

# Progressive multifocal leukoencephalopathy developing after obinutuzumab treatment for chronic lymphocytic leukemia

---

Pejša, Vlatko; Lucijanić, Marko; Jonjić, Željko; Prka, Željko; Vukorepa, Gorana

Source / Izvornik: **Annals of Hematology, 2019, 98, 1509 - 1510**

Journal article, Accepted version

Rad u časopisu, Završna verzija rukopisa prihvaćena za objavljivanje (postprint)

<https://doi.org/10.1007/s00277-018-3552-x>

Permanent link / Trajna poveznica: <https://um.nsk.hr/um:nbn:hr:105:238889>

Rights / Prava: [In copyright](#)/[Zaštićeno autorskim pravom.](#)

Download date / Datum preuzimanja: **2024-08-20**



Repository / Repozitorij:

[Dr Med - University of Zagreb School of Medicine Digital Repository](#)





## Središnja medicinska knjižnica

**Pejša V., Lucijanić M., Jonić Ž., Prka Ž., Vukorepa G. (2019) *Progressive multifocal leukoencephalopathy developing after obinutuzumab treatment for chronic lymphocytic leukemia*. Annals of Hematology, 98 (6). pp. 1509-1510. ISSN 0939-5555**

<https://link.springer.com/journal/277>

<https://doi.org/10.1007/s00277-018-3552-x>

<https://medlib.mef.hr/3693>

University of Zagreb School of Medicine Repository

<http://medlib.mef.hr/>

**Title:** Progressive multifocal leukoencephalopathy developing after obinutuzumab treatment for chronic lymphocytic leukemia

**Authors:** Vlatko Pejša<sup>1,2</sup>, Marko Lucijanić<sup>1</sup>, Željko Jonjić<sup>1</sup>, Željko Prka<sup>1</sup>, Gorana Vukorepa<sup>3</sup>

**Affiliations:**

<sup>1</sup>Hematology Department, University Hospital Dubrava, Zagreb, Croatia

<sup>2</sup>School of Medicine, University of Zagreb, Zagreb, Croatia

<sup>3</sup>Neurology Department, University Hospital Dubrava, Zagreb, Croatia

**Corresponding author:** Vlatko Pejša, MD, PhD, Professor, Department of Hematology, Chair, University hospital Dubrava, Av. Gojka Suska 6, 10000 Zagreb, Croatia. mail: vpejsa@kbd.hr

**Funding:** none

**Conflict of interest:** VP, ML and ZP have received a speaker honorarium from Roche. Other authors declare that they have no conflict of interest.

**Ethical statement:** All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2008.

**Informed consent:** Patient's family provided informed consent for publishing.

Dear Editor,

Obinutuzumab is a humanized anti-CD20 monoclonal antibody that is currently recommended in combination with chlorambucil for first-line treatment of chronic-lymphocytic-leukemia (CLL) in patients unfit for fludarabine-based therapy. Although shown to be superior than rituximab in this setting [1], safety profile of obinutuzumab is not as well established. Progressive-multifocal-leukoencephalopathy (PML) is a severe, fatal, demyelinating disease of central-nervous-system (CNS) caused by reactivation of John-Cunningham (JC) virus. Although very rare, it is associated with exposure to immunosuppressive agents like rituximab and other monoclonal antibodies. Only three PML cases have been reported in association with obinutuzumab exposure, but all of them were confounded with prior rituximab therapy [2]. Here we report the first documented case of PML developing after exposure to obinutuzumab in a treatment-naïve patient treated for CLL.

A 62-year-old female patient was diagnosed with CLL in 2005. Her medical history included tuberculosis of left tibia in the childhood, pulmonary emphysema and recurrent pneumonias, but no previous neurological disorders. Due to CLL progression and presence of comorbidities, she started obinutuzumab and chlorambucil in 10/2017 and received total of 6 cycles ending in 4/2018, achieving complete remission. She had no chronic therapy for previous conditions and was concomitantly treated with alopurinol and ranitidine. In 5/2018 she started complaining of progressively worsening blurred vision. Ophthalmologic examination did not identify the cause, but the CT and subsequent magnetic-resonance T2-weighted-images showed hyperintensive subcortical lesions (Figure), initially indicative of posterior-reversible-encephalopathy-syndrome (PRES). However, further radiologic progression of brain lesions, lack of clinical improvement and confirmation of JC virus by polymerase-chain-reaction in the cerebrospinal-fluid defined the diagnosis of PML. Despite radiologic progression of brain lesions, patient exhibited stable clinical course with only visual impairment for 5 months after first symptoms, but then rapid cognitive and neurologic deterioration occurred. Course of intravenous-immunoglobulins was instituted, but with no clinical benefit. Patient remains alive, but seriously disabled, unable to care for herself with tendency for further deterioration at the time of this report, now 6 months after first occurrence of neurological symptoms.

PML is a serious demyelinating disease of CNS with no effective treatment available and almost always fatal outcome. Although limited number of PML cases in association with obinutuzumab have been reported in the literature, all of these patients were exposed to prior rituximab therapy, thereby confounding the possible role of obinutuzumab as an incriminated agent. Our case clearly demonstrates that association between obinutuzumab and PML exists and undoubtedly confirms the safety precaution from the drug-label. Obinutuzumab is more potent in terms of B-cell depletion than rituximab [3] and it is expected to be increasingly used in the treatment of CLL and indolent B-cell lymphomas. Our case underlies the fact that the current incidence of PML during obinutuzumab treatment is unknown and further investigations regarding exposure to obinutuzumab, as well as number of incident cases associated with exposure are needed to clearly establish safety of such potent therapy. Question arises, whether PML-risk-management-strategies, such as used in the case of natalizumab [4], should be undertaken in obinutuzumab candidates as well.

## References:

1. Goede V, Fischer K, Busch R, Engelke A, Eichhorst B, Wendtner CM, Chagorova T, de la Serna J, Dilhuydy MS, Illmer T, Opat S, Owen CJ, Samoylova O, Kreuzer KA, Stilgenbauer S, Dohner H, Langerak AW, Ritgen M, Kneba M, Asikanius E, Humphrey K, Wenger M, Hallek M (2014) Obinutuzumab plus chlorambucil in patients with CLL and coexisting conditions. *The New England journal of medicine* 370 (12):1101-1110. doi:10.1056/NEJMoa1313984
2. Raisch DW, Rafi JA, Chen C, Bennett CL (2016) Detection of cases of progressive multifocal leukoencephalopathy associated with new biologicals and targeted cancer therapies from the FDA's adverse event reporting system. *Expert opinion on drug safety* 15 (8):1003-1011. doi:10.1080/14740338.2016.1198775
3. Edelman J, Gribben JG (2016) Obinutuzumab for the treatment of indolent lymphoma. *Future oncology* 12 (15):1769-1781. doi:10.2217/fon-2016-0084
4. Fernandez O (2013) Best practice in the use of natalizumab in multiple sclerosis. *Therapeutic advances in neurological disorders* 6 (2):69-79. doi:10.1177/1756285612470401

**Figure:** Patient presented with bilateral occipital and right periinsular subcortical lesions. **A)** Initial T2 weighted magnetic resonance (MR) brain image (6/2018) showing hyperintensive subcortical lesions bilaterally occipitally. **B)** Progression of occipital lesions was observed on follow-up MR images (10/2018).

