

COST-MINIMIZATION OF VENETOCLAX WITH RITUXIMAB VERSUS IBRUTINIB IN R/R CLL IN THE BRAZILIAN PRIVATE HEALTHCARE SYSTEM

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INTRODUCTION

- CLL is a lymphoproliferative disease characterized by the persistency of a minimum of $5 \times 10^9/L$ type B monoclonal lymphocytes. These lymphocytes can accumulate in peripheral blood, lymph nodes, blood marrow and spleen. More frequent in elders and considered a rare disease, CLL has a global incidence between <1 and 5.5 cases per 100,000 inhabitants. (1,2)
- Although a rare disease, the CLL is the most common type of leukemia in adults, being responsible for about 32% of total leukemias. (3)
- It is an indolent disease, in which about 60% of patients at the time of diagnosis may be asymptomatic, while other 40% may have several inespecific clinical and laboratory changes, such as fatigue, weakness, or more specific symptoms like lymphadenomegaly, hepatomegaly, splenomegaly, cytopenias for autoimmune mechanisms (autoimmune anemia and thrombocytopenia) and constitutional symptoms such as fever, weight loss and night sweats. (4,5)
- The presence of 17p deletion (17p Del), TP53 mutation and unmutated IGHV indicate worse clinical results with fast disease evolution. The 17p Del varies between 30% to 50% in R/R CLL patients. (6)
- A commonly used regimen for chronic lymphocytic leukemia has been bendamustine in combination with rituximab. Recently, novel targeted oral agents, such as venetoclax and ibrutinib, have provided greater survival with modest toxicity. (7)
- Venetoclax is an orally administered potent and selective BH3 mimetic that targets the BCL-2 (B-Cell Leukemia/Lymphoma 2 Gene) inhibitor, exhibiting significant apoptotic activity. While ibrutinib is a once-daily, oral covalent inhibitor of Bruton's tyrosine kinase, which inhibits B-cell receptor signaling (7)
- NICE's committee believe venetoclax plus rituximab to have similar or better efficacy to ibrutinib, and that venetoclax is unlikely to be inferior to ibrutinib. (8)
- According to ANS' rol (mandatory list of drugs and procedures), with regards to R/R CLL, only patients with 17p Del are contemplated with ibrutinib.

OBJECTIVE

Develop a cost-minimization analysis of venetoclax plus rituximab (V+R) versus ibrutinib in adult patients with Chronic Lymphocytic Leukemia (R/R CLL) who have received at least one previous therapy, according to the perspective of the Brazilian private healthcare system.

METHODS

- In a systematic review developed by authors, it was not found any direct-comparison between venetoclax and ibrutinib. Once indirect-comparisons have limitations, it was developed a cost-minimization analysis assuming equivalency in therapeutic efficacy between V+R and ibrutinib.
- The cost-minimization analysis has compared in terms of incremental costs the total drugs-related treatment costs in a pre-defined time horizon (24 months).

Figure 1. Treatment scheme: venetoclax + rituximab.



Figure 2. Treatment scheme: ibrutinib.



- The initial dose of venetoclax is 20mg (02 tablets of 10mg), weekly ramping-up until reaching 400mg (04 tablets of 100mg) at the beginning of week 5. From that point on patient will follow the maintenance 400mg dosage per day until the end of the 24th month.
- Drugs acquisition costs were obtained from the price-reference list, published by the Brazilian Regulatory Agency (ANVISA) considering list prices (PF), with 18% tax (PF 18%) over circulation of merchandise and services (ICMS). The prices considered in this analysis were based in the April 2019 list edition. (9)
- Table 1 shows treatment monthly cost of venetoclax, rituximab and ibrutinib. For the calculation of monthly costs it was considered that one month had 30 days.
- All costs are presented in american dollars (USD). Currency rate used was R\$3.92 to USD 1.00. It represents the average rate of last 60 days (07/08/2019 to 09/06/2019). (10)

Table 1. Price of drugs used in the analysis.

Drugs	Dosage Forms	List Price (PF18%)
Venetoclax (start-kit)*	(10 mg x 14 tablets – week 1)	\$ 1,899.27
	(50 mg x 7 tablets – week 2)	
	(100 mg x 7 tablets – week 3)	
	100 mg x 14 tablets – week 4)	
Venetoclax (maintenance dose)	100 mg x 120 tablets	\$ 8,799.67
Rituximab	10 mg/mL x 10 mL bottle	\$ 349.06**
Ibrutinib	140 mg x 90 tablets	\$ 9,852.72

* Related to the 1st month of treatment.
** PF 0%: product exempt from ICMS.

- Rituximab dose calculation was based on patients body surface area, defined according to Mosteller formula, based on Brazilian antropometric data. (11)
- Weight: 67.2 kg
- Height: 164.5 cm;
- Body surface area: 1.75 m².

METHODS (CONTINUED)

Table 2. Monthly treatment cost.

Drugs	Dosage Forms	List Price (PF18%)
Venetoclax	1 st month (start-kit)	\$ 1,899.27
Venetoclax	Following months (maintenance dosage)	\$ 8,799.67
Rituximab	1 st Cicle: 375 mg/m ² (month 1)	\$ 2,293.46
	2-6 Cicles: 500 mg/m ² (months 2-6)	\$ 3,057.94
Ibrutinib	30 days (bottle with 90 tablets)	\$ 9,852.72

Table 3. Annual treatment cost.

Drugs	1 st year	2 nd year
Venetoclax + rituximab	\$ 116,278.83	\$ 105,596.06
Ibrutinib	\$ 118,232.04	\$ 118,232.04

- Cost-minimization is exclusively based in two parameters, drugs price and dosage, thus the only parameter subject to uncertainty is purchasing price of the drugs analyzed. These prices are uncertain and depend on negotiations between pharmaceutical companies and HMOs, which makes it unfair any comparison based on prices different than those defined by Anvisa's list of price-reference.
- Considering these uncertainties it was developed an univariate sensitivity analysis of the results presented in the monthly treatment costs (Table 4), applying a variation of -10% over 18% PF prices of venetoclax, rituximab and ibrutinib in order to analyze the impact of treatment costs. Superior limit was not applied once PF represents the maximum for drugs price. Results are presented in Table 6.

Table 4. Treatment monthly cost.

Purchasing cost of...	Base Cost	Inferior limit	Superior limit
Ibrutinib	\$ 9,852.71	\$ 8,867.44	-
Venetoclax (start-kit)	\$ 1,899.26	\$ 1,709.33	-
Venetoclax (maintenance)	\$ 8,799.67	\$ 7,919.70	-
Rituximab	\$ 349.06	\$ 314.15	-

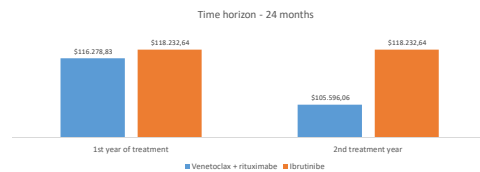
- An alternative scenario of 56 months time-horizon was also considered, according to NICE's appraisal of V+R (8), which assumed that the average treatment duration with ibrutinib by R/R CLL patients was 56 months, and 22 months for V+R. However, it was adopted a more conservative approach in this analysis, considering 25 months of treatment duration for venetoclax + rituximab, according to product label.

RESULTS

Table 5. Treatment yearly costs.

Drugs	1 st year of treatment	Incremental	% of savings	2 nd year of treatment	Incremental	% of savings
Venetoclax + rituximab	\$ 116,278.83	-	0%	\$ 105,596.06	-	0%
Ibrutinib	\$ 118,232.04	-\$ 1,953.81	-2%	\$ 118,232.04	-\$ 12,636.59	-11%

Figure 3. Yearly treatment costs comparison.

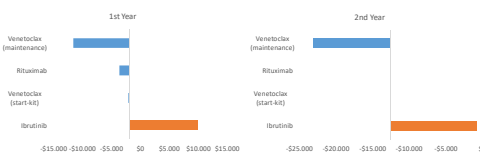


- According to treatment costs analyzed V+R demonstrates being the most economic alternative when compared to ibrutinib in R/R CLL patients. The adoption of V+R offers cost savings of about USD 2,000 (2%) per patient in the 1st year, even with the addition of rituximab. In the 2nd year, this adoption allows cost savings of approximately USD 12,500 (11%) per patient.

Table 6. Univariate analysis results (incremental cost of V+R versus ibrutinib considering inferior limit of prices).

Default Parameters	1 st year	2 nd year
Cost of venetoclax (start-kit)	-\$ 2,143.73	-\$ 12,636.59
Cost of venetoclax (maintenance)	-\$ 11,633.45	-\$ 23,196.19
Cost of rituximab	-\$ 3,712.13	-\$ 12,636.59
Cost of ibrutinib	\$ 9,869.46	-\$ 813.32

Figure 4. Univariate sensitivity analysis – Tornado Diagram.



RESULTS (CONTINUED)

- Results from the univariate sensitivity analysis indicate that if applied a 10% discount in ibrutinib over its PF18% price, the 1st year with V+R show an incremental cost of about \$9,950. This results is directly related to the addition of rituximab. However, even applying this discount, the following years show savings of around \$800, in favor of V+R. Discounts around 10% to the other parameters do not have significantly influenced the analysis results. Therefore, independently of the discounts applied to the other drugs (venetoclax and rituximab), the treatment with V+R remains with the lowest cost in comparison to ibrutinib.

Table 7. Results of cost-minimization analysis (per patient) – 56 months.

Medicamento	Venetoclax + rituximab	Ibrutinib	Incremental	% of savings
Cost of treatment	\$ 230,674	\$ 551,752	-\$ 321,077	-58%
Time in treatment	(complete duration of treatment)	average duration of treatment)	-	-
Drug	Venetoclax + rituximab	Ibrutinib		

- With duration of treatment of 56 months for ibrutinib and 25 months for V+R demonstrates resource savings of about \$321,077 per patient (58% cost savings). Which means that the cost of treating 10 R/R CLL patients with ibrutinib is the same cost of treating about 24 patients with venetoclax + rituximab.

Figure 5. Results of cost-minimization analysis (per patient) – 56 months.

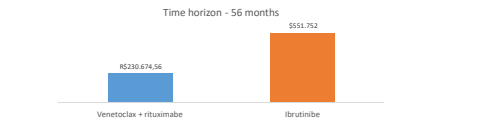


Figure 6. Accumulated costs (USD) comparison: 1st year.

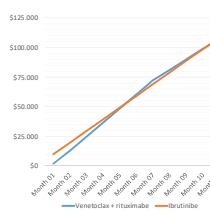


Figure 7. Accumulated costs (USD) comparison: from 1st to 5th year.



CONCLUSIONS

- Economic analysis suggest that combined treatment with V+R brings resource savings to the Brazilian private healthcare system. This results are specially related to its fixed treatment duration, with treatment interruption in 25 months.
- According to the cost-minimization analysis of V+R versus ibrutinib, V+R offers \$2,000 (2%) per patient in cost savings in the 1st year, and \$12,500 (11%) per patient in the 2nd year.
- In 56 months time-horizon cost-minimization analysis, based on NICE's average treatment duration, the adoption of V+R shows \$321,077 in resource savings per patient. Therefore, the cost of treating 10 R/R CLL patients with ibrutinib is the same cost of treating about 24 patients with venetoclax + rituximab.

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DISCLOSURES

Vieira, Fernando Meton: is researcher at Instituto COI de Educação e Pesquisa. Brito Filho, Clóvis de A; Vitale, Vinícius: are employees and stockholders of AbbVie. Vinícius Vitale coauthored the abstract/poster as a member of the Market Access organization and transferred to the Commercial organization after the content was finalized.

