



Case Reports

Lenalidomide and Temozolomide Combination in a Very Elderly Patient with CNS Relapse of Diffuse Large B-Cell Lymphoma

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Abstract. Central nervous system (CNS) relapse is an infrequent but severe complication for DLBCL patients, associated with poor prognosis. Intravenous prophylaxis with high-dose methotrexate has shown promising results but is rarely feasible in elderly and/or nephropathic patients.

A 83 years old woman with CNS relapse occurred 6 months after chemoimmunotherapy. The patient was defined ineligible for radiotherapy (RT) and started oral Temozolomide 250mg daily for 5 consecutive days without any improvement after 1st cycle.

We administered lenalidomide 25mg daily for 21 days every 28 days together with temozolomide 250mg daily for 5 days every 28 days. The patient experienced a rapid improvement of general and cognitive conditions; Gadolinium-enhanced brain MRI showed a wide reduction of neoplastic tissue. The patients maintained good clinical conditions with mild treatment toxicity until the end of the 6th cycle, when brain MRI showed disease progression and the patient died 1 month later.

We suggest lenalidomide could be a feasible option for CNS relapse in elderly DLBCL patients and it could be associated in future studies with other cytotoxic agents such as temozolomide.

Keywords: Lenalidomide, CNS lymphoma, therapy, survival.

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Introduction. Central nervous system (CNS) relapse is an infrequent but severe complication for diffuse large B-cell lymphoma (DLBCL) patients, associated with poor prognosis.¹ Several risk factors have been identified for CNS recurrences, such as localizations at testis, orbit, paranasal sinuses, more than 1 extranodal involved site and elevated lactate dehydrogenase (LDH). A new prognostic model has recently been proposed,

called CNS international prognostic index (IPI), including kidney and/or adrenal localization.^{2,3} However, CNS prophylaxis with intrathecal methotrexate and/or cytarabine is not possible in all patients, and current guidelines and recent studies suggest it is not sufficient in a majority of cases due to a prevalent parenchymal and not meningeal involvement in most relapsed DLBCL patients.^{4,5} Intravenous prophylaxis with high-dose

methotrexate has shown promising results but is rarely feasible in elderly and/or nephropathic patients.^{4,5}

Overall, very few agents pass through blood brain barrier (BBB), such as temozolomide, but long-term remissions in primary CNS lymphoma are seldom observed with this drug.⁶

Lenalidomide has a pleiotropic effect and has been widely used in relapsed DLBCL;⁷ there are some interesting reports about its efficacy in CNS relapse and its capacity to cross BBB.⁸⁻¹¹

According to this background, we would like to report our experience in a case of CNS relapse in an elderly patient.

Case Report. In 2015, April, an 83 years old woman was referred to our institution because of a diagnosis of DLBCL was made by a biopsy of a right orbit injury. Physical examination showed no enlarged lymph nodes, blood cell count was normal, LDH was mildly increased (249IU/l, normal value 135-225 IU/l). Bone marrow biopsy revealed no infiltration, computed tomography (CT) scan showed multiple mediastinal and celiac enlarged lymph nodes, together with parenchymal splenic localizations. ECOG performance status was 2. The patient was considered ineligible for i.v. high-dose methotrexate (MTX) and, according to conflicting results of i.t. prophylaxis, recent data by Muravski and colleagues and patient's willing, did not receive i.t. MTX.¹²

Immunochemotherapy with etoposide, mitoxantrone, cyclophosphamide, vincristine, prednisone, and bleomycin (VNCOP-B) was administered, in association with rituximab.^{13,14} The patient received chemotherapy weekly and rituximab every 2 weeks for 12 weeks, as previously published. The regimen was completed without dose delays or dose reductions; total body CT scan showed a complete remission (CR). Treatment toxicity was mild with only grade 1 peripheral neuropathy that disappeared after treatment completion; thank primary prophylaxis with filgrastim no neutropenia occurred.

The patient maintained CR for 6 months when she came to the emergency department because of a headache and cognitive impairment. Brain CT scan showed CNS relapse with a right frontal mass that extended to the ipsilateral frontal-basal areas, a wide ipsilateral vasogenic edema with ventricular compression and initial trans-falcial herniation. The patient was defined ineligible for

radiotherapy (RT) because of age, wide vasogenic edema and high risk of neurotoxicity and started intramuscular dexamethasone 8mg daily and oral temozolomide 250mg daily for 5 consecutive days without any improvement after 1st cycle; total body CT scan (**Figure 1 A**) showed a further increase of the right frontal mass (diameter 7cm) without other disease localizations.

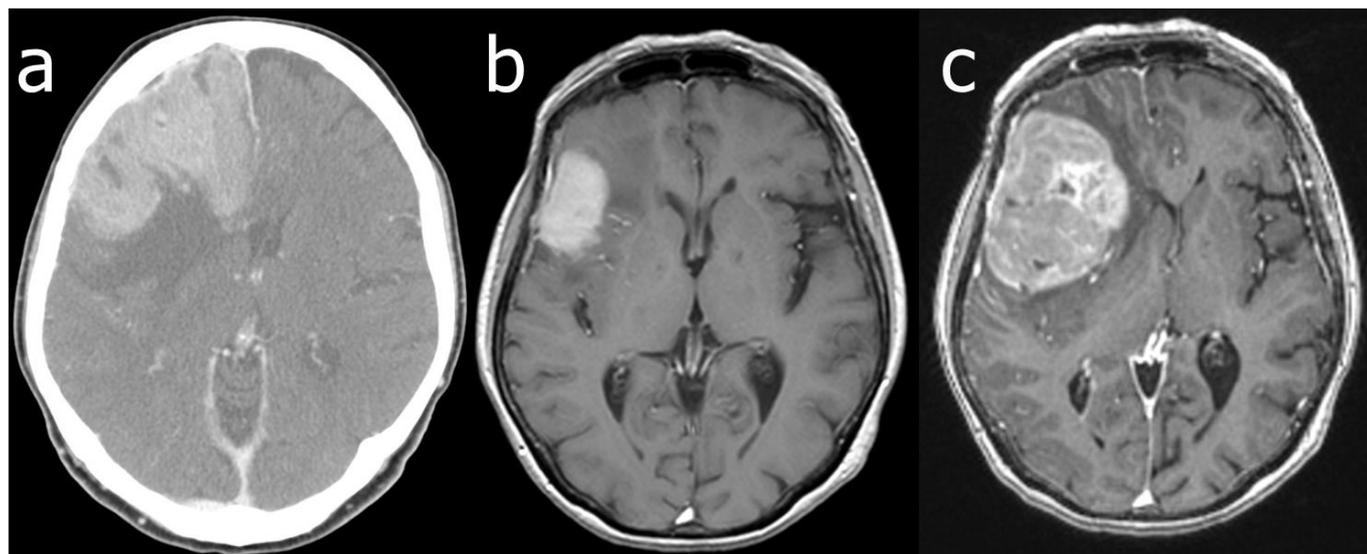
Given the promising data of lenalidomide use for CNS lymphoma and the lack of other treatment options, we decided to administer lenalidomide 25mg daily for 21 days every 28 days together with temozolomide 250mg daily for 5 days every 28 days. The patient experienced a rapid improvement in general and cognitive conditions after the 1st cycle, headache disappeared, both Activities of Daily Living (ADL) and Instrumental Activities of Daily Living (IADL) improved. We decided to continue this association; Gadolinium-enhanced brain MRI (**Figure 1 B**) was performed after the 2nd cycle and showed a wide reduction of neoplastic tissue (diameter 37 mm), vasogenic edema, and mass effect. In accordance with these promising results, the patients received other 4 cycles. Therapy was well tolerated, grade 2 neutropenia without infections and grade 2 thrombocytopenia that recovered after one-week dose delay were observed; no extra-hematological toxicity was observed, and no hospitalization was needed.

The patients maintained good clinical conditions until the end of the 6th cycle when a headache recurred. Gadolinium-enhanced brain MRI (**Figure 1 C**) showed disease progression. Clinical conditions rapidly worsened, the patient came to the hospital, we tried to administer steroid therapy, mannitol, and oral procarbazine, but the patient did not respond to treatment and died.

Discussion. CNS relapse in elderly DLBCL patients is an unmet clinical need to date.¹ These patients are usually not eligible for HD-MTX and/or HD cytarabine and have a dismal prognosis, mainly because there is a lack of cytotoxic agents that cross BBB with manageable toxicity. Whole brain RT is characterized by a substantial neurotoxicity, that limits its feasibility especially in older patients.¹⁵

Procarbazine, lomustine, and vincristine (PCV) was administered to 8 recurrent CNS lymphoma patients (age 36-72 years old) and showed an overall response rate (ORR) of 50% with a median

Figure 1. Neuroradiological follow-up: a) iodine contrast-enhanced computed tomography axial image obtained in 2016, March, at relapse; b) and c) gadolinium-enhanced T1-weighted magnetic resonance axial images obtained after the 2nd and the 6th cycle, respectively.



progression-free survival (PFS) of 7 months.¹⁶ Temozolomide, an alkylating agent that can penetrate into the brain, demonstrated promising results both as first-line treatment and for recurrent primary CNS lymphoma. In a retrospective series of 17 elderly patients CR rate was 47%, median PFS and overall survival (OS) were 5 and 21 months, respectively.⁶

The possibility for lenalidomide to accumulate in the cerebrospinal fluid was reported in a case of blastoid mantle cell lymphoma (9). Lenalidomide as salvage therapy for recurrent primary CNS lymphoma was administered to 6 elderly patients (median age 73.5 years, range 64-78), 2/6 patients achieved CR and 1/6 achieved partial remission (PR).⁸ Salati and colleagues showed a leptomeningeal relapse in a patient with DLBCL successfully treated with lenalidomide monotherapy.¹¹ The patient was elderly, had an early relapse after first-line chemoimmunotherapy of a double-hit DLBCL and received high-dose MTX and cytarabine as salvage treatment, alternating with bi-weekly liposomal cytarabine. MRI showed a significant reduction of

leptomeningeal contrast enhancement, the patient refused RT and was successfully consolidated with lenalidomide 15mg daily for 21 every 28 days, achieving a complete and durable response (month+9).

Moreover, an interesting phase I study of lenalidomide was presented at last International Conference on Malignant Lymphoma (ICML) meeting, 6 out of 8 patients achieved at least PR, in 2 patients a duration of response of more than 1 year was reported.¹⁷

Lenalidomide in combination has shown an unexpected toxicity, and a dose of 5 mg has been suggested.^{18,19} It is important to note that in our case the combination with temozolomide of lenalidomide daily dose of 15 mg was well tolerated.

Conclusions. According to these promising results and our experience in a very elderly patient, we suggest lenalidomide could be a feasible option for CNS relapse in aged DLBCL patients, and it could be associated in future studies with other cytotoxic agents such as temozolomide.

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