Venetoclax-rituximab is effective for patients with BTKi-exposed CLL, but durable treatment-free remissions are uncommon

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Background

Due to limited representation in the landmark phase III MURANO study, the efficacy of time-limited venetoclax-rituximab for patients with BTKi-exposed CLL is unknown. We sought to determine the efficacy of VEN-R in this specific patient population, and to determine the frequency of durable treatment-free remissions and therefore the potential for future venetoclax re-treatment.

Methods

We reviewed records of 47 consecutive patients treated at the Royal Melbourne Hospital and Peter MacCallum Cancer Centre (Melbourne), the Princess Alexandra Hospital (Brisbane) and the Royal North Shore Hospital (Sydney) between Nov 2016 and Feb 2023 who received VEN-containing therapy for BTKi-exposed CLL. Response was assessed by iwCLL 2018 criteria (Hallek *et al, Blood* 2018). Undetectable measurable residual disease (uMRD) was defined as <1 CLL cell per 10,000 leukocytes in the peripheral blood or bone marrow (PB/BM) by multiparameter flow cytometry analyzing ≥200,000 leukocytes (Rawstron *et al, Leukemia* 2007).

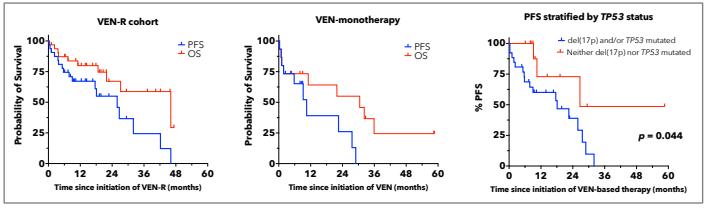
Results

The patient characteristics are shown in the Table. The median number of prior lines of therapy was 2 (1-7) and 89% of patients were chemoimmunotherapy (CIT) exposed. At the time of VEN treatment, the majority of patients had adverse disease genetics.

Among the VEN-R cohort, the median time to progression after BTKi initiation was 32 (range 6.3-83.1) months. The objective response rate to VEN-R was 81%, with complete responses in 59%. PB/BM uMRD was attained in 7 out of the 10 patients assessed (70%). At a median follow up of 20.6 (range <1-58.6) months, 10 (31%) patients remained on venetoclax and 22 (69%) had ceased therapy due to: progressive disease (PD) (*n*=9; 28%), completion of time-limited therapy (*n*=6; 19%), planned alloSCT (*n*=3, 9%), toxicity (*n*=1, 3%) or intercurrent malignancy (*n*=3, 9%). Of the six patients who completed time-limited therapy, three developed progressive CLL at 3, 5 and 17 months off treatment and three remain in remission at <1, 3 and 22 months after VEN cessation. The median PFS after VEN-R initiation was 25.9 (95%CI 9.2-42.2) months and the median OS was 46.1 (95%CI 21.9-NE) months. The median PFS and OS for patients receiving continuous VEN-monotherapy was 10.5 (95%CI 1.1-28.9) and 30.5 (95%CI 1.1-NE) months, respectively. Among the 12 patients with PD after VEN-R, disease histology was CLL (*n*=4, 33%), DLBCL-type Richter transformation (RT) (*n*=6, 50%), HL-type RT (*n*=1, 8%) and interdigitating dendritic cell neoplasm (*n*=1, 8%). On *a priori* planned univariable analyses of baseline clinic-pathologic variables, the presence of del(17p) and/or *TP53* mutations was significantly associated with inferior PFS after VEN-containing therapy (HR 3.55 [95%CI 1.03-12.17]; p=0.044).

Patient characteristics prior to VEN-containing regimen

	VEN-R	VEN-monotherapy	Whole cohort
n=	32	15	47
Age, years (median, range)	70.5 (49-84)	68 (47-86)	70 (47-86)
No. treaments prior to VEN (including cBTKi)	2 (1-5)	3 (1-7)	2 (1-7)
Chemoimmunotherapy exposed	28 (89%)	14 (93%)	42 (89%)
First cBTKi containing therapy			
Ibrutinib	23 (72%)	14 (93%)	37 (79%)
Acalabrutinib	1 (3%)	0 (0%)	1 (2%)
Zanubrutinib	8 (25%)	1 (7%)	9 (19%)
Reason for BTKi cessation			
PD	25 (78%)	13 (87%)	38 (81%)
Toxicity	7 (22%)	2 (13%)	9 (19%)
Time to progression after cBTKi initiation, months (median, range)	32 (6.3 - 83.1)	24.0 (1.1 - 90.7)	31.5 (1.1 - 90.7)
Intervening therapy between cBTKi containing regimen and VEN			
None	29 (91%)	13 (87%)	42 (89%)
Bendamustine-rituximab	0 (0%)	1 (7%)	1 (2%)
Methylprednisolone-rituximab	0 (0%)	1 (7%)	1 (2%)
Pirtobrutinib	3 (9%)	0 (0%)	3 (6%)
Genetics prior to VEN-containing regimen			
IGHV unmutated	13/15 (87%)	5/6 (83%)	18/21 (86%)
Complex karyotype (≥3 lesions)	14/17 (82%)	7/8 (87.5%)	21/25 (84%)
del17p and/or *TP53* mutated	17/24 (71%)	9/14 (64%)	26/38 (68%)
BTKi resistance mutation(s) detected	13/16 (81%)	2/5 (40%)	15/21 (71%)



Conclusions

Among patients with BTKi- and mostly CIT-exposed CLL, VEN-R induced frequent responses and comparable disease control as reported with pirtobrutinib or continuous VEN monotherapy. However, most patients developed PD during or shortly after completing therapy, and prolonged treatment-free remissions were uncommon, especially if *TP53* aberrations were present. RT at disease progression was common. In appropriate patients with disease responsive to VEN-R in this context, consolidation with alloSCT or other immune-based therapies should be considered. The generalizability of these results to patients who have received first-line BTKi is unknown.

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