither affected person had a detectable c-MYC rearrangement.

## Conclusion

The effects of the present day look at show that incorporation of intravenous systemic methotrexate at a dose of three.5g/m<sup>2</sup> into the usual R-CHOP remedy routine is related to reduced CNS recurrence threat as compared with the posted final results in excessive-threat sufferers who did now no longer acquire CNS prophylaxis. Our three-12 months development-unfastened survival fee drawing near 80% is specifically encouraging in a cohort of sufferers with a preponderance of excessive-threat capabilities for systemic ailment recurrence, together with excessive-threat IPI ratings and excessive Ki-sixty seven proliferation fractions.

## Conflict of Interest

None.

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**How to cite this article:** Amini, Afshin. "Intravenous Methotrexate Prophylaxis of CNS Recurrence with B-Cell Lymphoma." *Arch Surg Oncol* 8 (2022): 22