CASE REPORT

Temozolomide for Relapsed Primary CNS Lymphoma

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ABSTRACT

Primary CNS lymphoma (PCNSL) is an aggressive form of non-Hodgkin's lymphoma that accounts for 3% of all primary brain tumours. No clear risk factors for PCNSL in immunocompetent patients are known. The disease is more common in men and in elderly persons. Patients with AIDS who have low CD4+ counts are at the greatest risk for PCNSL. Virtually all PCNSLs in patients with AIDS express an *Epstein-Barr virus* (EBV)-related genome. PCNSL is less frequently associated with EBV in patients without AIDS. A 42 years old gentleman diagnosed with primary CNS lymphoma with negative serological test for *human immunodeficiency virus* was initially treated with Modified De Angelis protocol relapsed after treatment. He underwent gamma knife stereotactic surgery which lead to further deterioration clinically and progression of disease on imaging. Later, he was treated with salvage high dose methotrexate, but after completion of six cycles there was a radiological progression of disease. Relapsed disease was further treated with a single agent temozolomide and the disease went in remission.

Key words: *Primary CNS lymphoma (PCNSL). Temozolomide (TMZ). High dose methotrexate (HD MTX).*

INTRODUCTION

Primary CNS lymphoma accounts for 3% of all primary brain tumours with median age of onset of about 62 years.[1] The disease is more common in men (the male-to-female ratio is 2:1). The nature, intensity, and duration of immune suppression are factors in determining the risk of developing PCNSL. Patients with AIDS who have low CD4+ counts are at the greatest risk for PCNSL. It is an aggressive form of non-Hodgkin's lymphoma that develops within brain, spinal cord, eye or leptomeninges without evidence of systemic involvement. In majority of the cases, it presents as unifocal and multifocal enhancing lesions on MRI, frequently adjacent to ventricles. Biopsy is the diagnostic procedure of choice revealing high-grade malignant non-Hodgkin's B-cell lymphoma in more than 90% cases. Pathologically, it is an angiocentric neoplasm composed of a dense monoclonal proliferation of lymphocytes usually diffuse large B cells.[2] Despite recent progress, results following the treatment for primary CNS lymphoma patients remain disappointing, typically producing a 5 years survival rate of 22-40%.[3] Chemotherapy followed by radiotherapy is the cornerstone of first line treatment of primary CNS lymphoma.[4,5] The principal agent in its management is high dose methotrexate (HD MTX) which yields 30-65% complete responses.[6] As no other simple agent is prospectively proven active against primary CNS lymphoma, it is presently impossible to attribute a therapeutic benefit of any single agent apart from HD MTX. Temozolomide is an oral alkylating agent that spontaneously undergoes clinical conversion of the cytotoxic metabolite MTIC (5-[3-methyl-1-triazeno] imidazole-4-carboxamide) at physiological Ph, without metabolic conversion. Temozolomide depletes methyl-transferase in various cell types. Temozolomide activity against primary CNS lymphoma has been (anecdotally) reported.[7]

We present a case of primary CNS lymphoma which progressed on various chemotherapy regimens but responded to a single agent temozolomide.

CASE REPORT

A 42 years old gentleman with no medical or family history presented to Emergency Room in 2007 with a single episode of generalized tonic clonic seizures followed by unconsciousness. After regaining consciousness there was no neurological deficit and no lymph nodes palpable on examination.

The full blood count, calcium, urea, electrolytes and liver function test were within normal range and the serological test for *human immunodeficiency virus* was negative. MRI brain showed a tumour in the right temporal region.

The CT scan of neck, chest, abdomen and pelvis were normal. Craniotomy and biopsy of lesion was consistent with primary diffuse large B cell lymphoma (high grade). Tumour showed LCA, CD 20, CD 3 positivity with MIB 1 positive in approximately 90% of neoplastic cell.

The patient was treated with Modified De Angelis protocol for primary CNS lymphoma. After completion of therapy, the MRI brain showed increase in size of lesion in the occipital horn of right ventricle and another on left side (progression) of disease. In one month, the patient developed right hemiplegia and aphasia. Patient's family

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took the option of gamma knife stereotactic surgery, which lead to further deterioration of his symptoms. Subsequently he was treated with salvage high dose methotrexate. Patient improved clinically after two cycles and MRI also showed responsive disease. After completion of six cycles imaging showed slight progression of disease (Figure 1A). At this time he was switched to salvage temozolomide 150 mg/m^2 per orally daily for 5 days a month.[10] After three cycles imaging showed complete resolution of disease, but patient was experiencing frequent episode of headaches, so the dose of temozolomide was decreased to 100 mg/m^2. On completion of his tenth cycle the brain imaging again showed resolution of disease (Figure 1B).

The patient remained in remission 3 years from his initial presentation and has a good quality of life. He has no neurological deficit, has normal mental functions and is not dependant for daily chores.

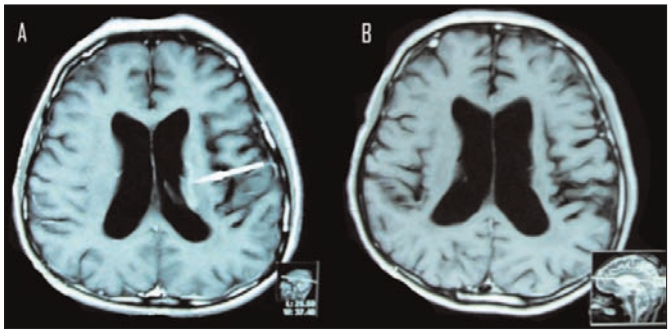

Figure 1: (A) MRI brain with contrast shows nodular area of the mass involving the thalamus measuring 2 cm transverse, 2 cm anterioposterior and 2.1 cm craniocaudal extent as indicated with white arrow (before Temozolomide). **(B)** No enhancement seen on contrast to suggest residual/ recurrent disease.

DISCUSSION

Primary CNS lymphoma has an aggressive course. The prognosis of patients with relapse or refractory CNSL is even poorer and with median survival of only 2 months.[8] Methotrexate is the most effective agent against primary CNS lymphoma. It is used in combination with other drugs such as vincristine, procarbazine, cytarabine and rituximab. High dose MTX 3.5 gm/m^2 overcomes blood brain barrier.[6] It is followed by consolidation radiation as initial treatment to maximize response and improve outcomes. Radiation results in tumour regression as well as partial repair and closure of blood brain barrier behind the tumour. HD-MTX in primary CNS lymphoma has substantially improved the survival of patients with the disease.[4] Salvage therapy with HD-MTX appears to be effective for patients with CNS lymphoma who relapse after initial complete remission to MTX. In a study, overall response rate was 91% to first salvage HD-MTX and 100% to second salvage. Median survival was 61.9 months after first relapse and 91.9 months overall.[9]

Temozolomide has also been effective as a single agent as salvage therapy in relapse primary CNS lymphoma. In a phase-2 trial assessing the activity of TMZ with recurrent primary CNS lymphoma, previously treated with HD-MTX containing chemotherapy and radiotherapy, 9 out of 36 patients had a complete response (25%; 95% CI 11-39%) and 2 had a partial response (6%; 95% CI 0-14%). The study was closed at this time as the target of 10 objective responses were achieved. Median progression-free survival was 2.8 months (interquartile range 1-8 months), median overall survival was 3.9 months (interquartile range 1.7-16 months) and 1-year overall survival was 31% (95% confidence interval 16-46%).[10] In this study 28 patients (78%) had first recurrence and only 8 patients had multiple recurrent disease having failed to respond to other salvage treatment. Median number of cycles were 2 (range 1-12). Toxicities were mild; 2 patients had 1 episode of grade 4 neutropenia and 1 patient had grade 3 vomiting in a single cycle. None of the patients had headaches.

Single-agent temozolomide can be considered as salvage treatment for patients with primary CNS lymphoma. It is well tolerated in even patients with poor performance status. Its non-cumulative and modest toxicities makes it potentially useful agent for maintenance therapy.

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