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# Adverse Events During Single-Agent Phase of Venetoclax Therapy

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## INTRODUCTION

The side effects and toxicity of Venetoclax are now well known, but the summary of product characteristics (SmPC) is not specific on the intensity of monitoring recommended during the single-agent/maintenance phase of therapy. Since the drug is relatively new, several services have adopted the conservative approach of monthly full blood counts throughout therapy.

## AIM

We wanted to analyze the incidence of unexpected adverse events during different phases of Venetoclax therapy for CLL at our centers.

## METHOD

We retrospectively reviewed data from patients who received Venetoclax therapy, either as a single agent or in combination with a CD20 monoclonal antibody, at two major hospitals in Northwest London. We considered three phases of therapy:

- **Incremental phase of Venetoclax therapy** (3 months)
- **Combination phase with a monoclonal antibody**: this phase spanned from the second week of Venetoclax at maximum dose until the end of CD20 therapy, totaling 66 months for Venetoclax-Rituximab (VR) and 60 months for Venetoclax-Obinutuzumab (VO).
- **Single-agent phase**: this phase covered the period from the end of CD20 therapy until the end of treatment, totaling 136 months for VR and 78 months for VO. For patients on Venetoclax monotherapy, this phase extended from the end of the induction phase until the end of treatment, totaling 200 months.

We considered the monthly incidence of side effects.

## RESULTS

We reviewed data from 42 patients, with time on Venetoclax therapy ranging between 3 and 29 months and an age range between 46 and 96 years.
Of these, 36 patients (85.71%) remain on therapy, while 6 patients (14.29%) discontinued the medication due to severe adverse effects.
Among the 36 patients still on therapy, 11 (30.56%) did not report any side effects, whereas 25 (69.44%) experienced some adverse events. 13 received VO, 14 received VR, and the remaining patients were treated with Venetoclax as a single agent throughout the duration of the therapy.
During the incremental phase, the incidence of neutropenia was 9.52%, followed by thrombocytopenia and anemia with 2.38% each.

| Incremental phase | Neutrop | Thrombocytop | Anemia | Infections | Fatigue | Diarrhea |
|---|---|---|---|---|---|---|
| VO | 0 | 0 | 0 | 0 | 0 | 0 |
| VR | 1 | 0 | 0 | 0 | 0 | 0 |
| Venetoclax | 3 | 1 | 1 | 0 | 0 | 0 |
| Total | 4 | 1 | 1 | 0 | 0 | 0 |
| Incidence | 0.095 | 0.023 | 0.023 | 0 | 0 | 0 |

During the combination phase, we considered the incidence of side effects over 60 months for VO and 66 months for VR.
We reported the following incidence rates: 3.96% for neutropenia and infections, 2.38% for thrombocytopenia, anemia, and fatigue, and 1.58% for diarrhea.

| Combination phase | Neutrop | Thrombocytop | Anemia | Infections | Fatigue | Diarrhea |
|---|---|---|---|---|---|---|
| VO | 1 | 2 | 0 | 2 | 2 | 1 |
| VR | 4 | 1 | 3 | 3 | 1 | 1 |
| Incidence | 0.039 | 0.023 | 0.023 | 0.039 | 0.023 | 0.015 |

Patients who received a single-agent regimen after the combination phase experienced fewer adverse events.
We analyzed a total of 414 months of therapy (78 months on single-agent Venetoclax after Obinutuzumab, 136 months after Rituximab, and 200 months on Venetoclax monotherapy).
The incidence rates were 0.96% for neutropenia, thrombocytopenia, anemia and diarrhea, 0.48% for infections, and 0.24% for fatigue.
Overall, unexpected adverse events were significantly less frequent during the single-agent therapy phase ($p < 0.01$).

| Single-agent phase | Neutrop | Thrombocyto | Anaemia | Infections | Fatigue | Diarrhea |
|---|---|---|---|---|---|---|
| Single agent after VO | 2 | 0 | 1 | 0 | 0 | 1 |
| Single agent after VR | 1 | 1 | 1 | 1 | 1 | 0 |
| Venetoclax | 1 | 3 | 2 | 1 | 0 | 3 |
| Incidence | 0.009 | 0.009 | 0.009 | 0.004 | 0.002 | 0.009 |

| Phases | Neutrop | Thrombocytop | Anaemia | Infections | Fatigue | Diarrhea |
|---|---|---|---|---|---|---|
| Total induction | 0.095 | 0.024 | 0.0244 | 0 | 0 | 0 |
| Total combination phase | 0.039 | 0.023 | 0.023 | 0.039 | 0.023 | 0.015 |
| Total single-agent phase | 0.009 | 0.009 | 0.009 | 0.004 | 0.002 | 0.009 |

One tailed p value: 0.00299511

Comparing the data of the age groups of patients who received combination therapy, we noticed that among those under 70 years old at the time of therapy initiation, only one patient experienced adverse effects during the single-agent phase (fatigue, which did not require treatment).

## CONCLUSIONS

During the single-agent phase of Venetoclax therapy, the most common symptoms observed were thrombocytopenia, anemia, infections, and neutropenia. Overall, the incidence of unexpected side effects was lower in this phase compared to the combination therapy phase.
Among patients who received combination therapy, most did not experience side effects after completing the combination phase, with only one patient (2%) developing an infection that required medical admission. These findings suggest that, with appropriate patient education, a reduced intensity of monitoring during the single-agent phase of Venetoclax therapy may be safe and effective.

## REFERENCES

1.NCI. National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) v5.0. 2017, https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_5x7.pdf.
2. Venetoclax [Summary of Product Characteristics] (2018) AbbVie Ltd, December 2018, https://www.ema.europa.eu/en/documents/product-information/venclyxto-epar-product-information_en.pdf.
3. Rituximab [Summary of Product Characteristics] (2018) Roche Products Limited, March 2021, https://www.ema.europa.eu/en/documents/product-information/mabthera-epar-product-information_en.pdf.
4. Obinutuzumab [Summary of Product Characteristics] (2018) Roche Products Limited, 2021, https://www.ema.europa.eu/en/documents/product-information/gazyvaro-epar-product-information_en.pdf
5. Clinical experiences with venetoclax and other pro-apoptotic agents in lymphoid malignancies: lessons from monotherapy and chemotherapy combination, Lew and Seymour Journal of Hematology & Oncology (2022) 15:75 https://doi.org/10.1186/s13045-022-01295-3
6. Real-world outcomes and management strategies for venetoclax-treated chronic lymphocytic leukemia patients in the United States, Haematologica 2018 Volume 103(9):1511-1517
7. Comprehensive Safety Analysis of Venetoclax Monotherapy for Patients with Relapsed/Refractory Chronic Lymphocytic Leukemia, Clin Cancer Res; 24(18) September 15, 2018
8. Venetoclax-based chemotherapy in acute and chronic myeloid neoplasms: literature survey and practice points, Gangat and Tefferi Blood Cancer Journal (2020) 10:122 https://doi.org/10.1038/s41408-020-00388-x

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