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Case series on MATRix Chemoimmunotherapy

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Abstract

Primary central nervous system lymphoma (PCNSL) is a non-B-cell Hodgkin's lymphoma (NHL) that primarily affects the brain, spinal cord, leptomeninges, or eye without systemic involvement. Diffuse large B cell (DLBC) lymphomas account for around 95% of primary CNS lymphomas; the remaining accounts for low-grade B cell lymphomas, T cell lymphomas, and Burkitt lymphomas. Matrix regimen is the current standard of care for PCNSL. We have used this regimen for our patients of PCNSL to understand its applicability in LMICs. This Manuscript details our early experience.

Keywords: CNS Lymphoma; Matrix; Chemoimmunotherapy

Abbreviations: PCNSL: Primary Central Nervous System Lymphoma; NHL: Non-B-Cell Hodgkin's Lymphoma; DLBC: Diffuse Large B Cell.

Introduction

PCNSL has no definitive treatment; however the majority of studies have shown that high-dose (3.5 g/m2) intravenous MTX followed by WBI can improve the prognosis [1]. Rituximab and thiotepa were added to the standard methotrexate-cytarabine regimen (the MATRix regimen), and this resulted in a significant improvement in the complete remission rate, progression-free survival, and overall survival with only a minor increase in haematological toxicity and no increased risk of severe complications [2]. It is now standard practice to treat newly diagnosed PCNSL patients with the MATRix protocol, which consists of four cycles given every three weeks, followed by consolidation high-dose chemotherapy and autologous stem cell transplantation HDT-ASCT or WBRT. This protocol serves as a benchmark for upcoming randomised trials [3].

Sl. NO	Age/ Sex	Location	C-MYC+/-	RT Y/N	ASCT Y/N	Treatment duration	Max response	Duration of followup	Status at last follow up	Comments
1	55/M	Left capsulo ganglionic region	NA	Y	N	4 months	Partial remission	10 months	Partial emission	Financial constrains
2	47/F	Left cerebellum,let frontal and right parietal lobes	NA	N	N	5 months	Stable disease	5 months	Stable disease	Financial constrains
3	44 /M	Left basal ganglia,left perieto – temporal region	+	N	N	13 days	NA	13 days	death	Death due to sepsis

Table 1: We intend to present 3 cases of PCNSL which were treated in a tertiary care facility in Bangalore, India.

Compared to 25% in western literature, Indian studies reveal misdiagnosis rates as high as 54% to 100% and unintentional open surgical resection in 36-57% of PCNSL patients. Additionally, although prospective studies show that only 9% of patients who are referred from primary care need corticosteroid therapy for life-threatening conditions, unintentional steroids are administered before diagnosis in up to 2/3 of those individuals [4]. Indian medical facilities have historically combined WBRT and chemotherapy, with or without Rituximab, with little success [5] (Table 1).

Case 1

A 55-year-old male patient was presented to Outpatient department with complains of slurring of speech, headache, blurring of vision since one week and imbalance while walking since 2-3 months along with notable loss of weight and appetite. The patient was a known case of diabetes mellitus and hypertension and was on routine treatment. MRI examination of brain showed well defined intra axial lesion in left capsuloganglionic region of 5.2 X 3.5 cm and midline shift of 6 mm to the right side which was suggestive of high-grade lymphoma. A histopathological examination showed CD 20, BCL2, MUM 1 focal positive and highlights of reactive T lymphocytes positive for CD3. The ki 67 showed 60-70 % and was negative for CD10 and BCL 6. The patient was diagnosed with diffuse large B cell lymphoma (DLBCL) with non-germinal centre type along with primary CNS lymphoma and was planned to start chemotherapy as per the MATRix protocol every 21 days for 4 cycles with adequate monitoring.

First cycle MATRix regimen with rituximab 375mg/m^2 on day 1, methotrexate 3500 mg/m^2 on day 2, cytarabine 200 mg/m^2 on day 3 and day 4 and thiotepa 30 mg/m^2 was administered for a total of 4 days and any signs of toxicity was noted. The patient tolerated the chemotherapy well but continued to have right hemiparesis. After 2 days of chemotherapy the patient was found to have a heart rate of 60 beats / min with episodes of vomiting and headache with epigastric burning sensation. CT brain was done which showed reduction in the size of the lesion with significant perilesional oedema and minimal midline shift of 3mm as compared with previous scans.

Every 21 days the patient received chemotherapy with MATRix regimen consisting of rituximab 375mg/m2 on day 1 , methotrexate 3500 mg/m2 on day 2 , cytarabine 200 mg/m2 on day 3 and day 4 and thiotepa 30 mg/m2 for a total of 4 days for next 2 cycles . Post 4th cycle of MATRix regimen the patient had multiple episodes of chemotherapy induced vomiting which were managed by adequate anti emetics, and also had sudden desaturation for which he was shifted to intensive care unit and managed symptomatically. USG abdomen scan revealed thickened and irregular walls of urinary bladder. Acute kidney injury after the use of methotrexate was observed along with sepsis after profound neutropenia.

PET CT scan after 4th cycle showed persistent ill-defined T2 hypo intensity with cystic gliosis and atrophy of left gangliocapsular region which shows post treatment changes having small focus of diffusion restriction in adjacent cerebral peduncle which shows partial remission of the disease. Post 10 Months of treatment after RT the patient showed partial remission and treatment was stopped due to financial constraints.

Case 2

A 47-year-old female patient was presented with complains of headache for 20 days and swaying towards left side while walking which was improved upon taking steroids. F-FDG PET CT examination showed well defined enhancing lesion in the left cerebellar hemisphere of the brain measuring around 2.2 X 1.9 cm associated with mild perilesional edema. The lesion was observed to cause mild compression of the 4th ventricle and there was no evidence of hydrocephalus. The patient was suspected to have hypermetabolic lesions in the brain which was suspected to be lymphoma or glioma and no abnormal hypermetabolism was seen elsewhere in the body.

One-week later CT SCAN of brain was done which showed multiple enhancing neuroparenchymal lesions involving the left cerebellum, left frontal and right parietal lobes which was likely to be of neoplastic etiology. A neuro navigation guided biopsy of cerebellar tumour was done with left sub- occipital craniotomy where the biopsy was suggestive of high-grade B cell lymphoma with lymphoid cells positive for CD 20, BCL2, BCL6 (focal) and highlights of CD 3 on the T cells having KI – 67 of 90 %. There was no evidence of presence of CD 5, cyclin D1 and CD10. The patient was then selected for treatment with MATRix regimen for 3 cycles followed by a transplant.

1st cycle of MATRix regimen was started after 2 weeks of diagnosis with rituximab 375mg/m^2 on day 1, methotrexate 3500 mg/m^2 on day 2, cytarabine 200 mg/m^2 on day 3 and day 4 and thiotepa 30 mg/m^2 for a total of 4 days. After the first day mild discomfort in epigastric region was observed which was treated symptomatically. On the second day the patient complained of having vomiting, hypertension and bradycardia along with headache and increased intracranial pressure. CT scan of brain revealed interval increase in size of left cerebellar lesion which was measuring 3.1 X 2.8 cm compared to previous 3.0 X x2.1 cm with edema in right parietal lobe having no evidence of midline shift mass effect or herniation. Post intervention changes were noted in left occipital burr hole. The patient was managed with

dexamethasone 4 mg and Q6H and mannitol 100 ml Q8H. Two days later the patient was stable and discharged.

The patient was then given next two cycles of MATRix regimen with rituximab 375mg/m^2 on day 1, methotrexate 3500 mg/m^2 on day 2 , cytarabine 200 mg/m^2 on day 3 and day 4 and thiotepa 30 mg/m^2 for a total of 4 days with minimal or no toxicity.

After 2 weeks from the 3rd cycle of MATRix regimen the patient was observed to have weakness and thrombocytopenia which was adequately managed with sufficient hydration and platelet transfusions. PET CT was done after 3 months of treatment which showed marked interval regression of previously noted metabolically active left cerebellar lesion with persistent ill-defined hypodensity in the left cerebellar hemisphere without significant metabolic activity which could likely represent post intervention changes. there was interval resolution of white matter edema in left frontal lobe and previously noted subpleural fibro atelectasis in bilateral lower lobe lung parenchyma.

Since the patient was observed to have stable disease, it was advised to go ahead for transplant after the 3rd MATRix cycle, due to financial constrains patient's wants to go for 4th cycle of MATRix regimen.

Case 3

A 44-year-old male patient was presented to our hospital with aphasia and low GCS. The patient experienced a similar episode a month back elsewhere and histopathology showed features of DLBCL After which crainiotomy was done. The patient developed COVID 19 pneumonia for which his chemotherapy was delayed. The patient intubated with low GCS and an emergency craniotomy was done to relive the pressure.

CT scan of brain showed post operatibve changes with haemorrhage in the left parieto-temporo-occipital lobe with mass effect and midline shift of 1 cm to the right side. Hyperdensities in the bilateral lateral ventricles were suggestive of intraventricular haemorrhage. Extra vascular haematoma along the left parieto – temporal convexity, ill – defined hypodense areas with gyral thickening in left fronto parietal lobes, mildly bulky and hypodense left basal ganglia was a concern of residual disease. On the next day MRI of brain with contrast was done which showed similar results.

HRCT chest showed subtle ground glass opacities which was suggestive of infectious etiology. Immunohistochemistry report showed features of primary DLBCL. The neoplastic cells were strongly positive for CD20 and are negative for CD3, CD5, CD10 and cyclin D1. It was found to be non-germinal center type with both MUM1 and BCL6 being positive. Double expressor phenotype was detected with C-MYC and BCL2 strongly positive approximately 80 % and 100 % respectively. Ki 67 was 98 % with EBER being negative in neoplastic cells.

1st cycle of MATRix regimen was started post crainiotomy day 14 with rituximab 375mg/m^2 on day 1, methotrexate 3500 mg/m^2 on day 2, cytarabine 200 mg/m^2 on day 3 and day 4 and thiotepa 30 mg/m^2 for a total of 4 days. After third day patient experienced hypogastric tenderness and difficulty while passing urine with urinary retention followed post two days the patient was found to be drowsy and was having chronic constipation, fever with tachycardia and desaturation (85% with 6L oxygen support) and was shifted to ICU for further management.(30/09/23). The patient was found to have hyperbilirubinemia with total bilirubin 12 mg/dl and procalcitonin 34.8. After 13 Days of chemotherapy patient condition deteriorated and was inotropes, following with the patient expired with multi organ dysfunction syndrome secondary to sepsis along with PCNSL.

Highlights

- MATRix Regimen can be used for the treatment of PCNSL in LMICs.
- Resource constraints may preclude the completion of Treatment plan (auto SCT).

Discussion

PCNSL is a specific type of non-Hodgkin lymphoma with poor prognosis, with overall survival of 1.5 months when untreated, and a 5-year survival rate of 30% [6]. The majority of PCNSLs (>95%) are DLBCL, with only a small proportion comprising Burkitt, lymphoblastic, marginal zone, or T-cell lymphoma. Incidence rates are higher among the elderly population and immunocompromised. The immunocompromised are diagnosed at the age of early 30-40's whereas the immunocompetent patients often get diagnosed between 50- 70 [1], focal neurologic impairments are present in up to 80% of individuals, and symptoms are related to the lesion's site [7]. Behavioral and mental status changes, increased intracranial pressure, less frequently seizure, headache, cranial or spinal neuropathy, decreased visual acuity, photophobia, blurry vision, and floaters are observed in PCNSL which often resolves with steroids administered after definitive diagnosis. To distinguish between these various entities and track the progression of the disease, advanced MRI techniques (MR diffusion, spectroscopy, and perfusion) and metabolic imaging, such as Fluorodeoxyglucose Positron Emission Tomography (FDG-PET) or amino acid PET (using methionine),are done. CSF predicts prognosis and response to treatments [8,9].

The standard treatment for PCNSL is unclear. In this study, the combination of four drugs MATRix is the mainstay of treatment. Studies indicated survival can improve to more than 30 months with HD-MTX followed by WBRT or autologous stem cell transplantation. The WBRT dose used for PCNSL is typically 30–50 Gy. The MATRix protocol is given in 4 cycles with an interval of 21 days. It is possible to combine rituximab (an anti- CD20 monoclonal antibody) with high-dose methotrexate-based chemotherapy, but many specialists question its ability to cross the BBB and its primary benefit in PCNSL also remains unclear [10]. The BBB can be crossed by the alkylating drug thiotepa, which has a 100% plasma-to- CSF ratio. Combination with methotrexate-cytarabine, makes antimetabolites more cytotoxic [2]. The side effects of MATRix regimen include immediate: nausea and vomiting that can controlled by the use of appropriate anti- emetics, cytarabine syndrome (flu like symptoms) that resolves 24 hours after completion of therapy, neurotoxicity induced by cytarabine, headache, ocular toxicities due to high dose cytarabine that can be managed by concurrent administration of corticosteroid eye drops during the treatment; early: neutropenia, thrombocytopenia, oral mucositis, anorexia, cutaneous effects, fatigue, nephrotoxicity; late: anemia, alopecia, cognitive changes, pulmonary toxicity. Adequate hydration, urinary alkalinization, avoidance of penicillin, and other drugs that interact with methotrexate are ways to mitigate toxicity. Higher dosing methods for leucovorin and the use of the enzyme carboxypeptidase G2 promotes methotrexate clearance via the kidneys [1]. Moreover, it is strongly advised to pay close attention to supportive care and dose reductions, especially during cycle1, to prevent complications related to the treatment.

Conclusion

The MATRix Chemoimmunotherapy regimen is highly effective in patients with newly diagnosed primary DLBCL of PCNSL. The addition of RTX to HD-MTX may improve response rates and lengthen PFS durations. This case series upholds a positive co relation between MATRix Chemoimmunotherapy and positive response rate in the patients. CD 20, BCL2, MUM 1 and BCL6 (focal) expressions on the lymphoid cells can be observed which can be suggestive that PCNSL shows a good response with MATRIX Chemoimmunotherapy. Further addition of specific targeted therapies according to immunohistochemistry can be associated with further improvement in survival rate which can be debatable and studied further in future in order to develop a better effective regimen for PCNSL.

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