

Safe administration of rituximab in patients with chronic lymphocytic leukemia and a history of obinutuzumab-associated anaphylaxis

To the Editor Chronic lymphocytic leukemia (CLL) is the most common adult leukemia in Western countries, including Poland.¹ Despite the increasing importance of novel agents such as B-cell receptor inhibitors and Bcl-2 antagonists, immunotherapy using anti-CD20 monoclonal antibodies (MoAbs) remains an important component of the current treatment of CLL.² The glycoengineered type II anti-CD20 MoAb obinutuzumab in combination with chlorambucil has been approved as a frontline treatment for unfit CLL patients based on outcomes from the phase 3 CLL11 study.³ Updated results of this trial have shown progression-free survival (PFS) to be significantly prolonged with obinutuzumab and chlorambucil (O-Chl) compared with a rituximab and chlorambucil (R-Chl) regimen (median PFS, 29.2 vs 15.4 months).⁴ Nonetheless, therapy with obinutuzumab was associated with a considerably higher incidence of severe grade 3 or 4 infusion-related reactions (IRRs) (20% vs 4%), especially those that led to treatment discontinuation (7% vs <1%).³

Most of the severe IRRs to obinutuzumab occur early, typically during the first infusion.³ Patients experiencing grade 4 IRRs to obinutuzumab should discontinue infusion immediately and should not to be re-exposed to this drug. Importantly, further optimal treatment of CLL of such patients has not been established. The CLL11 study has demonstrated that continuing treatment with chlorambucil alone would clearly lead to significantly inferior PFS and overall survival.⁴ However, exposure to other anti-CD20 MoAbs, such as rituximab,³ ofatumumab,⁵ or ublituximab,⁶ raises concerns about the unknown risk of potentially life-threatening cross-reactions.

Interestingly, ofatumumab, a fully humanized anti-CD20 MoAb, has been recently shown to be safely administered to a patient with thrombocytopenic purpura who presented with anaphylaxis associated with human antichimeric antibodies

to rituximab.⁷ In contrast, a severe hypersensitivity reaction to ofatumumab has been observed in another patient with thrombocytopenic purpura who had previously suffered from rituximab-associated anaphylaxis.⁸ Here, we report 2 cases of CLL patients with a history of grade 4 IRRs associated with obinutuzumab, for whom rituximab was subsequently administered and no complications occurred.

In September 2017, a 79-year-old Caucasian man diagnosed with CLL in 2013 and who recently developed indications for therapy (B symptoms, symptomatic splenomegaly, and grade 3 anemia), was admitted to the Department of Hematology at the Institute of Hematology and Transfusion Medicine in Warsaw, Poland. Until hospitalization, this patient had been followed by a watch and wait strategy, and since 2015 he had been receiving immunoglobulin supplementation because of hypogammaglobulinemia and recurrent respiratory tract infections. The patient was referred for a frontline therapy with O-Chl due to clinically relevant comorbidities (prostate cancer, arterial hypertension, history of transient ischemic attack, and *Mycobacterium tuberculosis* infection), rated at 8 points on the Cumulative Illness Rating Scale. This treatment was started on September 15, 2017. Despite administration of the recommended premedication and withholding antihypertensive treatment, he developed severe hypotension and dyspnea immediately after obinutuzumab infusion had been started. Bradycardia and hypoxemia with impaired consciousness were also observed. The infusion was then stopped. Full recovery was achieved after fluid resuscitation, oxygen therapy, and the administration of glucocorticoids and antihistamine drugs.

Since chlorambucil monotherapy was considered suboptimal, the patient was referred for therapy with R-Chl. The first infusion of rituximab was started 5 days later and was performed under full anesthetic monitoring. Glucocorticoids (methylprednisolone), leukotriene receptor antagonist

(montelukast), acetaminophen, and antihistamine drugs were given as premedication. The infusion was carried out without any relevant complications. The patient was discharged home in a stable condition, and further R-Chl therapy was planned on an outpatient basis. However, due to severe *Clostridium difficile* infection, the patient did not continue immunochemotherapy and died several weeks later of pseudomembranous enteritis complications and CLL progression.

Following this observation, we performed a retrospective analysis based on a real-life approach to CLL patients who discontinued obinutuzumab due to severe IRRs at centers of the Polish Adult Leukemia Group. The most common strategy found was to continue chlorambucil in monotherapy. However, we identified one additional case of a patient with an anaphylactic reaction to obinutuzumab who was subsequently exposed to rituximab. This was a 68-year-old Caucasian man admitted to the Department of Hematology at Jagiellonian University in Kraków in October 2017 because of massive hepatomegaly and splenomegaly. He was referred for a frontline treatment with O-Chl. Despite the recommended standard premedication during the first obinutuzumab dose infusion, he developed severe hypotension, dyspnea, bronchospasm, and massive sweating. Moreover, he had hypoxemia and was highly anxious. The infusion was stopped, and the patient recovered after fluid resuscitation, oxygen therapy, and administration of glucocorticoids and antihistamine drugs. On the next day, treatment with rituximab in combination with bendamustine was started, preceded by standard rituximab premedication. No clinically relevant complications were observed. By the time of this report, the patient had completed 6 cycles of rituximab-bendamustine therapy with no adverse events so far.

An alternative strategy for minimizing the risk of severe IRRs to anti-CD20 MoAbs, particularly obinutuzumab, would be appropriate patient selection. However, predisposing risk factors for IRRs complicating obinutuzumab infusion are not well defined. Freeman et al⁹ have shown that higher CD20 expression in CLL cells and CD16 expression in natural killer cells, or the presence of a palpable spleen, were associated with a greater risk of developing IRRs during treatment with obinutuzumab. When immunophenotyping data were excluded, the risk factors for IRR found were the presence of trisomy 12, splenomegaly, and baseline thrombocytopenia. In our patients, only considerable splenomegaly was observed, while none of them had baseline thrombocytopenia or trisomy of chromosome 12. Therefore, it seems rather difficult to reliably predict IRRs associated with obinutuzumab in real-life clinical practice.

In conclusion, rituximab-based immunochemotherapy can be safely applied in patients after obinutuzumab-associated anaphylaxis. However, the existing risk of cross-reactivity should be considered, and thus careful monitoring of such patients during rituximab infusion is mandatory.

Author names and affiliations Aleksander Salomon-Perzyński, Agnieszka Końska, Daria Zawirska, Ewa Lech-Marańda, Krzysztof Jamrozak (AS-P, AK, EL-M, KJ: Department of Hematology, Institute of Hematology and Transfusion Medicine, Warsaw, Poland; DZ: Department of Hematology, The University Hospital in Krakow, Kraków, Poland; EL-M: Department of Hematology and Transfusion Medicine, Center of Postgraduate Medical Education, Warsaw, Poland)

Corresponding author Aleksander Salomon-Perzyński, MD, Department of Hematology, Institute of Hematology and Transfusion Medicine, ul. Indyry Gandhi 14, 02-776 Warszawa, Poland, phone: +48 22 349 63 21, email: salomon.perzynski@gmail.com

Conflict of interest The authors declare no conflict of interest.

How to cite Salomon-Perzyński A, Końska A, Zawirska D, et al. Safe administration of rituximab in patients with chronic lymphocytic leukemia and a history of obinutuzumab-associated anaphylaxis. *Pol Arch Intern Med.* 2018; 128: 494-495. doi: 10.20452/pamw.4327.

OPEN ACCESS This is an Open Access article distributed under the terms of the Creative Commons AttributionNonCommercialShareAlike 4.0 International License ([CC BY-NC-SA 4.0](https://creativecommons.org/licenses/by-nc-sa/4.0/)), allowing third parties to copy and redistribute the material in any medium or format and to remix, transform, and build upon the material, provided the original work is properly cited, distributed under the same license, and used for non-commercial purposes only. For commercial use, please contact the journal office at pamw@mp.pl.

REFERENCES

- 1 Putowski M, Podgórnjak M, Piróg M, et al. Prognostic impact of NOTCH1, MYD88, and SF3B1 mutations in Polish patients with chronic lymphocytic leukemia. *Pol Arch Intern Med.* 2017; 127: 238-244. [↗](#)
- 2 Routledge DJ, Bloor AJ. Recent advances in therapy of chronic lymphocytic leukaemia. *Br J Haematol.* 2016; 174: 351-367. [↗](#)
- 3 Goede V, Fischer K, Busch R, et al. Obinutuzumab plus chlorambucil in patients with CLL and coexisting conditions. *N Engl J Med.* 2014; 370: 1101-1110. [↗](#)
- 4 Goede V, Fischer K, Engelke A, et al. Obinutuzumab as frontline treatment of chronic lymphocytic leukemia: updated results of the CLL11 study. *Leukemia.* 2015; 29: 1602-1604. [↗](#)
- 5 Hillmen P, Robak T, Janssens A, et al. Chlorambucil plus ofatumumab versus chlorambucil alone in previously untreated patients with chronic lymphocytic leukaemia (COMPLEMENT 1): a randomised, multicentre, open-label phase 3 trial. *Lancet.* 2015; 385: 1873-1883. [↗](#)
- 6 Sharman JP, Farber CM, Mahadevan D, et al. Ublituximab (TG-1101), a novel glycoengineered anti-CD20 antibody, in combination with ibrutinib is safe and highly active in patients with relapsed and/or refractory chronic lymphocytic leukaemia: results of a phase 2 trial. *Br J Haematol.* 2017; 176: 412-420. [↗](#)
- 7 Crowley MP, McDonald V, Scully M. Ofatumumab for TTP in a patient with anaphylaxis associated with rituximab. *N Engl J Med.* 2018; 378: 92-93. [↗](#)
- 8 Cohen Aubart F, Haroche J, Amoura Z. More on ofatumumab for TTP. *N Engl J Med.* 2018; 378: 1364-1365. [↗](#)
- 9 Freeman CL, Dixon M, Houghton R, et al. Role of CD20 expression and other pre-treatment risk factors in the development of infusion-related reactions in patients with CLL treated with obinutuzumab. *Leukemia.* 2016; 30: 1763-1766. [↗](#)