Application of Lenalidomide on Diffused Large B-cell Lymphoma: Salvage, Maintenance, and Induction Treatment

Li-Yangxue Ma, Li Su

Department of Hematology, Xuanwu Hospital, Capital Medical University, Beijing 100053, China

Diffuse large B-cell lymphoma (DLBCL) is the most common lymphoid neoplasms in adults. Through the decades, rituximab, cyclophosphamide, doxorubicin, prednisone, and vincristine (R-CHOP) therapy has dramatically improved the clinical outcome due to the introduction of rituximab. Even so, still about 30–40% of patients ultimately relapse or progress, which become difficult to manage. A study has shown that patients with primary refractory DLBCL or early relapse after rituximab-containing therapy have a very poor prognosis,[1] which makes the introduction of novel drugs to DLBCL regimen definitely an urge demand.

The history of immunomodulatory drugs (IMiDs) was originated from the application of thalidomide to prevent nausea during pregnancy in 1950s. A few years later, it was withdrawn because deformed infants with phocomelia began to surface. The inhibition of thalidomide on new formations led to the discovery of new pharmacological antiangiogenic effect and its new application in tumor therapy. The clinical outcomes in the treatment of malignant diseases were impressive, especially in hematological malignant diseases. Lenalidomide, one of the second-generation IMiDs, had shown its efficacy on multiple myeloma (MM), myelodysplastic syndrome (MDS) associated with deletion 5q, and mantle cell lymphoma in various clinical trials. Consequently, lenalidomide has been approved by Food and Drug Administration for the treatment of those diseases. Notably, the latest National Comprehensive Cancer Network guideline recommended lenalidomide as the regimen of the first-line treatment of MM and MDS associated with del(5q). Based on its mechanisms that have been explored, several clinical trials have been executed to explore the efficacy of lenalidomide on B-cell lymphoma,[2] especially R/R DLBCL. Until now, lenalidomide has shown impressive activity in both monotherapy and combination therapy on R/R DLBCL patients, especially in elderly patients. This review highlights the new insight into its mechanism on treating lymphoma and the studies exploring efficiencies of lenalidomide on DLBCL patients for salvage, maintenance, and introduction, both as a single agent and in combinations.

Lenalidomide, an analog of thalidomide, makes itself distinct from both traditional chemotherapy and monoclonal antibody-based therapy. The mechanism that has been demonstrated includes antiproliferative, immunomodulatory, and antiangiogenic properties.

Cereblon (CRBN), a substrate adaptor of E3 ubiquitin ligase, was identified as the primary target for lenalidomide-induced teratogenesis.[3] The pharmacologic mechanism of action includes binding to the $CRL4^{CRBN}$ E3 ubiquitin ligase complex (E3 complex) through CRBN and modulating substrates (such as IKZF1 and IKZF3), which leads to the interference with life circle of cells. IKZF1 and IKZF3 encode two transcription factors IKAROS and AIOLOS, respectively, regulating the vital transcriptional network. In particular, IKZF3 regulates the expression of interferon regulatory factor 4, which is in dominate position of a positive feedback loop with MYC as well as many other genes essential to cell survival. In addition, a study[4] has shown that the ETS transcription factor SPI-B, which is overexpressed in ABC-DLBCL and required for its survival, is one of the targets of IKAROS. The reduction of IKZF1 by lenalidomide leads to downregulating the level of SPI-B mRNA and resulting in the subsequent death of ABC-DLBCL cells.

The mechanism of immunomodulation has been shown to involve three different aspects: cytokine modulation, T-cell co-stimulation, and antibody-dependent cellular

Address for correspondence: Prof. Li Su,
Department of Hematology, Xuanwu Hospital, Capital Medical University,
Beijing 100053, China
E-Mail: suli9000@sina.cn

Access this article online

Quick Response Code:

Website: www.cmj.org

DOI: 10.4103/0366-6999.243567

Received: 22-05-2018 **Edited by:** Li-Shao Guo
How to cite this article: Ma LY, Su L. Application of Lenalidomide on Diffused Large B-cell Lymphoma: Salvage, Maintenance, and Induction Treatment. Chin Med J 2018;131:2510-3.

cytotoxicity (ADCC) regulation.[5] Some studies suggest that the immunomodulation property depends on the proper functioning of E3 complex.[6] The level of IKZF1 and IKZF3 has been shown to affect the production of interleukin-2 and other cytokines,[7] subsequently enhance the antigen presentation by dendritic cells (DC), promote the interaction between T cells and DC, and alter the shift of T helper differentiation. ADCC has been increased by IMiDs through enhancing natural killer (NK) cells through the stimulation of DC and modification of the cytokine microenvironment.[8] IMiDs upregulate the abundance of monocyte chemotactic protein-1, tumor necrosis factor-α, and interferon-γ[9] to stimulate the expression of functional receptors on NK cells.

The first generation of IMiDs drew attention mostly because of the reports of deformed infants with phocomelia; the growth of limbs has been restricted due to the deficiency of new blood capillaries. Both the bad reputation and its withdrawal led to the discovery of the antiangiogenic mechanism. A research showed that IMiDs exhibited antiangiogenic effects on lymphoma in mice.[9] With the upregulation of SPARC, a tumor-suppressor gene that displays antiproliferative, antiadhesive, and antiangiogenic properties in 5q– syndrome, lenalidomide was considered antiangiogenesis *in vivo*.[10] In 2009, Dredge *et al*.[11] revealed that lenalidomide inhibited the phosphorylation of vascular endothelial growth factor-induced Akt-1 in endothelial cells and offered more solid proof for this mechanism. However, based on clinical outcomes that have been published, the application of lenalidomide on the treatment of solid tumor seems not promising. Research on deeper understanding of its molecular mechanism is still needed.

In 2008, Wiernik *et al*.[12] reported the first clinical trial about lenalidomide monotherapy in R/R aggressive non-Hodgkin's lymphoma. The efficacy of lenalidomide treatment for R/R DLBCL patients was first demonstrated, and safety was claimed manageable. After that, most researchers started with relapsed and refractory patients. Czuczman *et al*.[13] reported a trial that 102 R/R DLBCL patients received lenalidomide (25 mg/d, 21 days of 28-day cycle) or investigator's choice (R-CHOP, R-ICE, R-DHAP, R-GemOx, etc). Patients in lenalidomide arm had an overall response rate (ORR) of 27.5% versus 11.8% with IC treatment, and median progression-free survival (PFS) of patients received lenalidomide was increased with greater improvements in non-Germinal Center B (GCB, cell-like lymphoma) patients compared with GCB cell-like lymphoma. Treatment-emergent adverse events (TEAEs) in both arms were similar and acceptable. Although the IC arm could be a limitation, these results were promising, proving both better efficacy and safety of lenalidomide compared with current clinical treatments.

The combination with traditional regimens also demonstrated its potential, according to Wang's Phase 2 clinical trial.[14] After lenalidomide-rituximab therapy, ORR and the rate of complete response (CR) of 32 enrolled patients were 28% and 22%, respectively. The combination was claimed well tolerated and effective. The efficacy of lenalidomide-rituximab therapy could serve as a framework for further rational combination with other agents, and stem cell translation after lenalidomide-rituximab was claimed associated with prolonged response duration.

The combination of lenalidomide and rituximab therapy for elderly patients showed high and continuous CR, according to Zinzani *et al*.'s trial.[15] Twenty-three elderly patients with R/R DLBCL were enrolled and given lenalidomide and rituximab as induction treatment, and ORR was 35% ($n = 8$). Ten patients were enrolled in lenalidomide maintenance afterward, 8 of them achieved CR. The updated outcomes[7] revealed the median duration of CR were 5 years and a disease-free survival was 75% at 6 years. Six patients (26%) obtained a very long-term continuous CR which may represent an indication of high efficacy of the combination maintenance.

These trials showed impressive outcomes for R/R DLBCL. Moreover, some other clinical trials of salvage treatment for patients with R/R DLBCL since 2010 are listed in Table 1. The rate of CR and duration of PFS differ greatly probably because of the different design and small sample.

With the encouraging benefit obtained from salvage treatment of lenalidomide alone or with other regimes, it is conceivable that lenalidomide could be added into

Table 1: Selected studies of lenalidomide in R/R DLBCL

Reference	Design	Disease status	Number of patients	Median age (years)	ORR	CR	Median PFS (months)
Hernandez-Ilizaliturri *et al*., 2011[16]	L: 25 mg/d d1–d21	R/R DLBCL	40	66	27.5% (non-GCB 53%, GCB 9%)	15% (non-GCB 29.4%, GCB 4.3%)	6.4 (non-GCB 10.8, GCB 3.3)
Witzig *et al*., 2011[17]	L: 25 mg/d d1–d21	R/R NHL	ALL: 217 DLBCL: 108	66	ALL: 35% DLBCL: 28%	ALL: 13% DLBCL: 7%	ALL: 3.7 DLBCL: 2.7
Mondello *et al*., 2016[10]	Retrospect L: 15 or 25 mg/d d1–d21	R/R DLBCL	123	64	37%	17%	34
Zinzani *et al*., 2015[18]	L: 10–25 mg/d d1–d21	R/R NHL	ALL: 64 DLBCL: 19	71	ALL: 42.2%	ALL: 42.2% DLBCL: 42.1%	DLBCL: 10.9
Ivanov *et al*., 2014[19]	Retrospective L: 20 mg/d d1–d21 + rituximab	R/R DLBCL	17	62	41.20%	35.30%	2-year PFS: 38%

DLBCL: Diffuse large B-cell lymphoma; GCB: Germinal center B-cell like lymphoma; NHL: Non-Hodgkin's lymphoma; ORR: Overall response rate; CR: Complete response; PFS: Progression-free survival; ALL: All patients involved.

maintenance therapy. Rituximab, targeted agents enzastaurin and everolimus, used to be involved as maintenance therapies. However, no reports showed more efficacy than risk[20] for DLBCL patients. Compared with those drugs mentioned above, lenalidomide is a kind of oral medicine with better tolerance, meaning better compliance and controllability.

The REMARC study,[21] which was a multicenter, double-blind, randomized, placebo-controlled Phase III trial, explored the difference between lenalidomide and placebo as maintenance in responding elderly patients with previously untreated DLBCL. Six hundred and fifty patients (60–80 years old) were enrolled, and median PFS was not reached for lenalidomide arm. However, in placebo arm, the median PFS was 58.9 months. The study demonstrated that lenalidomide maintenance significantly prolonged PFS in elderly patients, with no more TEAEs. However, this trial showed almost no difference among subtypes and was lack of overall survival (OS) benefit.

Based on the conclusion of recent trials that lenalidomide provided more benefits for R/R and responding patients in sequence treatment, researchers have expected efficacy of lenalidomide in induction treatment. A Phase 2 study[22] showed the safety and efficiency of lenalidomide plus R-CHOP (R2CHOP) in newly diagnosed DLBCL (subtype was non-GCB). Sixty patients received R2CHOP. The ORR was 98% and CR was 80%. OS rates at 24 months were 78%. The R2CHOP therapy showed no difference in PFS or OS between subgroups of GCB and non-GCB, which may lead to a wider application despite different subtypes.

With the difficulty of improving the outcome of R-CHOP on ABC-type DLBCL, the introduction of lenalidomide may be the key to the revolution. ROBUST,[23] a clinical trial protocol focused on the upgrading results of R2CHOP over placebo on ABC-type DLBCL, is enrolling at centers in different continents. Solid data and probably promising outcomes could be expected. More clinical trials with large sample and randomized double-blind design are needed for better evidence-based medicine.

Acknowledgment

We thank CQ Xia, MD. PhD and Mr. Will Donelan, for critical reading and assistance with the manuscript.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

References

1. Gisselbrecht C, Glass B, Mounier N, Singh Gill D, Linch DC, Trneny M, *et al.* Salvage regimens with autologous transplantation for relapsed large B-cell lymphoma in the rituximab era. J Clin Oncol 2010;28:4184-90. doi: 10.1200/JCO.2010.28.1618.
2. Garciaz S, Coso D, Schiano de Colella JM, Bouabdallah R. Lenalidomide for the treatment of B-cell lymphoma. Expert Opin Investig Drugs 2016;25:1103-16. doi: 10.1080/13543784.2016.1208170.
3. Ito T, Ando H, Suzuki T, Ogura T, Hotta K, Imamura Y, *et al.* Identification of a primary target of thalidomide teratogenicity. Science 2010;327:1345-50. doi: 10.1126/science.1177319.
4. Solomon LA, Batista CR, DeKoter RP. Lenalidomide modulates gene expression in human ABC-DLBCL cells by regulating IKAROS interaction with an intronic control region of SPIB. Exp Hematol 2017;56:46-570. doi: 10.1016/j.exphem.2017.09.002.
5. Schafer PH, Gandhi AK, Loveland MA, Chen RS, Man HW, Schnetkamp PP, *et al.* Enhancement of cytokine production and AP-1 transcriptional activity in T cells by thalidomide-related immunomodulatory drugs. J Pharmacol Exp Ther 2003;305:1222-32. doi: 10.1124/jpet.102.048496.
6. Fink EC, Ebert BL. The novel mechanism of lenalidomide activity. Blood 2015;126:2366-9. doi: 10.1182/blood-2015-07-567958.
7. Zinzani PL, Pellegrini C, Argnani L, Broccoli A. Prolonged disease-free survival in elderly relapsed diffuse large B-cell lymphoma patients treated with lenalidomide plus rituximab. Haematologica 2016;101:385-6. doi: 10.3324/haematol.2016.147256.
8. Krieg S, Ullrich E. Novel immune modulators used in hematology: Impact on NK cells. Front Immunol 2012;3:388. doi: 10.3389/fimmu.2012.00388.
9. Reddy N, Hernandez-Ilizaliturri FJ, Deeb G, Roth M, Vaughn M, Knight J, *et al.* Immunomodulatory drugs stimulate natural killer-cell function, alter cytokine production by dendritic cells, and inhibit angiogenesis enhancing the anti-tumour activity of rituximab *in vivo*. Br J Haematol 2008;140:36-45. doi: 10.1111/j.1365-2141.2007.06841.x.
10. Pellagatti A, Jädersten M, Forsblom AM, Cattan H, Christensson B, Emanuelsson EK, *et al.* Lenalidomide inhibits the malignant clone and up-regulates the SPARC gene mapping to the commonly deleted region in 5q – syndrome patients. Proc Natl Acad Sci U S A 2007;104:11406-11. doi: 10.1073/pnas.0610477104.
11. Dredge K, Horsfall R, Robinson SP, Zhang LH, Lu L, Tang Y, *et al.* Orally administered lenalidomide (CC-5013) is anti-angiogenic *in vivo* and inhibits endothelial cell migration and Akt phosphorylation *in vitro*. Microvasc Res 2005;69:56-63. doi: 10.1016/j.mvr.2005.01.002.
12. Wiernik PH, Lossos IS, Tuscano JM, Justice G, Vose JM, Cole CE, *et al.* Lenalidomide monotherapy in relapsed or refractory aggressive non-Hodgkin's lymphoma. J Clin Oncol 2008;26:4952-7. doi: 10.1200/JCO.2007.15.3429.
13. Czuczman MS, Trněný M, Davies A, Rule S, Linton KM, Wagner-Johnston N, *et al.* A phase 2/3 multicenter, randomized, open-label study to compare the efficacy and safety of lenalidomide versus investigator's choice in patients with relapsed or refractory diffuse large B-cell lymphoma. Clin Cancer Res 2017;23:4127-37. doi: 10.1158/1078-0432.
14. Wang M, Fowler N, Wagner-Bartak N, Feng L, Romaguera J, Neelapu SS, *et al.* Oral lenalidomide with rituximab in relapsed or refractory diffuse large cell, follicular and transformed lymphoma: A phase II clinical trial. Leukemia 2013;27:1902-9. doi: 10.1038/leu.2013.95.
15. Zinzani PL, Pellegrini C, Gandolfi L, Stefoni V, Quirini F, Derenzini E, *et al.* Combination of lenalidomide and rituximab in elderly patients with relapsed or refractory diffuse large B-cell lymphoma: A phase 2 trial. Clin Lymphoma Myeloma Leuk 2011;11:462-6. doi: 10.1016/j.clml.2011.02.001.
16. Hernandez-Ilizaliturri FJ, Deeb G, Zinzani PL, Pileri SA, Malik F, Macon WR, *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;117:5058-66. doi: 10.1002/cncr.26135.
17. Witzig TE, Vose JM, Zinzani PL, Reeder CB, Buckstein R, Polikoff JA, *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.doi: 10.1093/annonc/mdq626.
18. Zinzani PL, Rigacci L, Cox MC, Devizzi L, Fabbri A, Zaccaria A, *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. doi: 10.3109/10428194.2014.964702.
19. Ivanov V, Coso D, Chetaille B, Esterni B, Olive D, Aurran-Schleinitz T, *et al.* Efficacy and safety of lenalinomide combined with rituximab in patients with relapsed/refractory diffuse large B-cell lymphoma. Leuk Lymphoma 2014;55:2508-13. doi: 10.3109/10428194.2014.889822.
20. Reddy NM, Thieblemont C. Maintenance therapy following induction chemoimmunotherapy in patients with diffuse large B-cell lymphoma: Current perspective. Ann Oncol 2017;28:2680-90. doi: 10.1093/annonc/mdx358.
21. Thieblemont C, Tilly H, Gomes da Silva M, Casasnovas RO, Fruchart C, Morschhauser F, *et al.* Lenalidomide maintenance compared with placebo in responding elderly patients with diffuse large B-cell lymphoma treated with first-line rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone. J Clin Oncol 2017;35:2473-81. doi: 10.1200/JCO.2017.72.6984.
22. Nowakowski GS, LaPlant B, Macon WR, Reeder CB, Foran JM, Nelson GD, *et al.* Lenalidomide combined with R-CHOP overcomes negative prognostic impact of non-germinal center B-cell phenotype in newly diagnosed diffuse large B-cell lymphoma: A phase II study. J Clin Oncol 2015;33:251-7. doi: 10.1200/JCO.2014.55.5714.
23. Nowakowski GS, Chiappella A, Witzig TE, Spina M, Gascoyne RD, Zhang L, *et al.* ROBUST: Lenalidomide-R-CHOP versus placebo-R-CHOP in previously untreated ABC-type diffuse large B-cell lymphoma. Future Oncol 2016;12:1553-63. doi: 10.2217/fon-2016-0130.