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Case Report

# Severe Pancytopenia after Obinutuzumab-Chlorambucil Therapy for CLL with Fatal Outcome

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**Abstract**

Standard first-line treatment of Chronic Lymphatic Leukemia (CLL) usually consists of immune-chemotherapy and results in long-lasting remissions in most cases. Overall survival with the second-generation anti-CD20 antibody obinutuzumab was shown to be better than with rituximab when given together with chlorambucil. Although the treatment is generally well tolerated, there seems to be a trend towards more Severe Adverse Events (SAEs) with obinutuzumab than with rituximab and more fatal obinutuzumab-related SAEs being observed in clinical practice than reported in clinical trial treatments. Here, we report the case of a 72-year-old female patient with CLL that developed severe pancytopenia shortly after starting of obinutuzumab-chlorambucil treatment. She presented with neutropenia-related bilateral lung infiltrates, required invasive ventilation for acute hypoxic respiratory failure, and finally died from fatal bilateral stroke under prolonged thrombocytopenia. This case highlights that vigilance is required for rare but potentially fatal prolonged myelotoxicity related to treatment protocols containing anti-CD20 antibodies, specifically obinutuzumab, and for potentially fatal adverse thrombotic arterial events despite the presence of thrombocytopenia, specifically ischemic strokes.

**Keywords:** Obinutuzumab; Pancytopenia; Hematotoxicity; Chronic lymphatic leukemia; Fatal adverse event; Bilateral stroke

## Introduction

Obinutuzumab is a novel type II anti-CD20 monoclonal Antibody (mAb) recently approved for first-line treatment in patients with Chronic Lymphatic Leukemia (CLL) in combination with chlorambucil [1]. Therapeutic efficacy of obinutuzumab is superior to rituximab in the approved CLL setting, but there seems to be a trend towards higher hematotoxicity and more Severe Adverse Events (SAEs) with obinutuzumab than with rituximab [2,3]. Moreover, fatal obinutuzumab-related SAE rates appear to be higher in clinical practice (7.3%) [4] than those reported in clinical trial treatments (≤4%) [1-3]. We report a case of severe prolonged pancytopenia after obinutuzumab-chlorambucil therapy for CLL resulting in death from fatal bilateral strokes under invasive ventilation required for respiratory failure caused by pulmonary infiltrates.

## Case Presentation

A 72-year-old female patient presented to the emergency department due to fever and Acute Respiratory Failure (ARF) in June 2019. Since March 2019, she had dual antiplatelet therapy (aspirin, ticagrelor) after implantation of drug-eluting stents for acute coronary syndrome. Between April and May 2019, she had been treated with two 14-day cycles chlorambucil (administered orally at 0.5 mg/kg on days 1,2 and 3) and one cycle chlorambucil plus obinutuzumab (administered intravenously at 1.000 mg on days 1, 8 and 15) for B-CLL (total doses: 108 mg of chlorambucil, and 3.000 mg of obinutuzumab). Prior to B-CLL therapy, blood cell counts showed atypical lymphocytosis (counts 95.000 x$10^9$/L) with mild pancytopenia (hemoglobin 9.4 g/dL, neutrophils 1.5 x$10^9$/L, platelets 120 x$10^9$/L). At presentation, the patient had severe pancytopenia (hemoglobin 5.7 g/dL, leucocytes 0.1 x$10^9$/L, neutrophils 0 x$10^9$/L, platelets 4 x$10^9$/L). Physical examinations (including blood pressure, pulse rate, neurologic and cardiologic status), ultrasound examinations (including echocardiography and carotid Doppler), and laboratory tests were normal except increased inflammatory parameters (CRP 318 mg/L). Arterial blood gas analysis showed hypoxic ARF ($PaO_2$ 61 mmHg, $PaCO_2$ 28.5 mm Hg, $PaO_2/FiO_2$ 135), and CT-scans revealed bilateral pulmonic infiltrates (Figure 1). The initial working diagnosis was hypoxic ARF due to pneumonia under severe post-therapeutic pancytopenia, and the patient received antibiotic treatment (piperacillin/tazobactam, clarithromycin), Granulocyte Colony Stimulating Factor (G-CSF), Red Blood Cell (RBC) and platelet transfusions, and oxygen. Dual antiplatelet therapy was interrupted.

On day 3, the patient's respiratory status worsened ($PaO_2$ 47 mmHg, $PaCO_2$ 28.4 mm Hg, $PaO_2$ /$FiO_2$ 111) and referral to the Intensive Care Unit (ICU) for Noninvasive Ventilation (NIV) and subsequently Invasive Mechanical Ventilation (IMV) became necessary. Bronchoalveolar Lavage (BAL) showed lymphocytic alveolitis (CD-20-, CD-56-, absence of neutrophils) and was negative for some opportunistic microorganisms (CMV, pneumocystis, candida, and aspergillus). Laboratory tests, including CMV, EBV, HSV, and HIV serology, coagulation parameters, antiphospholipid profiles, and biweekly blood and urine cultures were normal. Bone marrow biopsy revealed severe drug-induced trilineage hypoplasia with residual infiltration by B-CLL. Pharmacological treatment included empirical intravenous administration of antibiotics (meropenem/vancomycin), antimycotics (voriconazole, fluconazole, amphotericin B), high dose cotrimoxazole (5 days), corticosteroids (8 days), immunoglobulins (10g for 5 consecutive days) and




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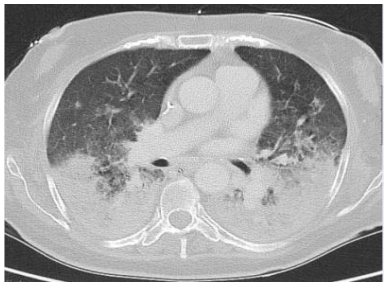

**Figure 1:** Contrast-enhanced thorax CT scan demonstrates diffuse bilateral infiltrates involving >50% of lung parenchyma with dorsal consolidation areas.

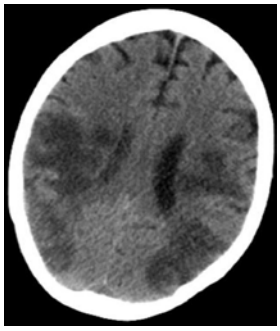

**Figure 2** Non-contrast brain CT scan shows large fresh bilateral ischemic infarctions at the middle cerebral artery territories with a narrowing of the right lateral ventricle due to compression by swelling brain parenchyma.

intermittent inotropic support. Hematologic therapy consisted of RBC (6 times) and platelet (4 times) transfusions and subcutaneous G-CSF (daily 300 µg) application. Respiratory management included 5 days NIV and subsequently 36 days of IMV using a lung protective ventilation strategy (tidal volume of 6 mL/kg, PEEP level of 8-12 cm $H_2O$). On day 31, neutrophils recovered (counts >0.5 x$10^9$/L), but thrombocytes remained depleted (counts 0-8 x$10^9$/L). In parallel, CT-scans showed regression of the pulmonary infiltrates, but the patient remained comatose despite the withdrawal of sedation. CT-scans of the brain displayed large, fresh bilateral ischemic infarctions (Figure 2) indicating a dismal prognosis, and the patient died on day 41 of ICU-admission.

## Discussion/Conclusions

Hypoxic ARF due to lung infiltrates is the leading cause for ICU admission in neutropenic patients, and clinical management differs from that in non-neutropenic patients. Firstly, neutropenic patients need prompt empirical antibacterial and antifungal therapy, as >90% of lung infiltrates are caused by bacterial or opportunistic fungal infections [5]. Secondly, NIV may obviate IMV in ~30% of neutropenic patients, but otherwise, NIV failure with delay of intubation might be deleterious [5,6]. Thirdly, during IMV, ~50% of neutropenic patients will develop ARDS caused by inflammatory response to infect-related lung injury, which is mediated by lymphocytic alveolitis and not by alveolar recruitment of neutrophils [5-7]. Finally, sterile BAL cultures are frequent but do not exclude pulmonary infection, particularly in the setting of empiric antimicrobial treatment [6,7]. In our case, BAL ruled out some opportunistic infections and pulmonary CLL involvement whilst revealing lymphatic alveolitis, which had impact on our treatment decisions, including the administration of corticosteroids for potential ARDS [5-7]. Notably, administration of G-CSF (long-term for reducing neutropenia duration) and corticosteroids (short-term for potential ARDS) likely had a beneficial effect in our case, as the pulmonary infiltrations regressed during their administration in parallel with neutrophil recovery.

The prognosis in concomitant thrombocytopenia, neutropenia, IMV and ARDS is worse than that of either pathologic condition alone. Because the greatest risk of thrombocytopenia is bleeding, we decided to withhold antiplatelet agents or anticoagulants. However, our case highlights that vigilance is also required for a link between thrombocytopenia and Adverse Thrombotic Arterial Events (ATEs). Congenital, acquired and treatment-related forms of thrombocytopenia put patients at ~2-5-fold higher risk for ATEs including ischemic strokes, which are characterized by multiple lesions in neuroimaging, only weak association with known predisposing factors (e.g. carotid disease, atrial fibrillation, thrombophilia), and poor outcome [8-11]. Growing evidence supports that thrombocytopenia may provoke procoagulant effects in hemostasis, which can lead to pathological thrombogenesis and thrombotic events, including arterial ones [10,11]. Whether drugs (e.g. corticosteroids, G-CSF) and/or platelet transfusions improve the risks of stroke among patients with thrombocytopenia is currently unclear, but it is important to note that we used platelet transfusions only for invasive procedures [10-12]. Taken together, the incidence and pathophysiology of ATEs and ischemic strokes in critical ill hematologic patients with severe prolonged pancytopenia is undefined and underexplored. In particular, studies are needed that measure the effects of administration or withholding of anticoagulant or antiplatelet medications on clinical outcomes, including bleeding, stroke and survival.

The underlying SAE in our case was a severe prolonged myeloablative effect after CLL treatment with obinutuzumab-chlorambucil. The phase IIIb GREEN study evaluated 972 patients who had received obinutuzumab alone or obinutuzumab-chemotherapy combinations for untreated or relapsed/refractory CLL [4]. Grade ≥3 AEs occurred in 80,3% of patients (neutropenia: 49.9%; thrombocytopenia: 16.4%, pneumonia: 9.0%), and SAEs and fatal SAEs were seen in 53.1% and 7.3% of patients, of whom most (85.8%) were considered related to obinutuzumab [4]. These safety data representative of real-life treated CLL patients suggest that obinutuzumab-related fatal SAEs rates are higher in clinical practice (7.3%) [4] than that in clinical trials (≤4%) [1-3] and/or with chlorambucil alone (≤1%) [13,14]. Noteworthy, in a recent phase 2 study assessing the single-agent activity of obinutuzumab in 78 previously untreated CLL patients, 6 patients (7.7%) were withdrawn from the study drug because of neutropenia or thrombocytopenia [15]. Taken together, the safety profile in broad-spread obinutuzumab use is still undefined, in particular regarding the incidence of unusual fatal SAEs.

The present case of a severe prolonged myelotoxicity resulting in death in a patient treated for CLL with the current state-of-the-art first-line treatment consisting of obinutuzumab and chlorambucil highlights that clinicians should be aware of the hematotoxicity risk related to such treatment protocols. Severe prolonged treatment-

related pancytopenia puts these patients at risk for infections, most frequently pulmonary infections, which may require IMV for hypoxic ARF. This vulnerable IMV patient population has a high mortality risk of >50% overall, mostly related to ARDS, sepsis, multi-organ failure and/or bleeding complications. Our case also outlines that those patients are at additional risk for ATEs despite the presence of thrombocytopenia, specifically fatal ischemic strokes. As the clinical application of the anti-CD20-antibody obinutuzumab is likely increasing in CD20+ malignancies in the future, our case points out that clinical validation of the safety profile in broad-spread use is still needed and may help to prevent or better manage rare but serious and potentially fatal treatment-related complications.

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