

# Severe Lymphocytosis in a Case of Diffuse Large B-Cell Lymphoma Treated by Ibrutinib

İbrutinib ile Tedavi Edilen Bir Diffüz Büyük B Hücreli Lenfoma Olgusunda Ciddi Lenfositoz

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## To the Editor,

We would like to report extreme leukocytosis in a case of diffuse large B-cell lymphoma (DLBCL) treated by ibrutinib [1]. To the best of our knowledge, this is the first case of a very high white blood cell (WBC) count in a patient with DLBCL.

A 63-year-old man was diagnosed with stage IV-B DLBCL with bone marrow (BM) infiltration. He had double-hit lymphoma and Ki67 was 90%. Two cycles of a dose-adjusted rituximab, etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin (R-EPOCH) regimen were given with clinical and radiologic improvement. However, lymphomatous skin lesions confirmed by cytologic examination developed. Computerized tomography (CT) scans showed progressive disease. In the original biopsy sample, PD-L1 expression was detected in 30% of lymphoma cells. A rituximab-vinorelbine-gemcitabine-prednisolone regimen was given for two cycles as second-line treatment. However, rapid progression developed and an ibrutinib-nivolumab combination was planned and prescribed. Four days after ibrutinib treatment, WBC and lymphocyte/monocyte counts increased rapidly and peaked at  $100 \times 10^9/L$  on the 20<sup>th</sup> day of treatment. Mononuclear cells were larger than mature lymphocytes with nucleolus-like bodies. Flow cytometric surface analysis showed CD10: 96%, HLA-DR: 55.8%, cCD79a: 53.6%, CD45: 100%, CD19: 13%, CD20: 0% expression. Nivolumab was given on the 14<sup>th</sup> day of ibrutinib treatment. CT scans showed regression of abdominal lymph nodes. However, febrile complication developed and he died due to infection.

It is well known that lymphocytes with CD19 and CD5 positivity and CD3 negativity increase in such cases [2]. Lymphocytosis in cases of chronic lymphocytic leukemia (CLL) is due to tumor cells moving from infiltrated tissues to the blood. This phenomenon is associated with a class effect and driven by the efflux of cells from tissue compartments, paralleled by a substantial decrease in total tumor burden [2,3,4].

Lymphocytosis has been reported in 34% of cases of mantle cell lymphoma (MCL) [5]. Furtado et al. [6] reported lymphocytosis in cases of MCL treated by ibrutinib among patients with higher BM infiltration. The efficacy and safety of ibrutinib in cases of DLBCL have been analyzed in a meta-analysis; the overall

response rate was found to be 57.9% and 49.7% in cases of newly diagnosed DLBCL and relapsed/refractory cases of DLBCL, respectively [7]. We did not find any reports about lymphocytosis in cases of DLBCL treated by ibrutinib. Our patient had 100% BM infiltration and mononuclear cells increased rapidly with a peak at the 20<sup>th</sup> day of ibrutinib treatment (Figure 1). The very high volume of mononuclear cells was due to the BM infiltration and also the presence of very high tumor burden. The CD20 negativity in peripheral blood may be due to the previous rituximab treatment. To the best of our knowledge, this is the first case of a very high lymphocyte count in a patient with DLBCL treated by ibrutinib. The mechanism of this lymphocytosis is associated with mobilization of malignant cells related to the action of lymphocyte trafficking, and egress of lymphocytes from the protective stromal microenvironment occurred in our case as also seen in cases of CLL treated by Bruton's tyrosine kinase [8].

We suggest that peripheral blood cell counts may increase in patients with DLBCL with BM infiltration and/or high tumor burden as seen in CLL.

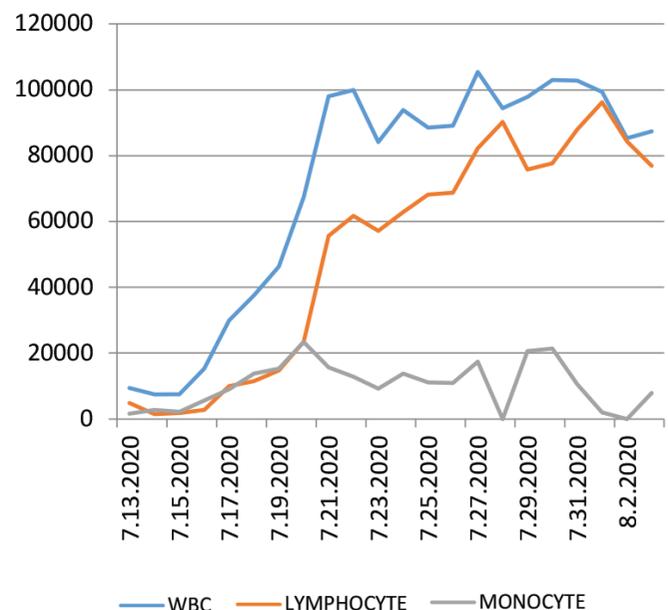


Figure 1. White blood cell (WBC), lymphocyte, and monocyte counts during ibrutinib treatment (/mm<sup>3</sup>).

**Keywords:** Ibrutinib, Lymphocytosis, Diffuse large B cell lymphoma

**Anahtar Sözcükler:** İbrutinib, Lenfositoz, Diffüz büyük B hücreli lenfoma

### Ethics

**Informed Consent:** Obtained.

### Authorship Contributions

Concept: S.P., E.B., M.T., T.Ö.; Design: S.P., E.B., M.T., T.Ö.; Data Collection or Processing: S.P., E.B., M.T., T.Ö.; Analysis or Interpretation: S.P., E.B., M.T., T.Ö.; Literature Search: S.P., E.B., M.T., T.Ö.; Writing: S.P., E.B., M.T., T.Ö.

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### References

1. Byrd JC, Furman RR, Coutre SE, Flinn IW, Burger JA, Blum KA, Grant B, Sharman JP, Coleman M, Wierda WG, Jones JA, Zhao W, Heerema NA, Johnson AJ, Sukbuntherng J, Chang BY, Clow F, Hedrick E, Buggy JJ, James DF, O'Brien S. Targeting BTK with ibrutinib in relapsed chronic lymphocytic leukemia. *N Engl J Med* 2013;369:32-42.
2. Chang BY, Francesco M, De Rooij MF, Magadala P, Steggerda SM, Huang MM, Kuil A, Herman SE, Chang S, Pals ST, Wilson W, Wiestner A, Spaargaren M, Buggy JJ, Elias L. Egress of CD19+CD5+ cells into peripheral blood following treatment with the Bruton tyrosine kinase inhibitor ibrutinib in mantle cell lymphoma patients. *Blood* 2013;122:2412-2424.
3. Herman SE, Niemann CU, Farooqui M, Jones J, Mustafa RZ, Lipsky A, Saba N, Martyr S, Soto S, Valdez J, Gyamfi JA, Maric I, Calvo KR, Pedersen LB, Geisler CH, Liu D, Marti GE, Aue G, Wiestner A. Ibrutinib induced lymphocytosis in patients with chronic lymphocytic leukemia: correlative analyses from a phase II study. *Leukemia* 2014;28:2188-2196.
4. Deeks ED. Ibrutinib: A review in chronic lymphocytic leukaemia. *Drugs* 2017;77:225-236.
5. Wang ML, Rule S, Martin P, Goy A, Auer R, Kahl BS, Jurczak W, Advani RH, Romaguera JE, Williams ME, Barrientos JC, Chmielowska E, Radford J, Stilgenbauer S, Dreyling M, Jędrzejczak WW, Johnson P, Spurgeon SE, Li L, Zhang L, Newberry K, Ou Z, Cheng N, Fang B, McGreivy J, Clow F, Buggy JJ, Chang BY, Beaupre DM, Kunkel LA, Blum KA. Targeting BTK with ibrutinib in relapsed or refractory mantle cell lymphoma. *N Engl J Med* 2013;369:507-516.
6. Furtado M, Wang ML, Munneke B, McGreivy J, Beaupre DM, Rule S. Ibrutinib-associated lymphocytosis corresponds to bone marrow involvement in mantle cell lymphoma. *Br J Haematol* 2015;170:131-133.
7. Hou K, Yu Z, Jia Y, Fang H, Shao S, Huang L, Feng Y. Efficacy and safety of ibrutinib in diffuse large B-cell lymphoma: a single-arm meta-analysis. *Crit Rev Oncol Hematol* 2020;152:103010.
8. Davids MS, Brown JR. Ibrutinib: a first in class covalent inhibitor of Bruton's tyrosine kinase. *Future Oncol* 2014;10:957-967.

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## Leg Ulcers Associated with Anagrelide

### Anagrelid ile İlişkili Bacak Ülserleri

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#### To the Editor,

A 77-year-old woman was referred to the dermatology department with a complaint of leg ulcers that had existed for a year. She had been treated with oral anagrelide at 0.5 mg twice a day for two years with the diagnosis of essential thrombocytosis (ET). Besides itching in her hands and legs, she had advanced non-healing leg ulcers that made walking difficult. A dermatologic examination revealed ulcers of 2x2 cm with demarcated, regular margins on the back of the left foot

and ulcers of 2x1.5 cm covered by sloughing necrotic tissue over the lateral malleolus of the left foot, as well as punched-out tiny ulcers on the lateral sides of both feet (Figures 1a and 1b). She also had comorbidities of chronic obstructive lung disease, hypertension, and deep vein thrombosis.

Her physical examination was unremarkable except for mild splenomegaly. Laboratory investigations including vasculitis and metabolic work-up showed no abnormalities. The complete blood count test revealed hemoglobin of 12 g/dL, a white blood