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EXPERTS' POSITION

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Polish Experts' Position Statement on the use of granulocyte colony-stimulating factor in the treatment of chronic lymphocytic leukemia with venetoclax combined with rituximab

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Abstract

Chronic lymphocytic leukemia (CLL) is the most common adult leukemia in Western countries. Venetoclax, a BCL-2 inhibitor, in combination with rituximab is an effective therapeutic option approved for the treatment of refractory and relapsed CLL. Neutropenia diagnosed before or during the above-mentioned therapy is a significant clinical problem, which often involves the need to reduce the dose or temporarily discontinue venetoclax in the initial period of therapy.

In Experts' opinion, the use of granulocyte colony-stimulating factor (G-CSF) during venetoclax–rituximab combined therapy is reasonable in patients with baseline neutrocyte count < 1000–500/mm^3 and with high-risk neutropenia. The second important group for the use of G-CSF are patients developing grade 3 asymptomatic neutropenia during venetoclax dose escalation. Using G-CSF can prevent episodes that affect the maintenance of the venetoclax dose intensity and treatment continuity.

Key words: chronic lymphocytic leukemia, granulocyte colony-stimulating factor, neutropenia, rituximab, venetoclax

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Introduction

Chronic lymphocytic leukemia (CLL) is the most common adult leukemia in developed countries, which accounts for 25–30% of all leukemias [1]. The incidence of CLL is 4–5 cases per 100 000 population annually and the median age of CLL diagnosis is 72 years [2]. However, due to the ageing of the Polish population, the number of CLL patients there will increase. One of the most clinically significant risk factors in CLL is the deletion of the short arm of chromosome 17 (del17p). Such a change leads to the absence of the *TP53* suppressor gene in tumour cells. Deletion of 17p is observed in 5–8% of patients that required first-line therapy and in 23–44% multiple-relapse cases [3]. The deletion results in faster disease progression, shortened survival time and resistance of tumour cells to treatment [4].

Venetoclax with rituximab for CLL treatment

Based on the results of the MURANO study [5] venetoclax in combination with rituximab has been registered for the treatment of patients with relapsed or refractory CLL. The aim of this open-label, randomized, phase III clinical trial was to compare the efficacy and safety of venetoclax and rituximab combination (VenR) to therapy with bendamustine with rituximab (BR). Therapy with VenR resulted in an 84.9% rate of 2-year progression-free survival (PFS), compared to 36.3% for BR ($p < < 0.001$). In the subpopulation of patients with the 17p deletion, the rate of 2-year PFS was 81.5% in VenR group and 27.8% in BR group [hazard ratio: 0.13; 95% confidence interval (CI): 0.05–0.29) [5].

Treatment with venetoclax in Poland as part of a drug program is aimed at the patient with:

- refractory or relapsed CLL after immunochemotherapy;
- refractory or relapsed CLL with a 17p deletion or with a *TP53* aberration;
- CLL with 17p deletion or *TP53* aberration after ibrutinib treatment failure [6].

Granulocyte-colony stimulating factor in neutropenia prophylaxis — American Society of Clinical Oncology (ASCO) guidelines

The most common adverse event in the MURANO study was neutropenia, which was observed in 60.8% of patients in the VenR group and 44.1% of patients in the BR group [5]. Neutropenia is most often related to the myelotoxic effects of chemotherapy and bone marrow infiltration during CLL (grades of neutropenia are presented in Table 1) [7].

Table 1. Grades of neutropenia according to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) v. 5.0 (source [7])

Grade	Neutrophil count
1	< LLN–1500/mm^3
2	< 1500–1000/mm^3
3	< 1000–500/mm^3
4	< 500/mm^3

LLN — lower limit of normal

Neutropenia is a risk factor for febrile neutropenia — a life-threatening condition requiring hospitalization and broad-spectrum antibiotic therapy [8]. An episode of febrile neutropenia frequently leads to drug dose reduction or treatment delay which may have a long-term impact on the patient's condition [9]. Granulocyte colony-stimulating factor (G-CSF) can be used in the prophylaxis of neutropenia. G-CSF stimulates the proliferation and differentiation of neutrophil precursor cells. Moreover, this class of drugs reduces the duration of neutropenia, increases cell half-life and increases phagocytic properties of neutrophils [10]. In clinical practice, G-CSF administration leads to:

- reduction of febrile neutropenia incidence;
- shortening of the duration of grade 4 neutropenia;
- reduction of the number of infection-related hospitalizations;
- avoidance of dose reduction of cancer treatment [10].

During the MURANO study, G-CSF could be administered as primary prophylaxis based on American Society of Clinical Oncology (ASCO) guidelines or each site's experience and standards [11]. According to ASCO recommendations, primary prophylaxis with a G-CSF is recommended in patients with a risk of febrile neutropenia ≥ 20%. Additional risk factors of febrile neutropenia include:

- age > 65 years;
- advanced disease stage;
- previous chemotherapy/radiotherapy;
- active neutropenia or bone marrow involvement;
- an open wound or recent surgery;
- poor performance or nutritional status;
- poor renal or liver function;
- cardiovascular disease;
- multiple comorbidities;

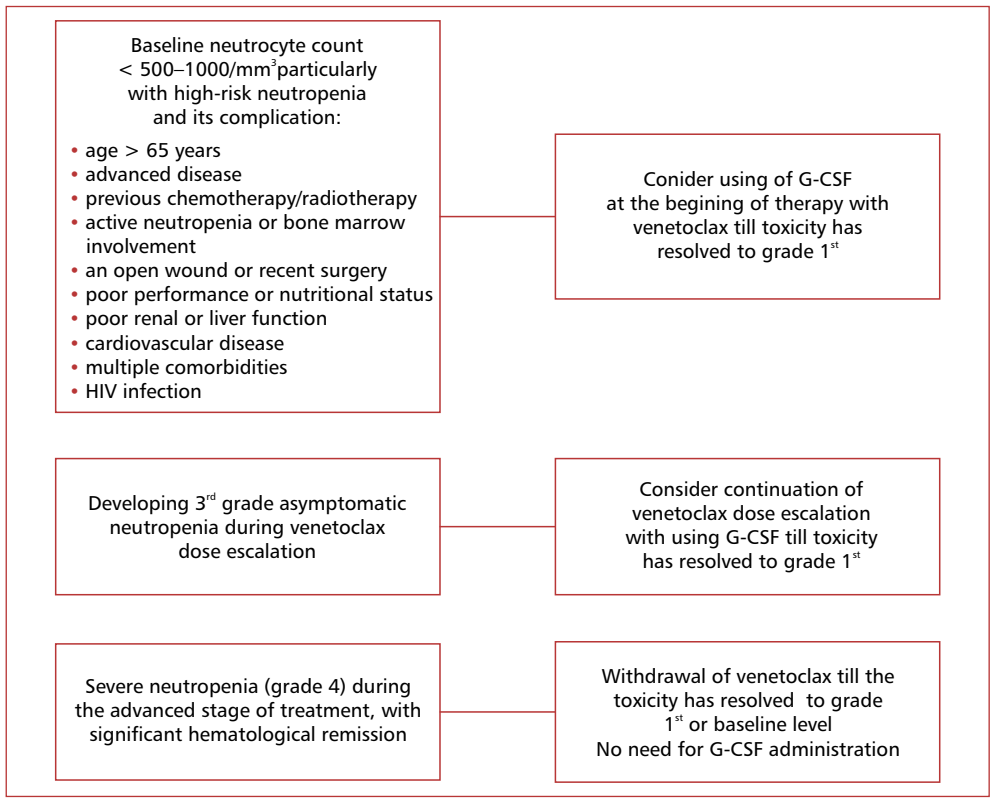

Figure 1. Algorithm for using granulocyte colony-stimulating factor (G-CSF) in the treatment of chronic lymphocytic leukemia (CLL) with venetoclax; HIV — human immunodeficiency virus

- human immunodeficiency virus (HIV) infection [11].

Using G-CSF in secondary prophylaxis is recommended for patients that exhibited an episode of neutropenia during the previous cycle of treatment. When dose reduction or treatment delay negatively affect treatment outcomes. G--CSF should not be used routinely in patients with febrile neutropenia. However, G-CSF treatment may be considered in patients with a high risk for complications related to infection or patients that have poor predictive outcomes. High-risk factors include:

- expected prolonged (>10 days) and profound ($< 0.1 \times 10^9$/L) neutropenia;
- age > 65 years;
- uncontrolled primary disease;
- pneumonia, hypertension, sepsis, or invasive fungal infection;
- hospitalization during fever development [11].

Experts' position statement

According to the Summary of the Product Characteristics of venetoclax, an episode of grade 3 or 4 neutropenia with infection or fever and grade 4 asymptomatic neutropenia are an indication for treatment suspension or dose reduction. Supportive treatment should then be considered.

However, in experts' opinion, the aim of G--CSF administration should be both the prevention of febrile neutropenia and reducing neutropenia what is crucial for maintaining venetoclax dose intensity, particularly at the beginning of therapy. Keeping patients on a reduced dose of venetoclax reduces the effectiveness of the treatment and increases the risk of therapy failure.

In the Experts' opinion, the use of G-CSF is reasonable in patients:

- with baseline neutrocyte count < 1000–500/mm^3 (at least grade 3 of neutropenia), particularly with high-risk neutropenia according to ASCO guidelines. Treatment with G-CSF should continue till toxicity has resolved to grade 1;
- developing grade 3 asymptomatic neutropenia during venetoclax dose escalation. Treatment with G-CSF should continue till toxicity has resolved to grade 1;

If a patient develops severe neutropenia (grade 4) during the advanced stage of treatment, with

significant haematological remission, venetoclax should be withdrawn without the need for G-CSF administration. Once the toxicity has resolved to grade 1 or baseline level, venetoclax may be resumed at the same dose.

Based on the Experts' experiences, an algorithm for using G-CSF in the treatment of CLL with venetoclax was created (Figure 1).

Experts' emphasize that:

- neutropenia is a frequent side effect of venetoclax treatment;
- neutropenia prophylaxis is intended for the prevention of febrile neutropenia and maintenance of dose intensity what is crucial for the effectiveness of this therapy;
- the dose and response to G-CSF should be strictly monitored.

Conclusion

Due to the heterogeneous character of CLL, treatment has to be tailored based on prognostic markers and mutations, including del17p. Venetoclax, a BCL-2 inhibitor, used alone or in combination with rituximab is a new drug for the treatment of relapsed or refractory CLL. Using G-CSF can prevent episodes of neutropenia and febrile neutropenia. Dose intensity during treatment of CLL has survival benefits. Reduction in venetoclax dose intensity is associated with a poor prognosis. The use of G-CSF helps maintenance of the venetoclax dose intensity and treatment continuity. The final decision on when to administer G-CSF should be made by a physician based on the patient's condition.

Statement

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Conflict of interest

Anna Wolska-Washer, Ewa Bodzenta, Sebastian Grosicki, Łukasz Bołkun declare no conflict of interest. Jan Maciej Zaucha: consultant/member of the advisory board/speaker: Takeda, Roche, Janssen, BMS, Abbvie, Roche, Amgen; clinical trials: BMS, Takeda. Tomasz Wróbel: consultant/member of the advisory board/speaker: AbbVie, Roche, Jansen. Joanna Drozd-Sokołowska: consultant/ /member of the advisory board/speaker: AbbVie, Roche, Janssen. Iwona Hus: consultant/member of the advisory board/speaker: AbbVie. Krzysztof Jamroziak: consultant/member of the advisory board/speaker: Janssen, Astra Zeneca, Roche, AbbVie; fees for lectures: AbbVie, Janssen, Astra Zeneca, Roche; research support: AbbVie, Janssen. Krzysztof Giannopoulos: consultant/member of the advisory board/speaker: Abbvie, Amgen, AstraZeneca, Bei-Gene, Janssen, Sanofi-Genzyme, Novartis, Takeda, Roche, Karyopharm, GSK, Gilead, Sandoz, Pfizer, Teva; research funding by: TG Therapeutics, Abbvie, Amgen, AstraZeneca, Bei-Gene, Janssen, Sanofi-Genzyme, Novartis, Takeda, Roche, Karyopharm, GSK, Gilead. Marek Dudziński: consultant/member of the advisory board/speaker: AbbVie, Roche, Janssen. Elżbieta Iskierka-Jażdzewska: consultant/member of the advisory board/speaker: Amgen, Abbvie, Janssen, Sandoz, Novartis. Agnieszka Samborska: employee AbbVie may be in possession of stocks or options of AbbVie.

References

1. Brusamolino E, Bacigalupo A, Barosi G, et al. Classical Hodgkin's lymphoma in adults: guidelines of the Italian Society of Hematology, the Italian Society of Experimental Hematology, and the Italian Group for Bone Marrow Transplantation on initial work-up, management, and follow-up. Haematologica. 2009; 94(4): 550–565, doi: 10.3324/haematol.2008.002451.
2. Hallek M, Shanafelt T, Eichhorst B. Chronic lymphocytic leukaemia. Lancet. 2018; 391(10129): 1524–1537, doi: 10.1016/s0140-6736(18)30422-7.
3. Tam CS, Stilgenbauer S. How best to manage patients with chronic lymphocytic leuekmia with 17p deletion and/or TP53 mutation? Leuk Lymphoma. 2015; 56(3): 587–593, doi: 10.3109/10428194.2015.1011641.
4. Jaśkowiak K, Golicki D. Biała księga. Przewlekła białaczka limfocytowa. HealthQuest, Warszawa 2017. https://docplayer.pl/47519942-Biala-ksiega-przewlekla-bialaczka-limfocytowa.html (September 20, 2021).
5. Kater AP, Seymour JF, Hillmen P, et al. Venetoclax-rituximab in relapsed or refractory chronic lymphocytic leukemia. N Engl J Med. 2018; 378(12): 1107–1120, doi: 10.1056/NEJMoa1713976, indexed in Pubmed: 29562156.
6. Załącznik B.103. Leczenie przewlekłej białaczki limfocytowej wenetoklaksem (ICD 10: C91.1). https://hematoonkologia.pl/upload/ /programy-lekowe/B103_od_01-2019.pdf (September 20, 2021).
7. Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0. Published: November 27, 2017. U.S. Department of Health and Human Services. https://ctep.cancer.gov/protocold-

evelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_5x7.pdf (September 20, 2021).
8. Kuderer NM, Dale DC, Crawford J, et al. Mortality, morbidity, and cost associated with febrile neutropenia in adult cancer patients. Cancer. 2006; 106(10): 2258–2266, doi: 10.1002/cncr.21847, indexed in Pubmed: 16575919.
9. Pettengell R, Schwenkglenks M, Leonard R, et al. Impact of Neutropenia in Chemotherapy-European Study Group (INC-EU). Neutropenia occurrence and predictors of reduced chemotherapy delivery: results from the INC-EU prospective observational European neutropenia study. Support Care Cancer. 2008; 16(11): 1299–1309, doi: 10.1007/s00520-008-0430-4, indexed in Pubmed: 18351398.
10. Spławiński J. Growth factors in the prophilaxis and treatment of chemotherapy-induced neutropenia. Hematologia. 2014; 5(4): 272–284.
11. Smith TJ, Bohlke K, Lyman GH, et al. American Society of Clinical Oncology. Recommendations for the use of WBC growth factors: American Society of Clinical Oncology Clinical Practice Guideline Update. J Clin Oncol. 2015; 33(28): 3199–3212, doi: 10.1200/JCO.2015.62.3488, indexed in Pubmed: 26169616.