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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**.**

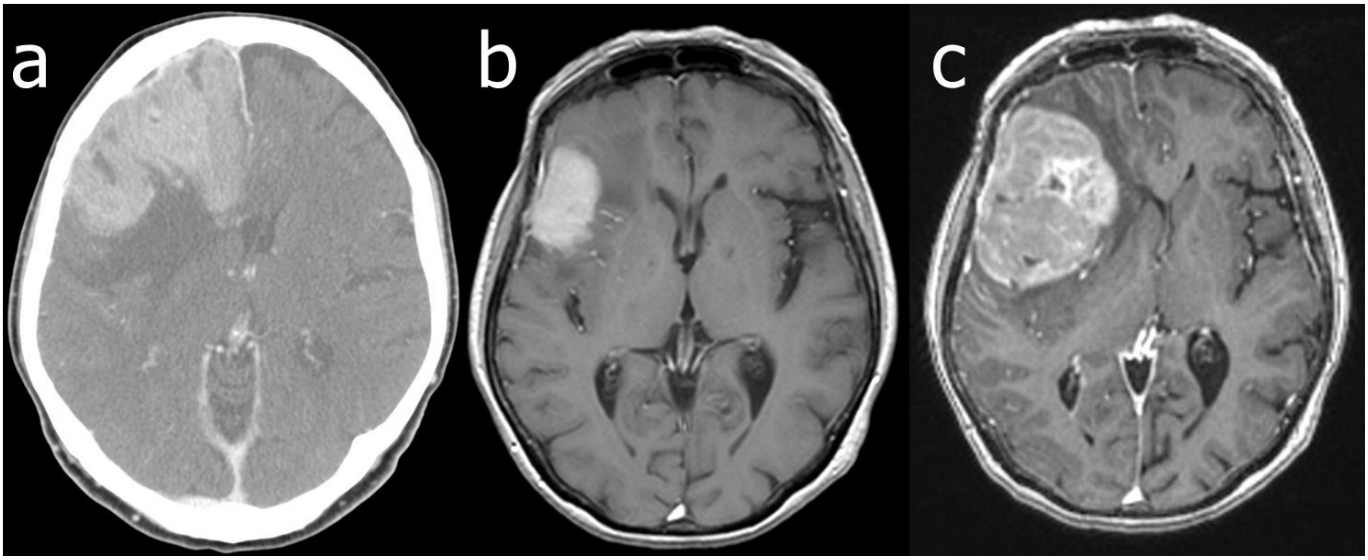
Given the promising data of lenalidomide use for CNS lymphoma and the lack of other treatment options, we decided to administer lenalidomide 25mg daily for 21 days every 28 days together with temozolomide 250mg daily for 5 days every 28 days. The patient experienced a rapid improvement in general and 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.

References:

1. A, Orfao A; Spanish Lymphoma Group (GELTAMO). Guidelines for diagnosis, prevention and management of central nervous system involvement in diffuse large B-cell lymphoma patients by the Spanish Lymphoma Group (GELTAMO). Haematologica, 2017; 102: 235-245 PMID:27846613 https://doi.org/10.3324/haematol.2016.149120
2. Schmitz N, Zeynalova S, Nickelsen M, Kansara R, Villa D, Sehn LH, Glass B, Scott DW, Gascoyne RD, Connors JM, Ziepert M, Pfreundschuh M, Loeffler M, Savage KJ. CNS International Prognostic Index: A Risk Model for CNS Relapse in Patients With Diffuse Large B-Cell Lymphoma Treated With R-CHOP. J Clin Oncol, 2016; 34: 3150-3156 PMID:27382100 https://doi.org/10.1200/JCO.2015.65.6520
3. Cheah CY, Seymour JF. Central nervous system prophylaxis in non-Hodgkin lymphoma: who, what, and when? Curr Oncol Rep, 2015; 17: 25 PMID:25912004 https://doi.org/10.1007/s11912-015-0450-4
4. Tilly H, Gomes da Silva M, Vitolo U, Jack A, Meignan M, Lopez-Guillermo A, Walewski J, André M, Johnson PW, Pfreundschuh M, Ladetto M; ESMO Guidelines Committee. Diffuse large B-cell lymphoma (DLBCL): ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol, 2015; 26: v116-125 PMID:26314773 https://doi.org/10.1093/annonc/mdv304
5. Ferreri AJ, Bruno-Ventre M, Donadoni G, Ponzoni M, Citterio G, Foppoli M, Vignati A, Scarfò L, Sassone M, Govi S, Caligaris-Cappio F. Risk-tailored CNS prophylaxis in a mono-institutional series of 200

patients with diffuse large B-cell lymphoma treated in the rituximab era. Br J Haematol, 2015; 168: 654-662 PMID:25312994 https://doi.org/10.1111/bjh.13194
6. Kurzwelly D, Glas M, Roth P, Weimann E, Lohner H, Waha A, Schabet M, Reifenberger G, Weller M, Herrlinger U. Primary CNS lymphoma in the elderly: temozolomide therapy and MGMT status. J Neurooncol, 2010; 97: 389-392 PMID:19841864 https://doi.org/10.1007/s11060-009-0032-0
7. Witzig TE, Vose JM, Zinzani PL, Reeder CB, Buckstein R, Polikoff JA, Bouabdallah R, Haioun C, Tilly H, Guo P, Pietronigro D, Ervin-Haynes AL, Czuczman MS. An international phase II trial of single-agent lenalidomide for relapsed or refractory aggressive B-cell non-Hodgkin's lymphoma. Ann Oncol, 2011; 22: 1622-1627 doi: 10.1093/annonc/mdq626. PMID:21228334 https://doi.org/10.1093/annonc/mdq626
8. Houillier C, Choquet S, Touitou V, Martin-Duverneuil N, Navarro S, Mokhtari K, Soussain C, Hoang-Xuan K. Lenalidomide monotherapy as salvage treatment for recurrent primary CNS lymphoma. Neurology, 2015; 84: 325-326 PMID:25527263 https://doi.org/10.1212/WNL.0000000000001158
9. Cox MC, Mannino G, Lionetto L, Naso V, Simmaco M, Spiriti MA. Lenalidomide for aggressive B-cell lymphoma involving the central nervous system? Am J Hematol, 2011; 86: 957 doi: 10.1002/ajh.22148. No abstract available. PMID:21990093 https://doi.org/10.1002/ajh.22148
10. Rubenstein JL, Treseler PA, Stewart PJ. Regression of refractory intraocular large B-cell lymphoma with lenalidomide monotherapy. J Clin Oncol, 2011; 29: 595-597 PMID:21519022 https://doi.org/10.1200/JCO.2011.34.7252
11. Salati M, Tarantino V, Maiorana A, Bettelli S, Luminari S. Durable remission in a patient with leptomeningeal relapse of a MYC/BCL6-positive double-hit DLBCL treated with lenalidomide monotherapy. Hematol Oncol 2016 [Epub ahead of print] PMID:27301994 https://doi.org/10.1002/hon.2315
12. Murawski N, Held G, Ziepert M, Kempf B, Viardot A, Hänel M, Witzens-Harig M, Mahlberg R, Rübe C, Fleckenstein J, Zwick C, Glass B, Schmitz N, Zeynalova S, Pfreundschuh M. The role of radiotherapy and intrathecal CNS prophylaxis in extralymphatic craniofacial aggressive B-cell lymphomas. Blood, 2014; 124: 720-728 https://doi.org/10.112/bl8ood-2013-10-535021 PMID:24939657
13. Fina M, Tani M, Stefoni V, Musuraca G, Marchi E, Pellegrini C, Alinari L, Derenzini E, Bacci F, Pileri S, Baccarani M, Zinzani PL. VNCOP-B plus rituximab in the treatment of diffuse large B-cell lymphoma in the elderly. Leuk Lymphoma, 2007; 48: 2167-2171. PMID:17990178 https://doi.org/10.1080/10428190701642102 PMid:17990178
14. Ishii K, Urase F, Nagare Y, Kimura H, Manabe M, Yagi T, Teshima H, Hayashi K, Shibano M, Tsukaguchi M, Katsurada T, Mugitani A, Kitayama H, Nomura S.VNCOP- B plus rituximab therapy in elderly patients with aggressive B-cell non-Hodkin lymphoma: A multicenter experience. Arch Gerontol Geriatr, 2010; 51:209-215. https://doi.org/10.1016/j.archger.2009.10 PMID:19926148
15. Kasenda B, Loeffler J, Illerhaus G, Ferreri AJ, Rubenstein J, Batchelor TT. The role of whole brain radiation in primary CNS lymphoma. Blood, 2016; 128: 32-66 PMID:27207798 https://doi.org/10.1182/blood-2016-01-650101
16. Kim YJ, Choe JH, Park JH, Hong YK. Efficacy of Procarbazine, Lomustine, and Vincristine Chemotherapy for Recurrent Primary Central Nervous System Lymphomas. Brain Tumor Res Treat, 2015; 3: 75-80 PMID:26605261 https://doi.org/10.14791/btrt.2015.3.2.75
17. Rubenstein JL, Formaker P, Wang X, Chen N, Fraser E, Munster P, Damato B. Lenalidomide is highly active in recurrent CNS lymphomas: phase I investigation of lenalidomide plus rituximab and outcomes of lenalidomide as maintenance monotherapy. Hematol Oncol (ICML abstracts) 2015; 33 :175.
18. Quach H, Fernyhough L, Henderson R, Corbett G, Baker B, Browett P, Blacklock Martín A, Redondo AM, Dlouhy I, Salar A, González-Barca E, Canales M, Montes-Moreno S, Ocio EM, López-Guillermo A, Caballero D; Spanish Group for Lymphomas and Autologous Bone Marrow (GELTAMO).. Lenalidomide in combination with R-ESHAP in patients with relapsed or refractory diffuse large B-cell lymphoma: a phase 1b study from GELTAMO group. Br J Haematol. 2016 Apr;173(2):245-52. https://doi.org/10.1111/bjh.13945
19. H, Forsyth C, Underhill C, Cannell P, Trotman J, Neylon A, Harrison S, Link E,Swern A, Cowan L, Dimopoulos MA, Miles Prince H. Upfront lower dose lenalidomide is less toxic and does not compromise efficacy for vulnerable patients with relapsed refractory multiple myeloma: final analysis of the phase II RevLitestudy. Br J Haematol. 2017 May;177(3):441-448. Epub 2017 Feb 15. PubMed PMID: 28197996. https://doi.org/10.1111/bjh.14562