Effect and Safety of Orelabrutinib and Lenalidomide Plus R-mini CDOP in Relapsed/Refractory Aggressive B-cell Non-Hodgkin Lymphoma

Relaps/Refrakter Agresif B-hücre Non-Hodgkin Lenfomada Orelabrutinib ve Lenalidomidle Birlikte R-Mini CDOP Kullanımının Etki ve Güvenilirliği

Ying Shang[1], Hongyu Zhao[2], Daqi Li[2]

[1]*Shandong First Medical University & Shandong Academy of Medical Sciences, Shandong, China*
[2]*Central Hospital Affiliated to Shandong First Medical University, Shandong, China*

To the Editor,

Aggressive B-cell non-Hodgkin lymphoma (B-NHL) progresses quickly and has poor prognosis, especially among elderly patients. Rituximab combined with low-dose cyclophosphamide, doxorubicin, vincristine, and prednisone (R-mini CHOP) is the first-line treatment for elderly patients [1]. However, the effects of the medicine become uncertain with the diminution of the dose of chemotherapy. As the latest type of Bruton tyrosine kinase (BTK) inhibitor, orelabrutinib has shown good safety and tolerance in long-term therapy because of its high selectivity [2]. We conducted a retrospective analysis of 11 elderly patients with relapsed/refractory (r/r) aggressive B-NHL to evaluate the efficacy and safety of combination therapy including orelabrutinib and lenalidomide plus R-mini CDOP (OR2-miniCDOP).

All patients had received combination regimens of OR2-miniCDOP. R-mini CDOP consisted of rituximab at 375 mg/m^2 intravenously once on day 1, pegylated liposomal doxorubicin at 25 mg/m^2 once on day 2, cyclophosphamide at 400 mg/m^2 once on day 2, vindesine at 2.5 mg/m^2 once on day 2, and 40 mg/m^2 of oral prednisone once daily on days 2-6. Oral orelabrutinib (150 mg once a day) and lenalidomide (25 mg once daily on days 2-8) were administered with adjustments of the doses and timing according to neutrophils, platelet levels, and other signs of tolerance during the treatment process.

A total of 11 eligible elderly patients with r/r aggressive B-cell NHL were included in this retrospective study. All patients were included in efficacy analysis (Table 1). According to computed tomography imaging, the partial response rate after two cycles of treatment was 82%. By the end of follow-up, excellent responses were achieved, including 6 complete responses, 3 partial responses, 1 case of stable disease, and 1 case of progressive disease, which resulted in an overall response rate of 81%. One patient died due to tumor progression. A total of 34 courses of treatment had been completed. Median progression-free survival and overall survival were not reached.

Thirty-five complications occurred in this group of patients. The most common were hematological adverse events (AEs), including anemia 10 (29%) times, hypokalemia 8 (23%) times, thrombocytopenia 5 (14%) times, and neutropenia 4 (11%) times. Non-hematologic adverse reactions are listed in Table 1. Grade 3 or higher AEs occurred 3 (9%) times, including neutropenia, hypokalemia, and anemia.

BTK is the key tyrosine kinase in the BCR signaling pathway, which plays a role in the BCR signaling of malignant B cells [3,4]. Thus, drugs aimed at BTK may inhibit the abnormal proliferation of B-NHL. Orelabrutinib is a highly selective BTK inhibitor with a low frequency of off-target adverse events [5]. Yu et al. [6] demonstrated that orelabrutinib combined with rituximab could maintain the function of NK-cell-mediated antibody-dependent cellular cytotoxicity (ADCC) induced by rituximab and produce combined antitumor effects in B-cell lymphomas.

The distinctly altered biodistribution pattern of liposomal doxorubicin reduced the drug exposure of heart muscles and thus the risk of cardiotoxicity [7,8]. A previous study showed that through NK cell-mediated and monocyte-mediated ADCC mechanisms in vitro, lenalidomide might enhance the rituximab-induced killing of B-NHL cells [9]. These factors make OR2-miniCDOP treatment safer and more effective.

Our findings have shown that OR2-miniCDOP treatment has good antitumor activity and acceptable toxicity and it might constitute a promising therapeutic strategy.

Keywords: Relapsed/refractory aggressive B-cell lymphoma, Orelabrutinib, Lenalidomide, R-mini CDOP

Anahtar Sözcükler: Relpas/refrakter agresif B-hücre lenfoma, Orelabrutinib, Lenalidomid, R-mini CDOP

Ethics

Informed Consent: Was obtained.

Table 1. Patients' clinical characteristics.

Patient no.	Age (years)	Sex	Diagnosis	Response	PFS, days	OS, days	AEs		
							Hematological AEs	Non-hematologic AEs	Grade ≥4 AEs
1	68	Male	DLBCL	PR	60	60	Anemia, hypokalemia, neutropenia	None	Anemia
2	61	Female	DLBCL	PD	35	70	Anemia, hypokalemia, thrombocytopenia	Lung infection	None
3	75	Female	DLBCL	CR	490	490	Anemia, hypokalemia	Lung infection	None
4	61	Female	DLBCL	CR	489	489	Anemia, hypokalemia	None	None
5	62	Female	DLBCL	CR	482	482	Anemia, hypokalemia	None	None
6	76	Female	MCL	PR	474	474	Anemia, hypokalemia, thrombocytopenia	Lung infection	None
7	72	Male	DLBCL	CR	439	439	Anemia, hypokalemia, Thrombocytopenia, neutropenia	Atrial fibrillation, lung infection	Hypokalemia
8	71	Female	DLBCL	PR	45	45	Anemia	Acute cerebral infarction	None
9	66	Male	DLBCL	CR	123	123	Anemia, neutropenia	None	None
10	69	Female	DLBCL	CR	64	64	Hypokalemia, neutropenia	Drug-induced liver injury, lung infection	Neutropenia
11	60	Male	DLBCL	SD	41	41	None	None	None

DLBCL: Diffuse large B-cell lymphoma, MCL: mantle cell lymphoma, CR: complete response, PR: partial response, SD: stable disease, PD: progressive disease, PFS: progression-free survival, OS: overall survival, AEs: adverse events.

Authorship Contributions

Surgical and Medical Practices: H.Y.; Concept: D.L.; Design: D.L.; Data Collection or Processing: Y.S.; Analysis or Interpretation: H.Z.; Literature Search: Y.S.; Writing: Y.S.

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Address for Correspondence/Yazışma Adresi: Daqi Li, M.D., Central Hospital Affiliated to Shandong First Medical University, Shandong, China
Phone : +8613370582167
E-mail : ldq9194@126.com ORCID: orcid.org/0000-0001-7887-2819

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