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

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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.

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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).