Ibrutinib and venetoclax associated with progressive multifocal leukoencephalopathy

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Introduction

Progressive multifocal leukoencephalopathy (PML) is an opportunistic infection of the central nervous system (CNS) caused by the JC polyomavirus (1). The majority of PML cases occur in patients co-infected with HIV. Other risk factors include haematological malignancies, autoimmune diseases (e.g. multiple sclerosis, sarcoidosis, rheumatoid arthritis) or immunosuppression following solid organ transplantation. Some medications have been associated with an increased risk of PML, such as B-cell depleting agents (rituximab) and VLA4-integrin antagonists (natalizumab). For other drugs, the association with PML is not clearly established (1–4). Cases of drug-induced PML most often manifest with motor and/or cognitive deficits with radiological lesions predominantly in the frontal and parietal regions (5). In oncological settings, drug-induced PML occurs on average 14 months after the introduction of the offending drug (5). We report on a patient who developed PML with likely involvement of ibrutinib and venetoclax in the context of chronic lymphocytic leukaemia (CLL).

Case report

A patient in his seventies with CLL diagnosed in 2014 was considered in remission after 15 cycles of rituximab and bendamustine (last administration in September 2019). Due to haematological relapse, venetoclax (Venclyxto®) 400 mg 1x/d and ibrutinib (Imbruvica®) 280 mg 1x/d were started in January 2022. The standard ibrutinib dosage was 420 mg 1x/d, but the patient received a lower dose due to a drug-drug interaction between ibrutinib and CYP3A4 inhibitors (i.e. amiodarone and diltiazem for atrial flutter). Other prescribed drugs were apixaban, olmesartan and cholecalciferol/

calcium. In December 2022, a rapid onset of cognitive impairment with memory loss and executive dysfunction was reported. In mid-February, the patient was admitted for investigation of an acute motor and hemineglect syndrome. Vital parameters upon admission: blood pressure 140/73 mmHg, heart rate 67 bpm, ambient O2 saturation 95%, body temperature 36.8°C. During the neurological examination, the patient was disoriented with right multimodal hemineglect, labial ptosis, right limb droop and Babinski sign on the right foot. Laboratory tests showed stable renal function with a creatinine level of 136 µmol/l (N 62-106 µmol/l) and liver parameters, including transaminases, within normal limits. A complete blood count showed no abnormalities associated with neutrophils. Regarding lymphocyte count: B cells were at 8 cells/mm³ (N 80-490 cells/mm³), CD4+ T cells at 359 cells/mm³ (N 490-1640 cells/mm³) and CD8+ T cells at 1709 cells/mm³ (N 170-880 cells/mm³). HIV serology was negative. Cerebral MRI findings were consistent with PML features: multifocal periventricular and subcortical areas with T2 hypersignal predominating in the bilateral fronto-parieto-occipital regions were reported. A lumbar puncture revealed elevated proteins at 707 mg/l (N 150-460 mg/l) but glucose and lactates remained in the normal range. There were no tumour cells identified on cytology and the cellularity was normal. CSF microbiology was positive for JC polyomavirus (PCR with 900 copies/mL). Reactivation of the JC virus was attributed to the immunosuppression associated with CLL and to the treatment with venetoclax and ibrutinib (both of which were stopped). The disease course was unfavourable and palliative care was initiated. The patient died four weeks after admission.

Discussion

The patient developed PML in the context of CLL one year after starting treatment with venetoclax and ibrutinib.

Venetoclax, as navitoclax, is a selective inhibitor of the anti-apoptotic protein BCL-2 (B-Cell Lymphoma): it inhibits the BCL-2 protein, resulting in mitochondrial cell apoptosis by activation of caspases, a family of protease enzymes playing essential roles in programmed cell death. The immunosuppressive effect of venetoclax is ultimately due to the protracted cytopenias (6). Neutropenia and lymphopenia with respiratory and urinary tract infections are common adverse events. However, opportunistic infections (such as reactivation of JC virus) are not reported as adverse drug effects, even in the long term. In the European Medicines Agency database, there are five cases of PML in association with venetoclax. According to a review by the European Society of Infectious Diseases, 3.6% of patients taking venetoclax develop opportunistic infections (including aspergillosis, pneumocystis, nocardiosis, toxoplasmosis). Yet the authors do not report an association between venetoclax and PML (7). To our knowledge, there is no case report describing an association between venetoclax and PML. By contrast, one case report mentioned a patient with CLL who survived PML. Approximately seven years after the diagnosis of PML, he presented with a recurrence of his malignancy. Treatment with venetoclax was introduced without reactivation of JC virus (8).

Ibrutinib is an inhibitor of Bruton's tyrosine kinase (BTK) which interferes in the pathogenesis of several B-cell malignancies. BTK plays a role in the proliferation, survival and differentiation of B cells. The occurrence of PML during ibrutinib treatment is labelled in the product information. In the European Medicines Agency database, there are currently 31 cases of PML in association with ibrutinib. In the literature, ibrutinib has been associated with an increased risk of PML. A study based on FDA post-marketing data observed the occurrence of PML with different biological agents and cancer treatments. For ibrutinib, they identified 10 cases of PML (9). One case series described five patients with CLL who died of PML after receiving ibrutinib (n = 1), ibrutinib + rituximab (n = 3), or ibru-

tinib + rituximab + bendamustine (n = 1). The median duration of ibrutinib treatment was 11 months (range: 1.5–24 months), and PML developed on average eight years after the diagnosis of CLL (range: 3–17 years) (10). The mechanism suggested to explain the association between PML and ibrutinib is the inhibition of B-cell proliferation by ibrutinib. B cells and the humoral immune response are thought to play a crucial role in the control of JC virus replication (interaction between B and T cells for the antiviral response) (5, 11).

In the present case, the last administration of rituximab and bendamustine was in September 2019. Their involvement in the occurrence of PML seems unlikely. The majority of PML cases with rituximab develop within two years of starting the treatment (12). The association between bendamustine and PML has not been established in the literature, and the long delay since the last administration makes this drug causality very unlikely (13–14).

About 10–20% of PML cases occurred in patients with haematological malignancies, most commonly non-Hodgkin lymphoma and CLL (1, 3). The treatments administered are often confounding factors in explaining the occurrence of PML in haematological malignancy. However, a case report described a case of a patient who was diagnosed with CLL and PML simultaneously, i.e. neither with prior chemotherapy nor immunosuppressive therapy (15).

Conclusion

PML is a rare disease occurring mainly in the context of specific immunosuppressive conditions, such as HIV or with VLA4-integrin antagonists. In this case presentation, venetoclax and ibrutinib, which are reported only in a few case reports, could be suspected as causative agents. As PML is a very rare event, hindsight is still too limited to exclude or infer a formal causal relationship for either drug (ibrutinib approved by the FDA since 2013 and venetoclax approved by the FDA since 2016). Nonetheless, the increasingly common combination of a selective BCL-2 inhibitor and a BTK inhibitor should make us vigilant about their contributory role in the occurrence of PML.

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