

Durable remission in a patient with leptomeningeal relapse of a MYC/BCL6-positive double-hit DLBCL treated with lenalidomide monotherapy

Running head: Durable remission with lenalidomide in CNS relapse of double-hit lymphoma

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Abstract

Secondary central nervous system (CNS) involvement is an uncommon event that typically occurs early in the natural history of diffuse large B-cell lymphoma (DLBCL) and presents as leptomeningeal dissemination in two-thirds of cases. The prognosis of this event is dismal and treatment options are meager. Although major validated risk factors for CNS dissemination are clinical, concomitant MYC/BCL2 rearrangements as well as MYC/BCL2 protein expression have been recently associated with an increased risk of this complication.

Here we present the first case, to our knowledge, of a MYC/BCL6-positive double-hit DLBCL relapsing in the leptomeninges that achieved an outstanding durable remission with single-agent lenalidomide following salvage chemotherapy.

Introduction

In September 2014, a 73-year old man was admitted at our institution complaining of lumbar back pain and paresthesias of lower extremities 2 months after the completion of a first-line immunochemotherapy treatment program. The patient was previously diagnosed with a stage IA bulky, germinal center B-cell type (GCB) (CD10+, BCL-6+, BCL-2+ by immunohistochemistry), DLBCL, harboring concurrent MYC and BCL6 rearrangements and due to a past medical history of ischaemic heart disease he had received 6 cycles of rituximab, cyclophosphamide, vincristine, prednisone and nonpegylated liposomal doxorubicin with the achievement of a complete response. At time of admission, neurological examination and laboratory tests were negative. A whole-spine MRI was performed showing a leptomeningeal enhancement from T6 to the medullary cone on a T1-weighted image; the concurrent MRI of the brain was negative. The patient underwent a lumbar puncture and the cerebrospinal fluid (CSF) findings were consistent with a leptomeningeal recurrence of a DLBCL. Indeed, the CSF analysis by flow cytometry revealed a CD19, CD20, CD79a positive cell population with a cell count of 312 cells/ μ l. Alike, the cytology of the CSF demonstrated large malignant lymphoid cell with basophilic cytoplasm and prominent nucleoli (Figure 1). A systemic relapse was excluded through total body CT scanning and bone marrow biopsy.

Based on the CNS relapse, the patient started receiving a salvage treatment consisting of high dose methotrexate and cytarabine alternating with bi-weekly administration of intrathecal liposomal cytarabine for 4 cycles with a prompt recover of symptoms. Major reported toxicities were G2 oral mucositis after the first cycle and G4 pancytopenia after the third cycle and they were successfully handled through supportive care. At the end of salvage treatment, a good response was attained with only 1 cell/ μ l identified by both CSF flow cytometry and cytology; accordingly, the spinal MRI revealed a significant reduction of pathological leptomeningeal contrast enhancement.

Given patient's refusal to receive consolidation whole-brain RT as well as the high-risk disease we decided to administer lenalidomide single-agent at a dose of 15 mg daily for 21 consecutive days

every 4 weeks as maintenance therapy. The dose was reduced to 10 mg after the second cycle due to G4 neutropenia and infectious pneumonitis. A disease assessment performed after 8 cycles of lenalidomide showed no evidence of lymphoma on FDG-PET and spinal MRI. Similarly, CSF analysis was negative. The treatment with lenalidomide is still ongoing (month +9) and after dose reduction is optimally tolerated.

Discussion

Lymphomatous meningitis or lymphoma in the leptomeninges is an uncommon but almost universally fatal complication occurring in 5 to 29% of DLBCL patients with a median survival of 2.2 months [1-3]. Involvement of > 1 extranodal site, of certain extranodal sites such as testes, orbit, paranasal sinuses, breast and elevated LDH level are the most reliable risk factors for CNS recurrence in the post-rituximab era [4]. Interestingly, kidney and/or adrenal involvement was recently added to the five International Prognostic Index factors (age, elevated LDH, poor performance status, advanced stage, and involvement of > one extranodal site) into a robust and reproducible model for predicting CNS dissemination [5].

The best therapeutic approach of lymphomatous meningitis is still an unmet medical need mainly due to the poor capability of the drugs, even the most systemically active as the anti-CD20 rituximab, to effectively cross the blood-brain barrier. Intrathecal administration of chemotherapeutic agents including methotrexate and liposomal cytarabine is the preferred treatment choice with the aim of relieving patients' symptoms. Systemic chemotherapy with high dose methotrexate and cytarabine as well as radiotherapy are other commonly used treatment options in this setting, though associated with high toxicity rates. Moreover, rituximab given intrathecally is a promising strategy and is currently under investigation in early phase clinical trials [6]. The improved knowledge of the molecular pathogenesis of the disease occurred over recent years has provided insights into key molecular pathways and genomic aberrations amenable to small molecule targeting. The vast majority of primary CNS lymphoma (PCNSL) expresses MUM-1 (95%) and BCL6 (50% to 80%) and shares disrupted pathways with ABC-type systemic DLBCL such as BCR, NFkB, JAK-STAT, mTOR and PIM kinases [7]. The deregulation of BCR signalling has given the rationale to investigate pharmacologic antagonists of the BCR and downstream mediators in CNS lymphoma [8]. In this regard, the BTK inhibitor ibrutinib is being evaluated in combination with temozolomide, etoposide, doxil, dexamethasone and rituximab (TEDDI-R) in patients with untreated and refractory/relapsed PCNSL [9]. In this phase I/II study, all of 5 evaluable patients

experienced a tumor reduction after 2 cycles of TEDDI-R, 3 achieved a CR and 1 achieved a PR. Of interest, ibrutinib has shown to achieve meaningful CSF concentration.

In the last decade, also the small molecule lenalidomide has emerged as a highly effective and well-tolerated compound in refractory/relapsed systemic DLBCL with an antineoplastic effect mediated by the downmodulation of MUM1/IRF-4, and subsequently, BCR-dependent NFkB activity [10-12]. The high expression of MUM-1/IRF-4 in lymphoma involving the CNS and its role in the pathogenesis of the disease made it an attractive therapeutical target.

A couple of clinical reports suggesting a significant role of lenalidomide in aggressive lymphomas relapsing at intraocular site have recently been described and, interestingly, lenalidomide has been shown to adequately concentrate in the CSF at the 23.3% of serum level [13-14]. Moreover, there is early evidence of the activity of lenalidomide either as monotherapy or as maintenance after salvage interventions in patients with refractory/relapsed CNS DLBCL. Among 8 patients treated with lenalidomide single-agent, 4 achieved a CR and 3 a PR after 1 month of therapy; for patients with inadequate response to lenalidomide, intravenous plus intraventricular rituximab were also administered. Likewise, in a cohort of 10 patients receiving maintenance lenalidomide, 5 maintained their response for ≥ 2 years [15].

We report herein a case of long-lasting complete response to lenalidomide as maintenance therapy after an uncomplete response to salvage chemotherapy in a patient with MYC/BCL6-positive double-hit DLBCL with leptomeningeal relapse. The remission is still ongoing at 9 months from treatment initiation with a survival outcome superior to those historically reported for this patient's population. The result achieved in our patient is even of greater interest given that he has a GCB-type DLBCL, whose response rate to lenalidomide has been showed to be lower (9%) than that of non-GCB-type (59%) [16]. However, owing to its favorable risk-to benefit ratio as well as its activity in the relapsed disease, we decided to give our patient lenalidomide as maintenance therapy. The ability of lenalidomide to achieve meaningful CSF concentration along with its mechanism of action aimed at targets overexpressed in CNS lymphoma such as MUM1/IRF-4 are potential key

elements of the therapeutic activity of the drug. Based on this and previously reported cases, its effectiveness across different subtype of NHLs as well as its capability of penetrating the blood-brain barrier, we believe that lenalidomide deserves further investigation either alone or in combination with chemotherapy as first-line treatment in patients with primary and secondary CNS lymphomas.

Author disclosures

The authors declare that they do not have any potential conflicts of interest.

Ethical considerations

The treatment was internally approved and administered in accordance with Italian policy.

Informed consent was obtained from the patient for publication of this Case report and any accompanying images.

Author contributions

Maiorana A. and Bettelli S. equally contributed to data analysis and interpretation. Salati M. and Tarantino V, equally contributed to collection and assembly of data. Luminari S. provided the case.

All authors contributed to conception and design, manuscript writing and final approval of manuscript.

References

1. Bernstein SH, Unger JM, Leblanc M, *et al.* Natural history of CNS relapse in patients with aggressive non-Hodgkin's lymphoma: a 20-year follow-up analysis of SWOG 8516 — the Southwest Oncology Group. *J Clin Oncol* 2009; **27**: 114-119.
2. Savage KJ, Sehn LH, Villa D, *et al.* The impact of concurrent MYC BCL2 protein expression on the risk of secondary central nervous system relapse in diffuse large B-cell lymphoma (DLBCL). *Blood* (ASH Annual Meeting Abstracts) 2014. p495a.
3. Ferreri AJ, Assanelli A, Crocchiolo R, *et al.* Central nervous system dissemination in immunocompetent patients with aggressive lymphomas: incidence, risk factors and therapeutic options. *Hematol Oncol* 2009; **27**: 61-70.
4. Fletcher CD, Kahl BS. Central nervous system involvement in diffuse large B-cell lymphoma: an analysis of risks and prevention strategies in the post-rituximab era. *Leuk Lymphoma* 2014; **55**: 2228-40.
5. Savage KJ, Zeynalova S, Kansara RR, *et al.* Validation of a Prognostic Model to Assess the Risk of CNS Disease in Patients with Aggressive B-Cell Lymphoma. *Blood* (ASH Annual Meeting Abstracts) 2014. p394a.
6. Rubenstein JL, Li J, Chen L, *et al.* Multicenter phase 1 trial of intraventricular immunochemotherapy in recurrent CNS lymphoma. *Blood* 2013; **121**: 745-51.
7. Kadoch C, Treseler P, Rubenstein JL. Molecular pathogenesis of primary central nervous system lymphoma. *Neurosurg Focus* 2006; **21**: E1.
8. Montesinos-Rongen M, Schafer E, Siebert R *et al.* Genes regulating the B cell receptor pathway are recurrently mutated in primary central nervous system lymphoma. *Acta Neuropathol* 2012; **124**: 905–906.

9. Dunleavy K, Lai C, Roschewski M, *et al.* Phase I/II of TEDDI-R with ibrutinib in untreated relapsed/refractory primary CNS lymphoma. *Hematol Oncol (ICML Abstracts)* 2015. **33**: 174-175.
10. Witzig TE, Vose JM, Zinzani PL, *et al.* An international phase II trial of single-agent lenalidomide for relapsed or refractory aggressive B-cell non-Hodgkin's lymphoma. *Ann Oncol* 2011; **22**: 1622-7.
11. Zinzani PL, Rigacci L, Cox MC, *et al.* Lenalidomide monotherapy in heavily pretreated patients with non-Hodgkin lymphoma: an Italian observational multicenter retrospective study in daily clinical practice. *Leuk Lymphoma* 2015; **56**: 1671-6.
12. Gribben JG, Fowler N, Morschhauser F. Mechanisms of Action of Lenalidomide in B-Cell Non-Hodgkin Lymphoma. *J Clin Oncol* 2015; **33**: 2803-11.
13. Rubenstein JL, Treseler PA, Stewart PJ. Regression of refractory intraocular large B-cell lymphoma with lenalidomide monotherapy. *J Clin Oncol* 2011; **29**: 595–597.
14. Cox MC, Mannino G, Lionetto L, *et al.* Lenalidomide for aggressive B-cell lymphoma involving the central nervous system? *Am J Hematol* 2011; **86**: 957.
15. Rubenstein JL, Formaker P, Wang X, *et al.* 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.
16. Hernandez-Ilizaliturri FJ, Deeb G, Zinzani PL, *et al.* Higher response to lenalidomide in relapsed/refractory diffuse large B-cell lymphoma in nongerminal center B-cell-like than in germinal center B-cell-like phenotype. *Cancer* 2011; **117**: 5058-5066.

Figure 1. CSF evaluation at time of CNS relapse.