LETTER TO THE EDITOR

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Ruxolitinib for the Treatment of Refractory Idiopathic Multicentric Castleman Disease: A Case Report

Refrakter İdiyopatik Multisentrik Castleman Hastalığının Tedavisinde Ruxolitinib: Bir Olgu Sunumu

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To the Editor,

A 46-year-old woman with a 4-month history of severe fatigue was admitted to our hospital in November 2018. Positron emission tomography/computed tomography revealed hepatosplenomegaly and multiple enlarged lymph nodes with slightly elevated ^{18}F-fluorodeoxyglucose uptake. Biopsy of the right axillary lymph node was consistent with the plasma cell subtype of Castleman disease (CD), with immunohistochemistry results revealing positivity for CD20, CD138, CD3, immunoglobulin (Ig) G, kappa, lambda, and Ki-67 (index: 10%). Laboratory tests showed mild anemia (hemoglobin: 113 g/L), elevated platelet count (406x10^9 cells/L), impaired renal function with elevated serum creatinine level (141 µmol/L), elevated C-reactive protein (CRP) (69.20 mg/L), and hypergammaglobulinemia (IgG, 30.48 g/L) without monoclonal gammopathy. The serum albumin level was 36 g/L. Human herpes virus-8 (HHV-8)/HIV test results were negative. According to the Castleman Disease Collaborative Network (CDCN) diagnostic criteria [1], she was diagnosed with non-severe idiopathic multicentric CD-not otherwise specified subtype (iMCD-NOS).

Siltuximab, the only US Food and Drug Administration-approved therapy, was not available in China at the time, and other recommended treatment options for non-severe iMCD, such as tocilizumab and rituximab, were off-label regimens in China and required additional intravenous administration. Therefore, the TCD regimen (thalidomide, cyclophosphamide, and dexamethasone) was initiated as the first-line therapy for this patient [2]. Six cycles were given, but her condition did not improve and was evaluated as stable disease according to the CDCN response criteria [3]. A subsequent BCD regimen (bortezomib, cyclophosphamide, and dexamethasone) [4] was started and partial remission (PR) was achieved after 3 months [3]. However, disease progression occurred soon, and ruxolitinib (10 mg/day) was started as a third-line treatment with a rapid response (Table 1). After 12 months, the patient was free of constitutional symptoms. Physical examination showed no abnormalities in superficial lymph nodes. Hemoglobin, albumin, and CRP values normalized and renal function was improved. PR was achieved again [3]. She has had no flares or adverse events for more than 2 years and is still receiving ruxolitinib treatment.

iMCD represents a group of poorly understood lymphoproliferative disorders [1]. Interleukin-6 (IL-6) is the most important established cytokine in iMCD and the overactivation of IL-6 signaling, probably through Janus kinase (JAK)-signal transduction and transcriptional activator 3 (STAT3), has been considered to be the main pathogenic pathway in at least a portion of iMCD cases [5,6]. IL-6 blocking, although ineffective in more than 50% of patients, is the recommended frontline treatment for iMCD regardless of severity classification [3,7]. Recent serum proteomics found that IL-6-JAK-STAT3 signaling was significantly enriched even in IL-6 blocking non-responders [5], and that result was further supported by lymph node tissue-based immunohistochemistry with significantly increased phosphorylated-STAT3 expression in both non-responders and responders. These results suggest that the JAK-STAT3 pathway may be generally involved in the pathogenesis of iMCD. In addition, links between type I interferon stimulation and mammalian target of rapamycin (mTOR) activation in patients with iMCD and furthermore between IL-6 and mTOR were described, both of which could be eliminated by JAK1/2 inhibition [6].

Therefore, targeting JAK1/2 may be useful in iMCD treatment. Ruxolitinib is a potent and selective JAK1/2 inhibitor approved for the treatment of myelofibrosis [8]. Successful treatment of iMCD-thrombocytopenia, anasarca, fever, reticulin fibrosis, and organomegaly (TAFRO) with ruxolitinib has been reported in some cases [9,10]. However, it is not evident whether these

Table 1. Changes in key features with ruxolitinib treatment.

	Months since initiation of ruxolitinib treatment										
Variables	-3	0	3	6	9	12	15	18	21	24	27
Treatment											
Ruxolitinib, mg/day	-	10	15	15	10	10	10	10	10	10	5
Dexamethasone, mg/week	20	20	10	5	5	-	-	-	-	-	-
Key features											
CRP, mg/L	56.26	59.06	21.34	23.15	14.17	7.9	16.06	10.2	-	7.18	9.08
Hemoglobin, g/L	133	127	124	121	130	142	140	134	139	134	132
Platelet count, $x10^9$/L	268	325	416	476	352	375	269	349	295	349	337
Albumin, g/L	42	41	42	43	43	46	45	46	46	45	44
Creatinine, µmol/L	123	113	120	103	96	108	107	108	106	104	111
IgG, g/L	10.16	11.38	9.83	12.14	11.7	12.95	12.2	13.18	-	13.68	-
IL-6, pg/mL	10.3	10.4	7.9	7.9	4.9	4.3	3.2	2.9	-	3.3	5
TNF-α, pg/mL	15.7	10.9	8.8	9.1	7.9	7.8	11.7	7.1	-	9.5	-

CRP: C-reactive protein; IgG: immunoglobulin G; IL-6: interleukin 6; TNF-α: tumor necrosis factor alpha.

findings can be generalized to a larger cohort of patients with iMCD, as patients with iMCD-NOS have different profiles from iMCD-TAFRO [1]. Our case provides original clinical data for JAK1/2 inhibition in iMCD-NOS. Future prospective studies are needed to determine the effectiveness of JAK1/2 inhibitors in the treatment of iMCD.

Keywords: Idiopathic multicentric Castleman disease, Janus kinase inhibitor, Ruxolitinib, Treatment

Anahtar Sözcükler: İdiyopatik multisentrik Castleman hastalığı, Janus kinaz inhibitörü, Ruxolitinib, Tedavi

Ethics

Informed Consent: Written informed consent was obtained from the patient for publication.

Authorship Contributions

Data Collection or Processing: M.H.D., L.Z.; Analysis or Interpretation: J.L., L.Z.; Writing: Y.H.G.

Conflict of Interest: No conflict of interest was declared by the authors.

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