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A CASE REPORT OF EXTREMES: THE STRIKING EFFICACY OF VENETOCLAX AND HIGH DOSE METHYLPREDNISOLONE RESCUE IN CLL

Péter Rajnics, MD Ph.D*[1], Péter Szörényi, MD[2], Ádám Kellner, MD[1], Balázs Kollár, MD[1], Éva Karádi, MD[1], Bődör Csaba, MD, Ph.D[3], Béla Kajtár, MD, Ph.D[4] and Miklós Egyed, MD, Ph.D[1]

[1]Kaposi Mór Teaching Hospital, Department of Hematology, Kaposvár, Hungary.
[2]Kaposi Mór Teaching Hospital, Intensive Care Unit, Kaposvár, Hungary.
[3]MTA-SE Lendulet Molecular Oncohematology Research Group, Semmelweis University, 1st Department of Pathology and Experimental Cancer Research, Budapest, Hungary.
[4]University of Pécs, Department of Pathology, Pécs.

***Corresponding Author: Péter Rajnics**

Kaposi Mór Teaching Hospital, Department of Hematology, Kaposvár, Hungary.

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ABSTRACT

Chronic lymphocytic leukemia (CLL) is a hematological disorder with a protracted course in the average case. The disease history of patients to be treated show a repetitive fashion speeding up in successive cycles: a clinically disease free status less and less insidiously metamorphose into a more aggressive progression that gives way to a dwindling regression following the subsequent line of therapy. The clinician has to cope with an even shorter disease lead time when treating patients carrying 17p deletion or *TP53* mutation. Despite the encouraging efficacy of Bruton's tyrosine kinase (BTK) and BCL-2 inhibitors, allogeneic bone marrow transplantation remains the only curative option for these patients. Our 50-year old male patient harboring 17p deletion presented an extremely rapid, eruptive disease progression after 28 months of BTKi therapy. The introduction of venetoclax treatment did not seem to reverse or even decelerate progression marked by prolymphocytic transformation, soaring peripheral blood ALC, and menacingly deteriorating lymphadenopathy and splenomegaly during dose ramp-up. The rapid enlargement of cervical lymph nodes leading to airway obstruction and cervical blood vessel compression necessitated a rescue of 1000 mg methylprednisolone supplementing venetoclax treatment. After massive clinical tumor lysis syndrome the patient achieved incomplete hematological remission within 3 days.

KEYWORDS: Chronic lymphocytic leukemia prolymphocytic venetoclax treatment.

INTRODUCTION

Chronic lymphocytic leukemia belongs to the group of indolent B-cell lymphoproliferative disorders [JOHNSTON ET AL., 2001]. Cases associated with 17p deletion or *TP53* mutation follow a more aggressive clinical course. The introduction of B-cell receptor signaling pathway inhibition (PI3KI, BTKI) greatly advanced the management of such cases. In patients not responding to or progressing during these treatments, promising results have been reported with BCL-2 inhibition [COUTRE *et al.*, 2018; JONES *et al.*, 2017; GILAD ITCHAKI ET AL., 2016]. While allogeneic bone marrow transplantation represents the only curative therapy, it entails considerable transplantation-related mortality and a high relapse rate in these heavily pretreated patients.

The BCL-2 inhibitor venetoclax was approved in the EU in December 2016 as a monotherapy for chronic lymphocytic leukaemia (CLL) in adult patients unsuitable for, or who have failed a B-cell receptor pathway inhibitor therapy.

High-dose methylprednisolone as a monotherapy achieved a response rate of 43% in CLL [BOSANQUET *ET AL.*, 1995]. When combined with chemo-/immunotherapy, high-dose methylprednisolone, administered in the first-line or in relapsed/refractory CLL resulted in response rates of 93% and 83% respectively [CASTRO *et al.*, 2009]. The concise explanation of the outstanding efficacy of high-dose methylprednisolone therapy is given by the fact that glucocorticoid-induced apoptosis is mediated by a p53-independent pathway [THORNTON *et al.*, 2003].

The efficacy of combined venetoclax and high dose methylprednisolone treatment has not yet been reported to date.

CLL of the 50-year old male patient was diagnosed in 2012 (Rai stage I; 17p deletion [60%]). In September 2014 he was enrolled to the R-bendamustine control arm of a clinical study evaluating a PI3Ki. After 4 cycles of treatment the patient was switched to ibrutinib in March 2015 due to progressing lymphadenopathy. By July 2015

ibrutinib treatment (420 mg/day) resulted in complete remission, while *TP53* mutation status was negative. Following the detection of a third progression in July 2017 venetoclax was introduced in the next month. On course of the dose escalation up to 100 mg/day as per SmPC (3 weeks) venetoclax therapy was associated with worsening lymphocytosis, progressive bilateral cervical lymphadenopathy and splenomegaly. The evaluation of peripheral blood smears and flow cytometry confirmed prolymphocytic transformation.

As the large masses of cervical lymph nodes threatened tracheal obstruction, 1,000 mg methylprednisolone was administered i.v. as a rescue. Alarming clinical and laboratory manifestations of tumor lysis syndrome ensued 12 hours later.

ECG showed bradycardia, broad QRS complexes and signs of left bundle branch block. The laboratory findings included hyperkalemia (8.59mmol/L), hypocalcemia (1.65mmol/L), lactic acidosis and an elevated LDH level (34,349 IU/L, normal range: 220-480 IU/L).

In view of the life-threatening derangement of laboratory parameters and hypotension continuous hemodiafiltration was performed for 24 hours in intensive care setting. Rasburicase was administered to control hyperuricemia, whereas hyperphosphatemia was treated with an aluminum/magnesium hydroxide phosphate binder.

The patient received GCSF treatment, packed RBC (6 units) and platelet (32 units) transfusions for pancytopenia. By the 36th hour of intensive therapy, peripheral blood pH, potassium, calcium, and lactate levels returned to normal range. Most strikingly, all enlarged cervical masses disappeared, no peripheral lymphadenopathy could be detected. A normal complete blood count was registered at the same time.

Bone marrow biopsy was performed 14 days later and showed a minimal residual disease of less than 5% CLL cells in BM. Venetoclax was re-introduced in December 2017. Following a repeated dose ramp-up schedule, the target dose of 400 mg/day venetoclax was reached. On maintenance, lymphadenopathy and peripheral lymphocytosis recurred and progressed, therefore methylprednisolone (32 mg QD) was also resumed. This time there were no signs of tumor lysis syndrome, whereas peripheral lymph nodes sizes and CBC values returned to normal ranges. The patient was scheduled for haploidentical stem cell transplantation.

In over 50% of patients with relapsed/refractory CLL, TP53 abnormalities step up during clonal evolution [LANDAU *et al*. 2013]. The loss of TP53 function may either stem from segmental chromosomal alterations [del(17p)] or mutations of the *TP53 gene*, or both. Under normal circumstances, TP53 acts via the intrinsic pathway of apoptosis inducing the expression of various BH3-only proteins [VILLUNGER ET AL. 2003], p53-upregulated modulator of apoptosis (PUMA) among others. As a consequence pro-apoptotic BH3-only proteins counterbalance such anti-apoptotic 'guardian' BCL2 family members as BCL2. CLL is characterized by high level expression of BCL2 protein [ROBERTSON ET AL. 1996]; a fact attributed to the loss of the microRNA-mediated suppression of the expression of the *BCL2* gene transcription [CIMMINO ET AL. 2005].

Bcl-2 acts as a stabilizer of the mitochondrial outer membrane (MOM), and its excessive production may prevent the glucocorticoid-induced decrease of the mitochondrial membrane potential and permeability. The increased membrane stability can prevent the release of cytochrome c and Apaf-1 (apoptotic protease activating factor-1) [SUSIN *et al*., 1999].

A number of *in vitro* experiments found that the over-expression of BCL-2 may result in a variable degree of resistance to glucocorticoid-induced apoptosis, whereas *in vivo* studies of animal models defective in BCL-2 expression showed the sensitization of hemopoetic cells to glucocorticoid-induced apoptosis [KAMADA *et al*., 1995; KFIR *et al*., 2007; and MEMON *et al*., 1995].

Based on these earlier data, it can be presumed that even low (100 mg QD) venetoclax doses may restore/increase the sensitivity of the intrinsic apoptosis pathway to glucocorticoid-induced apoptosis in CLL cells, that may have an outstanding significance in TP53 deficient cases with decreased MOMP. The subsequent administration of high-dose methylprednisolone could thus induce dramatic tumor lysis.

Besides the above potential PD interactions, venetoclax and methylprednisolone co-administration may also trigger PK interactions. Among other steroids, methlyprednsiolone is a relatively potent inhibitor of the multidrug resistance protein BCRP (breast cancer resistance protein, i.e. ABCG2) [PAVEK *et al*., 2005]. As venetoclax is both a substrate and an inhibitor of BCRP, a large (rescue) dose of methylprednisolone can presumably cause a significant and abrupt rise in venetoclax serum concentration. This may be of paramount importance in a clinical situation corresponding to the highly sensitive section of the dose response relation curve of venetoclax on week 2 and 3 of dose escalation. Though venetoclax label states (sections 4.4. and 4.5) that the co-administration BCRP inhibitors may lead to elevated venetoclax exposure, highlighting high dose steroid treatment in this respect is worth consideration.

In CLL, the first report of venetoclax, a potent and highly selective BH3-mimetic BCL2 antagonist was published in 2013 [ANDERSON *et al*, 2013]. When administered to treat CLL, venetoclax may cause tumor lysis syndrome, especially in cases with high tumor

burden (any lymph node with a diameter ≥5 cm or ALC ≥25 x 10^9/L). Preventive measures and a careful 5 week dose escalation prescribed by the current venetoclax label may help to avoid the vast majority of such untoward consequences when followed, however, special situations may always emerge that are not - and will not be - encompassed by the label. In our case, disease progression resumed during the first weeks of venetoclax dose titration. While venetoclax appeared to be ineffective at this stage, high-dose methylprednisolone administered as an add-on therapy caused massive tumor lysis (price), and an iCR within days (prize). With emergency and supportive measures the severe (life threatening) clinical TLS and pancytopenia were successfully managed. During a second venetoclax ramp-up the target dose of 400 mg/day was reached without further complications, and later supplemented with methylprednisolone therapy (32 mg QD). The patient has been in remission with satisfactory overall condition for 2 months now continuing on the above regime. Besides a persisting CTC Grade 2 thrombocytopenia attributed to venetoclax, the patient looks forward in a reassuring and promising status to haploidentical stem cell transplantation.

Our intention when presenting these impressive results of a truly challenging case is to draw attention to the synergistic effects of methylprednisolone and venetoclax. Besides the single case empirical evidence presented here, the rationale of that synergy is fairly well illuminated by potential PK and PD interactions. The optimization and refinement of our spontaneous/ emergency measures for a pre-planned future use may help to decrease prices payed (TLS risk) and maximize gains (remission). When deep remission is achieved in an almost hopeless clinical situation, this may render transplantation a feasible option again.

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CONFLICT OF INTEREST
No conflict of interest.

AUTHOR'S CONTRIBUTION
PR and PSz wrote the manuscript. PR, ÁK, ÉK, CSB, BK and KB analysed the data. ME reviewed the manuscript.

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